Synthesis of bacterial oligosaccharides : developments in the construction of cis-glycosidic linkages

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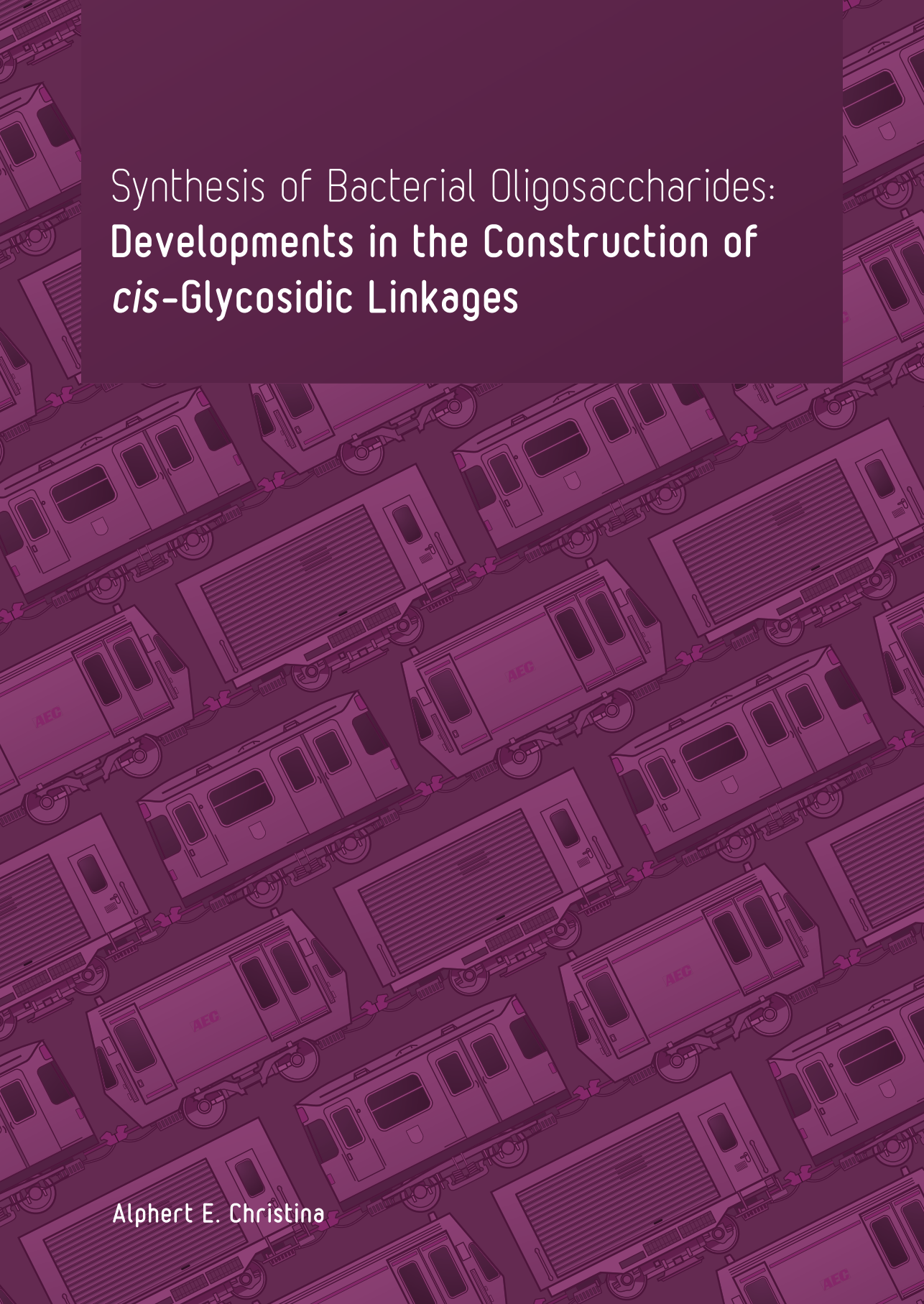

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Synthesis of Bacterial Oligosaccharides:

Developments in the Construction of *cis*-Glycosidic Linkages

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List of Abbreviations

AAT	2,4-diamino-2,4,6-trideoxy-D-galactose
Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
AIBN	azo-isobutyronitrile
An	4-methoxybenzoyl
aq.	aqueous
arom	aromatic
BAIB	[bis(acetoxy)iodo]benzene
Bn	benzyl
bs	broad singlet
BSP	1-benzenesulfinyl pipperidine
Bu	butyl
Bz	benzoyl
cat.	catalytic
Cbz	benzyloxycarbonyl
ClAc	chloroacetyl
COSY	correlation spectroscopy
C_q	quaternary carbon atom
Cq	quaternary carbon
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
dd	doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminium hydride
DiPEA	*N,N*-di-iso-propyl-N-ethylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
DMTST	dimethyl(thiomethyl)sulfonium triflate
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
equiv.	molar equivalents
Et	ethyl
Fuc	D-fucose
Gal	D-galactose
GalA	D-galacturonic acid
Gal*f*	D-galactofuranose
Gro	glycerol
GroAN	D-glyceramide
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoric triamide
HPAEC	high performance anion-exchange chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	Hertz
IAD	intramolecular aglycon delivery
IR	infrared spectroscopy
J	coupling constant
m	multiplet
M	Molar
Me	methyl
MHC II	major histocompatibility complex class II
MP	4-methoxyphenyl
Ms	methanesulfonyl
Ms	methanesulfonyl
n.d.	not determined
NAP	2-naphthylmethyl
NGP	neighbouring group participation
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
p	para
PE	petroleum ether

Ph	phenyl
Phth	phthaloyl
PMB	4-methoxy benzyl
ppm	parts per million
PS	polysaccharide
PS	polystyrene
q	quartet
quant	quantitative
RRV	relative reactivity value
rT	room temperature
s	singlet
sat.	saturated
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
TDS	thexyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
tert	tertiary
Tf	trifluoromethanesulfonyl
Tf_2O	trifluoromethanesulfonic anhydride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TLR	Toll-like receptor
TMS	trimethylsilyl
TOCSY	total correlation spectroscopy
Tol	*p*-tolyl
Ts	4-toluenesulfonyl
TTBP	2,4,6-tri-*tert*-butylpyrimidine
Z	benzyloxycarbonyl
ZPS	zwitterionic polysaccharide

Chapter 1

General Introduction: Challenges and Strategies in Modern Synthetic Carbohydrate Chemistry

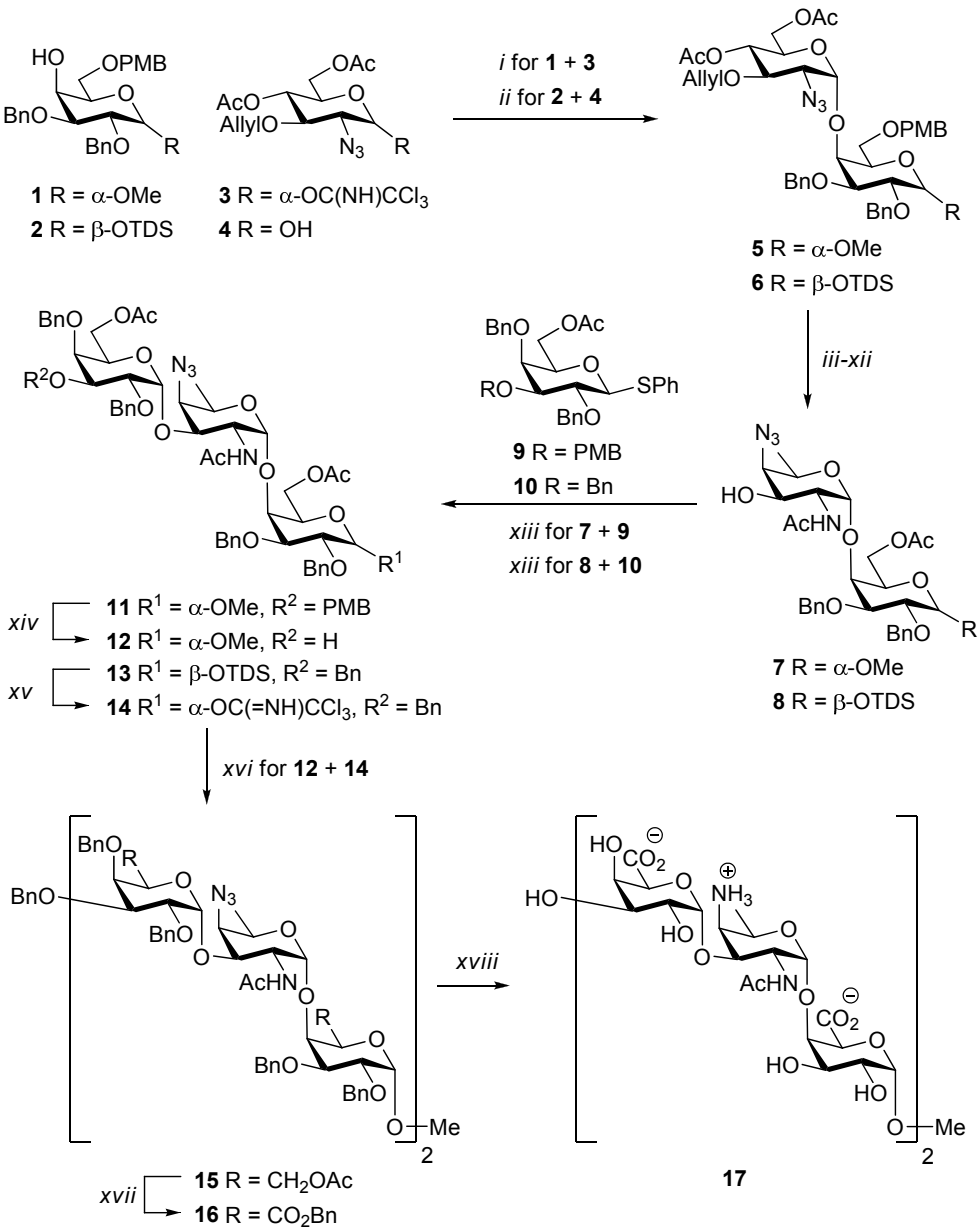
Introduction

Even though carbohydrates are classically typified by their function in the storage and transport of energy, they are involved in many more crucial biological processes such as fertilization, embryogenesis, cell–cell recognition, neuronal development, cell growth, tumor cell metastasis and immune defense. This functional variety reflects the structural diversity of these (polymeric) biomolecules and the monomeric residues they are built up from. Besides the unequalled amount of chiral stereocenters, in comparison with the other classes of biopolymers, carbohydrate ring size and regiochemistry in terms of interresidual connectivity are dimensions that contribute to the structural diversity. To unravel the mechanistic details concerning carbohydrate-mediated biological processes, pure and structurally well-defined oligosaccharides and glycoconjugates can serve as valuable tools. Extraction of carbohydrates or glycoconjugates from natural sources is often very difficult, if not impossible, or does not provide the samples in sufficient purity and/or quantity to allow for the establishment of their structure-activity relationships. Organic synthesis can provide a solution to these shortcomings.

One of the most challenging aspects in synthetic carbohydrate chemistry is the stereoselective introduction of glycosidic linkages.[1] 1,2-*Trans* bonds can generally be introduced in a reliable way by equipping a glycosyl donor with an acyl functionality on the C-2 position. Upon activation of the donor a transient dioxolenium ion is formed, directing the glycosylation event towards the 1,2-*trans* product. 1,2-*Cis* bonds however, are less straightforward to construct. By the hand of selected examples, this Chapter illustrates the challenges in modern synthetic carbohydrate chemistry and describes recently introduced strategies for the stereoselective introduction of *cis*-glycosidic bonds.

Zwitterionic polysaccharides (ZPSs) are the only known class of polysaccharides capable of eliciting a T-cell dependent immune response.[2] The availability of well-defined polysaccharide fragments can contribute to the elucidation of the mechanism of action at a molecular level. In addition, their structural complexity makes zwitterionic oligosaccharides attractive synthetic targets. Sp1 is a type 1 zwitterionic polysaccharide found on the outer layer of the cell wall of *Streptococcus pneumonia*. The repeating unit of Sp1 [α-D-GalA-(1→3)-α-D-Fuc(4-N)NAc-(1→4)-α-D-GalA-(1→3)] contains two negatively charged carboxylate groups on the GalA residues and one positively charged amino group on the rare 4-amino-*N*-acetyl fucosamine moiety. Bundle and co-workers were the first to synthesize monomeric and dimeric repeats of the Sp1 polysaccharide.[3] Their synthetic approach to construct the 1,2-*cis* glycosidic linkages entailed the use of C-6-*O*-acetyl esters as remote directing protective groups, during the glycosylation event (see Scheme 1). Although there is ongoing debate as to whether 6-*O*-acyl functions actually steer the stereochemistry of glycosylations, there are reports indicating the beneficial effect of remote acyl functionalities on the formation of α-glycosidic linkages.[4] The C-6-*O*-acetyl groups were also used as precursors for the GalA carboxylate functions to circumvent difficulties with the low reactivity of the GalA residues.[5] As a result, a strategy was developed in which the 4-amino-*N*-acetyl fucosamine moiety is constructed in a disaccharidic stage and the GalA carboxylate functions are introduced after the execution of all necessary glycosylation steps. Thus, galactoside acceptor **1** was glycosylated with diacetyl glucosazide imidate donor **3** using TMSOTf as promoter to provide disaccharide **5** in 60% with excellent α-selectivity. Because a trichloroacetimidate based glycosylation proved ineffective in the assembly of the second dimer **6**, a dehydrative coupling between lactol **4** and thexyldimethylsilyl galactoside **2** was employed. In this event dimer **6** was formed in 73% as a single anomer. Now, the glucosazide residue of both dimers was converted to a diamino fucose residue in 7 steps: azide reduction, *N*-acetylation, *O*-deacetylation, 6-*O*-mesylation, $NaBH_4$ reduction, triflation and azide substitution. Deprotection of the PMB group, acetylation and deallylation gave acceptors **7** and **8** in 10% and 20% over 10 steps, respectively. Dimers **7** and **8** were glycosylated with thioglycosides **9** and **10**, using NIS and a catalytic amount of silver triflate to provide trisaccharides **11** and **12**, respectively. Trimer **11** was transformed into acceptor **12** by treatment with DDQ (73%) and donor **14** was constructed from trisaccharide **13** by removal of the anomeric thexyldimethylsilyl (TDS) group and subsequent trichloroacetimidate formation. The union of the two trisaccharide parts required careful tuning of the reaction conditions (temperature,

Scheme 1



Synthesis of a Sp1-hexamer fragment. *Reagents and conditions:* (*i*) TMSOTf, CH_2Cl_2, -15°C → *r*T, 60%; (*ii*) Ph_2SO, Tf_2O, TTBP, CH_2Cl_2, -25°C, 73%; (*iii*) H_2S, pyridine, H_2O, Et_3N; (*iv*) Ac_2O, pyridine, 74% over two steps for **5**, 75% over two steps for **6**; (*v*) NaOMe, MeOH; (*vi*) MsCl, pyridine, -15°C→ 0°C, 71% over two steps (α-OMe), 95% over two steps (β-OTDS) ; (*vii*) DMSO, $NaBH_4$, 85°C, 80% (α-OMe), 85% (β-OTDS); (*viii*) Tf_2O, pyridine, CH_2Cl_2, -30°C; (*ix*) NaN_3, DMF, rT, 57% over two steps (α-OMe), 62% over two steps (β-OTDS); (*x*) α-OMe: TFA (1%) in CH_2Cl_2; β-OTDS: DDQ, CH_2Cl_2, H_2O; (*xi*) Ac_2O, pyridine, 80% over two steps (α-OMe), 80% over two steps (β-OTDS) dimer; (*xii*) $PdCl_2$, NaOAc, AcOH, H_2O, 53% (α-OMe), 66% (β-OTDS); (*xiii*) NIS, AgOTf, CH_2Cl_2, -30°C → rT, 79% (**11**), 66% (**13**); (*xiv*) CH_2Cl_2, H_2O, DDQ, 73%; (*xv*) (1) TBAF, HOAc, THF, 92%, (2) CCl_3CN, DBU, CH_2Cl_2, 71%; (*xvi*) TMSOTf, CH_2Cl_2, 85%; (*xvii*) (1) NaOMe,

MeOH; (2) TBABr, $NaHCO_3$, TEMPO, CH_2Cl_2, NaOCl; (3) HCl, *t*BuOH, 2-methylbut-2-ene, $NaClO_2$, NaH_2PO_4; (4) CsF, BnBr, DMF, 52%; (*xviii*) H_2, $Pd(OH)_2$, CH_2Cl_2, MeOH, H_2O, 53%.

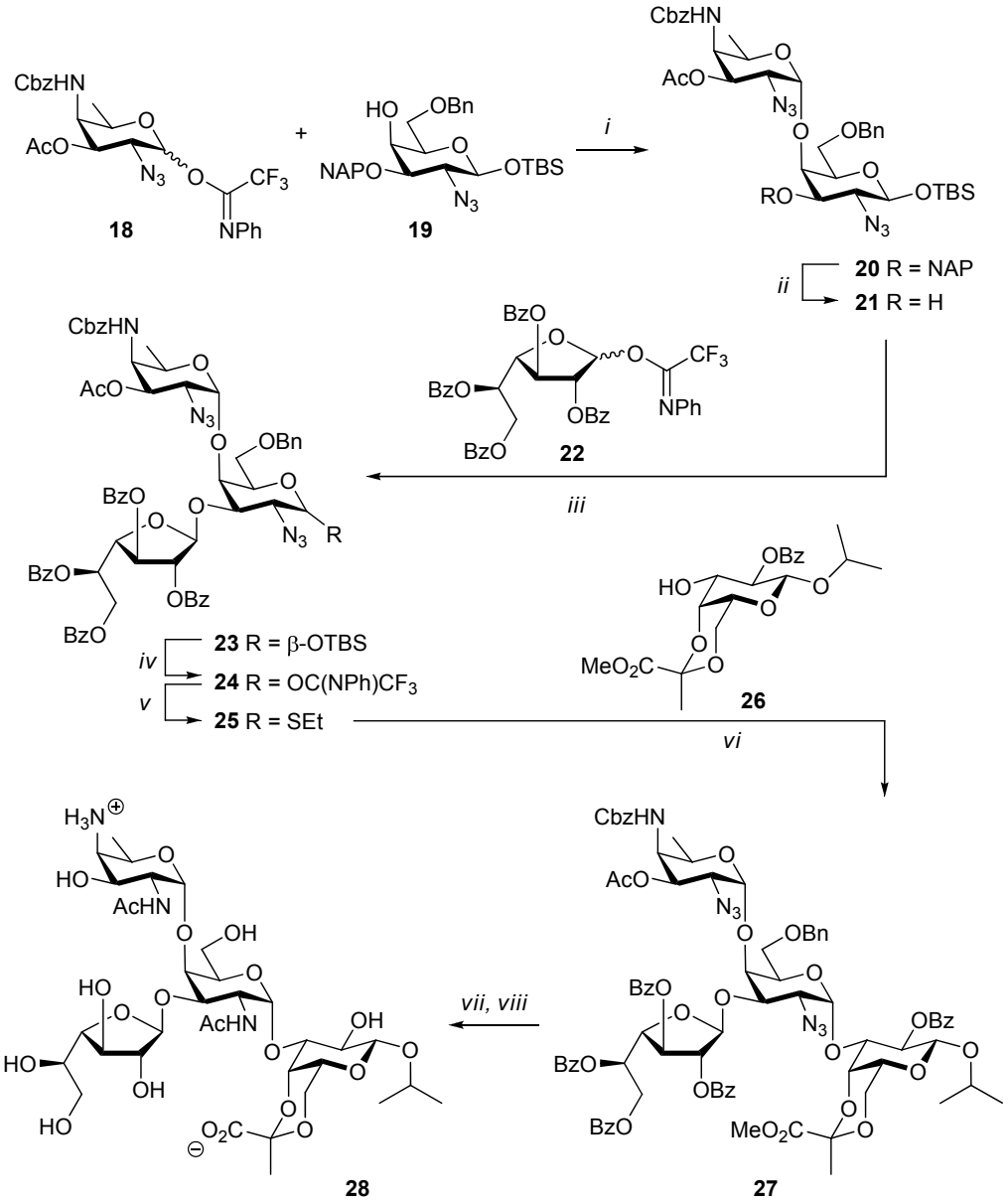
donor equivalents and amount of Lewis acid activator) and was accomplished in 85% yield. The fully protected hexasaccharide was deacetylated to give the tetraol, which was oxidized in a two-step procedure to provide the tetracarboxylate. Benzylation then gave hexamer **16** in 52% over the last steps. Hydrogenolysis of all benzyl ethers and esters and the two azide groups gave the zwitterionic hexasaccharide **17**.

Polysaccharide A1 (PS A1) is a ZPS which is found on the capsule of the commensal bacterium *Bacteroides fragilis*. It consists of the tetrasaccharide repeating unit [–3)-α-D-Fuc(4-N)NAc-(1–4)-[β-D-Gal*f*-(1–3)]-α-D-GalNAc-(1→3)-β-D-Gal-(1→3)] bearing a positive charge on a diaminofucose residue and a negative charge on a pyruvate that spans positions 4 and 6 of a galactose residue. The presence of two 1,2-*cis* linkages, one of which is connected to an axially oriented galactoside C-4-OH, and the previously encountered diaminofucose residue make PS A1 a challenging synthetic target. The first synthesis of a protected PS A1 tetrasaccharide repeating unit was reported by van den Bos *et al*.[6] and, more recently, the group of Seeberger described the synthesis of the repeating unit structure **28** (Scheme 2).[7]

Since two routes of synthesis, comprising coupling of a protected diaminofucose derivative onto the poorly nucleophilic axially oriented galactoside C-4-OH in a trimeric and dimeric stage failed, an alternative order of glycosylation events was followed. In the first coupling, galactosazide acceptor **19** was united with fucosyl donor **18** bearing a non-participating C-2-azido group, to afford α-linked disaccharide **20**. After DDQ mediated removal of the 2-naphthylmethyl (NAP) ether, the resulting acceptor **21** was coupled with galactofuranoside **22**. Neighbouring group participation (NGP) ensured the formation of the β-linkage in trisaccharide **23**. The anomeric tert-butyldimethylsilyl (TBS) group in this trimer was converted to an *N*-phenyl trifluoroacetimidate functionality to provide the requisite donor for the last glycosylation event. Since this donor proved to be ineffective for the construction of the tetramer, the imidate group was replaced by an anomeric thioethyl function. Several activation methods (NIS/AgOTf, MeOTf, Ph_2SO/Tf_2O) were examined to condense thioglycoside **25** and pyruvate galactoside **26** and eventually tetrasaccharide **27** was obtained in 58% when DMTST was used as a promoter. To complete the synthesis of fragment **28** the azido functions were first converted to acetamides by reaction with thiolacetic acid. Hydrogenation with Pearlman's catalyst preceeded basic removal of the ester groups because reversal of the reaction sequence led to the formation of a cyclic carbamate. The final basic treatment leading to target tetrasaccharide **28** was effectuated in THF to prevent acetyl migration to the 4-amino group of the diamino fucose residue.

The syntheses described above show that complex structures such as **17** and **28** can be assembled using state-of-the-art chemistry, but at the same time considerable optimization is required for the construction of the interglycosidic linkages. Although the in-

Scheme 2



Synthesis of the tetrasaccharide repeating unit of PS A1. *Reagents and conditions:* (*i*) TMSOTf, CH_2Cl_2, 0°C, 74%; (*ii*) DDQ, MeOH, CH_2Cl_2, 23°C, 86%; (*iii*) TMSOTf, CH_2Cl_2, -30°C, 90%; (*iv*) (1) TBAF, AcOH, THF, 0°C; (2) $F_3CC(NPh)Cl$, Cs_2CO_3, CH_2Cl_2, 23°C, 82% over two steps; (*v*) EtSH, TMSOTf, CH_2Cl_2, 0°C, 96%; (*vi*) DMTST, TTBP, 0°C, 58%; (*vii*) AcSH, pyridine, 23°C, 67%; (*viii*) (1) H_2, $Pd(OH)_2$/C, MeOH, 23°C; (2) THF, then 0.5 M NaOMe in 1:1 MeOH/H_2O, 23 °C, 46% over two steps.

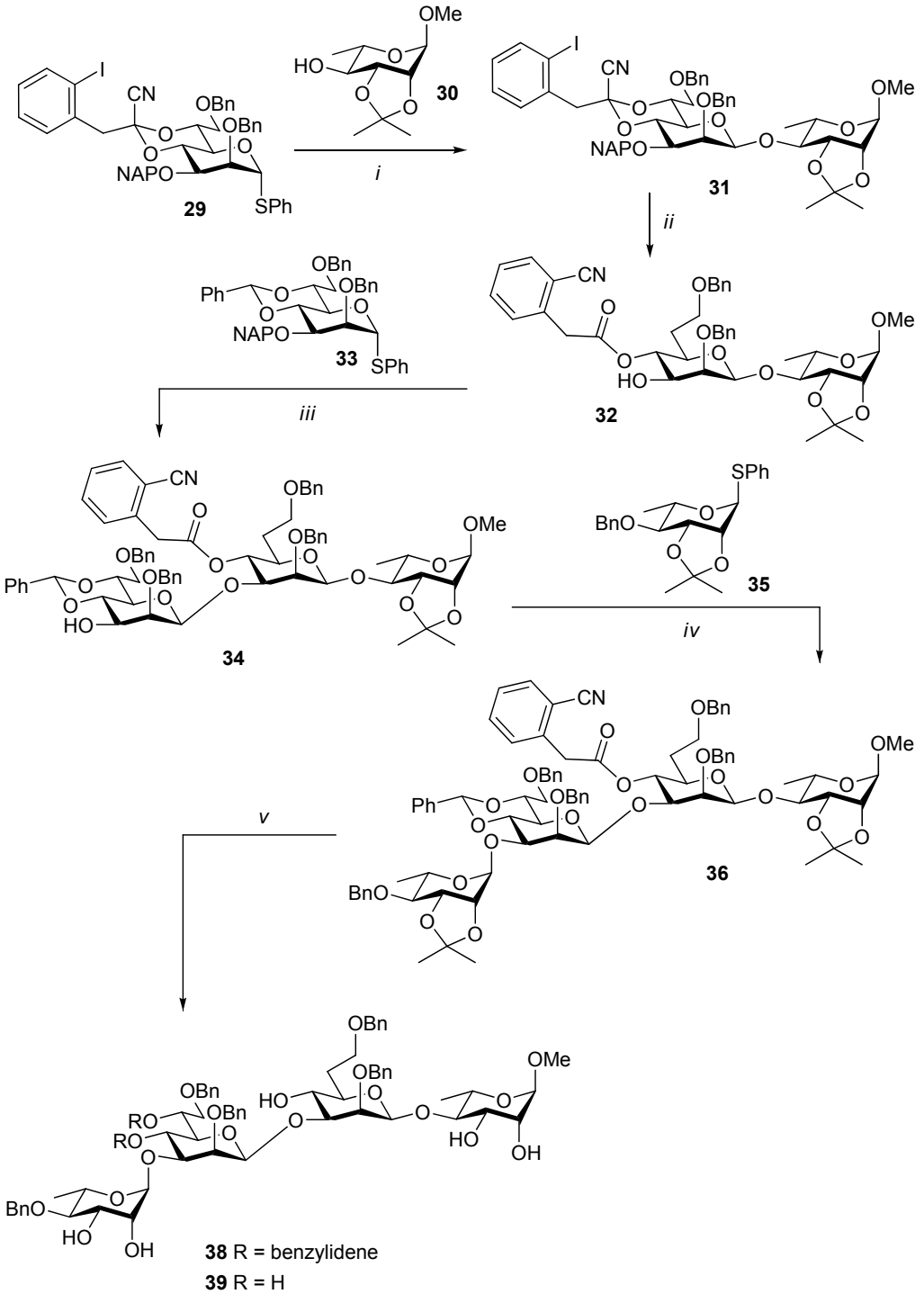
sight into the nature and reactivity of product forming intermediates in glycosylation reactions is continuously expanding, the optimization of a given glycosylation reaction often still is a game of trial and error. Further fundamental research is obviously warranted to get a better grip on the many factors at play in a glycosylation event to prevent the waste of precious building blocks in time and labor intensive optimization reactions.

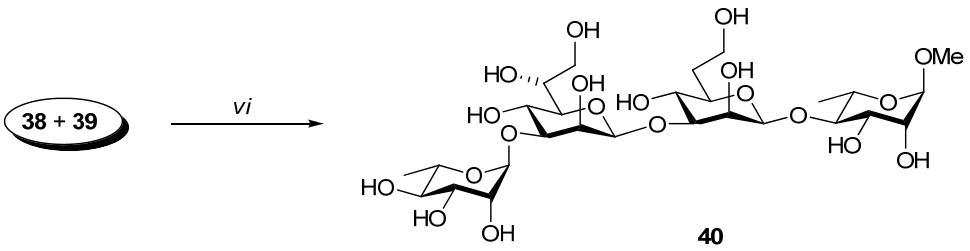
A major step forward in the understanding of product forming intermediates involved in glycosylation reactions was made by Crich and co-workers. They discovered that 4,6-*O*-benzylidene mannoside donors, featuring non-participating groups at the C-2 and C-3 position, provide β-mannosides with generally excellent stereoselectivity. Formation of this type of glycosidic linkage is problematic because of different unfavorable stereoelectronic effects (anomeric effect and Δ2-effect) and a sterically hindered trajectory of the incoming nucleophile due to the axially oriented C-2 substituent. Crich revealed that S_N2-like displacement of an anomeric triflate was at the basis of the observed β-selectivities in condensation reactions of 4,6-*O*-benzylidene mannosyl donors.[8]

In the synthesis of a tetrasaccharide subunit of a lipopolysaccharide from *Plesimonas shigelloides,* Crich *et al.* further extended the benzylidene β-directing principle (see Scheme 3).[9] The assembly of tetrasaccharide **40** comprised the incorporation of two uncommon β-linked heptose residues, one of which being a 6-deoxy moiety. Therefore the 1-cyano-2-(2-iodophenyl)ethylidene group was introduced as a 4,6-*O*-benzylidene surrogate set up for deoxygenation by radical fragmentation. The assembly of the target tetrasaccharide started off with the glycosylation of methyl rhamnoside **30** with thioglycoside donor **29** following a pre-activation protocol with the Ph_2SO/Tf_2O promoter combination. Because of the electron withdrawing cyano group on the benzylidene ketal the use of this promotor system was required, for it generates a somewhat more reactive electrophile in comparison to the BSP/Tf_2O reagent system, originally developed by Crich and co-workers.[10] Disaccharide **31** was obtained in 86% yield with complete β-selectivity. Treatment of this disaccharide with tributyltin hydride and AIBN afforded a 6-deoxy-*manno*-heptopyranoside, which was transformed into acceptor **32** by DDQ mediated removal of the 2-naphthylmethyl group. In the next preactivation based glycosylation event, this time using donor **33** in combination with the BSP/Tf_2O promoter system, the second 1,2-*cis* bond was introduced to provide the all *cis*-linked trisaccharide **34**. Oxidative cleavage of the 2-naphthylmethyl group then set the stage for the final coupling step with thiorhamnoside **35**. The α-directing nature of this donor had been previously established by the same group.[11] Thus pre-activation of thiorhamnoside **35** with BSP/Tf_2O and subsequent addition of trisaccharide **34** afforded tetrasaccharide **36** as a single α-stereoisomer in 73% yield. Saponification followed by acid treatment gave a mixture of benzylidene protected and unprotected tetrasaccharides **38** and **39** in 85% combined yield. Hydrogenolysis of the individual tetrasaccharides gave target **40** in 94% and 96% yield from **38** and **39**, respectively.

Van den Bos *et al.*[12] reported that mannuronic acid donors can also be used for the stereoselective construction of 1,2-*cis* mannosyl linkages. Interestingly, the triflates generated from mannuronic acid donors preferentially reside in a flipped $^1C_4$-chair conforma-

Scheme 3



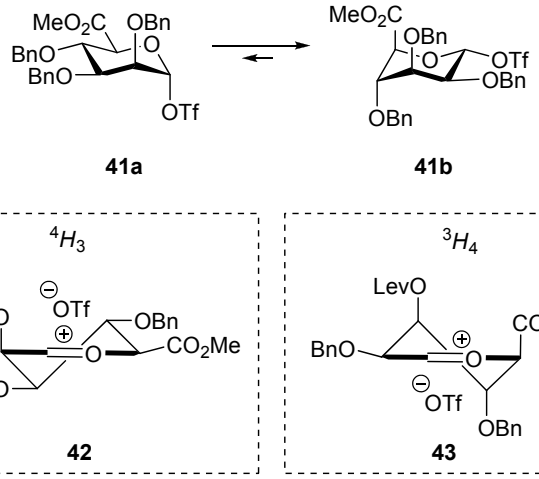


40

Synthesis of a tetrasaccharide subunit from *Plesimonas shigelloides*. *Reagents and conditions:* (*i*) **29**, Ph_2SO, Tf_2O, TTBP, CH_2Cl_2, -20°C then **30**, 86%; (*ii*) (1) Bu_3SnH, AIBN, xylene, Δ (2) DDQ, 57%; (*iii*) (1) **33**, BSP, Tf_2O, TTBP, CH_2Cl_2, -60°C then **32** (2) DDQ, 6:1 CH_2Cl_2/H_2O, 88%; (*iv*) **35**, BSP, Tf_2O, TTBP, CH_2Cl_2, -60°C then **34**, 73%; (*v*) (1) NaOMe, MeOH (2) TFA, CH_2Cl_2 then tris (2-aminoethyl) amine polymer, 36% (**38**) and 49% (**39**); (*vi*) H_2, $Pd(OH)_2/C$, MeOH, 94% from **38**, 96% from **39**.

tion, placing the anomeric triflate in an unfavorable equatorial position. Based on the work of the group of Woerpel[13] a rationale for this behavior was found in the most favorable conformation of the mannuronic acid oxocarbenium ion, which preferentially takes up a $^3H_4$ half chair conformation. Because the anomeric center of the mannuronic acid triflate bears significant carbocation character it takes up a conformation close in conformational space to the favorable $^3H_4$ half chair (Scheme 4).[14]

Scheme 4



Mannuronic acid triflate conformers and oxocarbenium ion half chairs depicted for comparison.

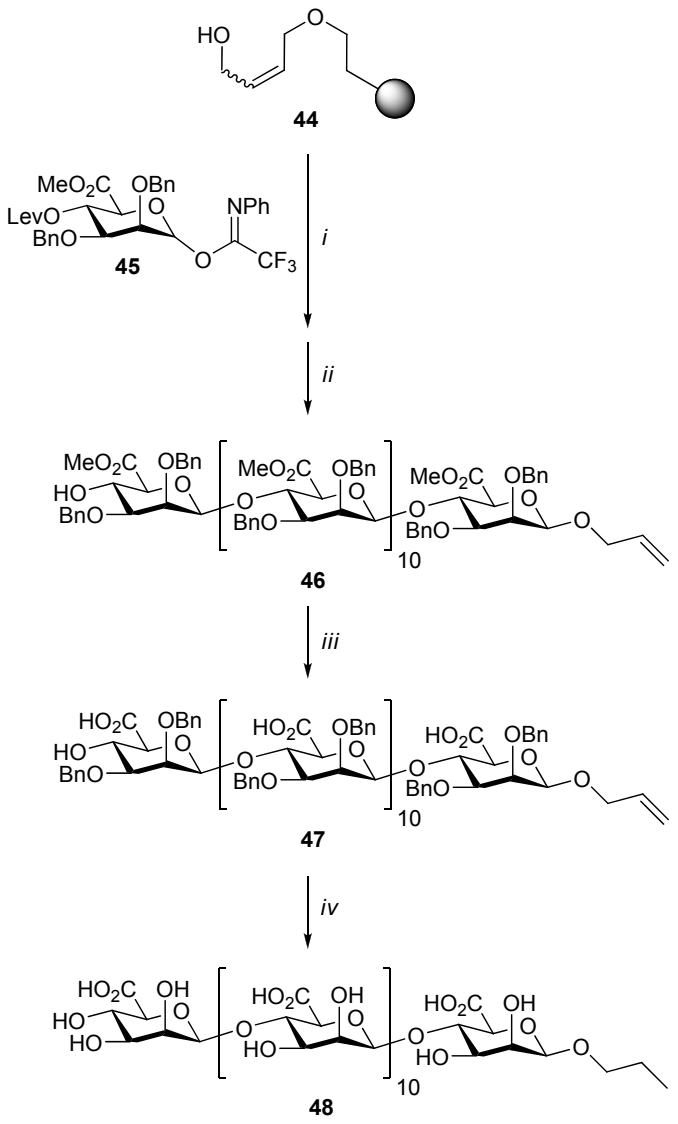
To date, the mannuronic acid donors are amongst the most reliable donors to provide β-mannoside linkages,[15] and this was efficiently exploited in the automated solid phase synthesis of β-(1,4)-mannuronic acid alginate oligomers by Walvoort *et al*.[16] In the optimization process prior to the synthesis, the optimal reaction cycle, including the types of

reagents, the stoichiometry, the reaction times, the temperature and wash procedures were established.

It was also found that performing the repetitive glycosylations at 0°C gave a 1:3 α/β mixture of anomeric diastereomers. To improve this anomeric ratio and assure the intermediacy of α-anomeric triflates, the reaction temperature was lowered just below the decomposition temperature of the intermediate triflate (-40°C). This resulted in completely β-selective glycosylation reactions. The synthesis of dodecasaccharide **48** is outlined in Scheme 5. Butenediol-functionalized polystyrene resin **44** was subjected to 12 repetitive automated coupling/deprotection cycles. After release from the resin by cross-metathesis, the methyl esters of alcohol **46** were saponified. At this stage, the target dodecamer was separated from smaller oligomannuronic acid fragments. Dodecamer **47**, featuring 12 *cis*-mannosyl linkages was obtained in 11% yield over 24 steps, representing an average yield of 90% per step. Hydrogenolysis catalyzed by palladium on charcoal gave the target propyl alginate **48**.

Another alginate fragment, built up of L-guluronic acid -the C-5 epimer of D-mannuronic acid- monomers, was synthesized by Hung and co-workers.[17] Their solution phase approach was hampered by the poor nucleophilicity of the axially oriented C-4-OH. To overcome this obstacle, Hung's group resorted to the use of 1,6-anhydrogulopyranosyl 4-alcohol **50** as a more reactive acceptor, because this rigid bicyclic building block places the 4-hydroxyl in an equatorial position. This key 1,6-anhydro bridge necessitated the construction of the target tetramer to be executed from the non-reducing to the reducing end (Scheme 6). Coupling of donor **49** with acceptor **50** gave the desired α-linked disaccharide in 70% yield along with 17% of the β-epimer. The authors ascribe the preferential formation of the α-linked product to the anomeric effect and nonparticipating nature of the O-2 benzyl group. However, other factors have been brought forward to account for the observed α-selectivity of gulose donors. The gulose substituents in the oxocarbenium-ion conformer generated upon activation are all positioned to favor the $^{3}H_{4}$ low energy conformer, which can be substituted from the □-face leading to the 1,2-*cis* product (Scheme 7).[18] The possible remote anchimeric assistance of the 6-*O*-acetyl group of donor **49** can also be of beneficial influence to the stereochemical outcome in this particular case. Next, opening of the anhydro-bridge followed by selective anomeric deacetylation with $H_2NNH_2{\cdot}AcOH$ gave lactol **52**. Conversion of this hemiacetal to the corresponding trichloroacetimidate primed the dimer for another coupling reaction with **50**. This glycosylation proceeded with complete α-stereoselectivity in 78% yield. Repetition of the last four steps gave tetramer **55** (coupling 68%, α product only). Again the bicyclic structure was disrupted under acidic conditions and the resulting diacetate was selectively deprotected. Initial attempts in a disaccharide stage to install an anomeric allyl functionality employing a TMSOTf catalyzed coupling with an imidate donor gave unsatisfactory results in terms of selectivity (8% α, 68% β). Since Williamson etherification afforded the desired α-product as a single isomer in good yield, this is the method of choice for the conversion of lactol **56** to allyl tetrasaccharide **57**. It was suggested that the observed high stereoselectivity is induced by chelation of the potassium counterion with the C-1

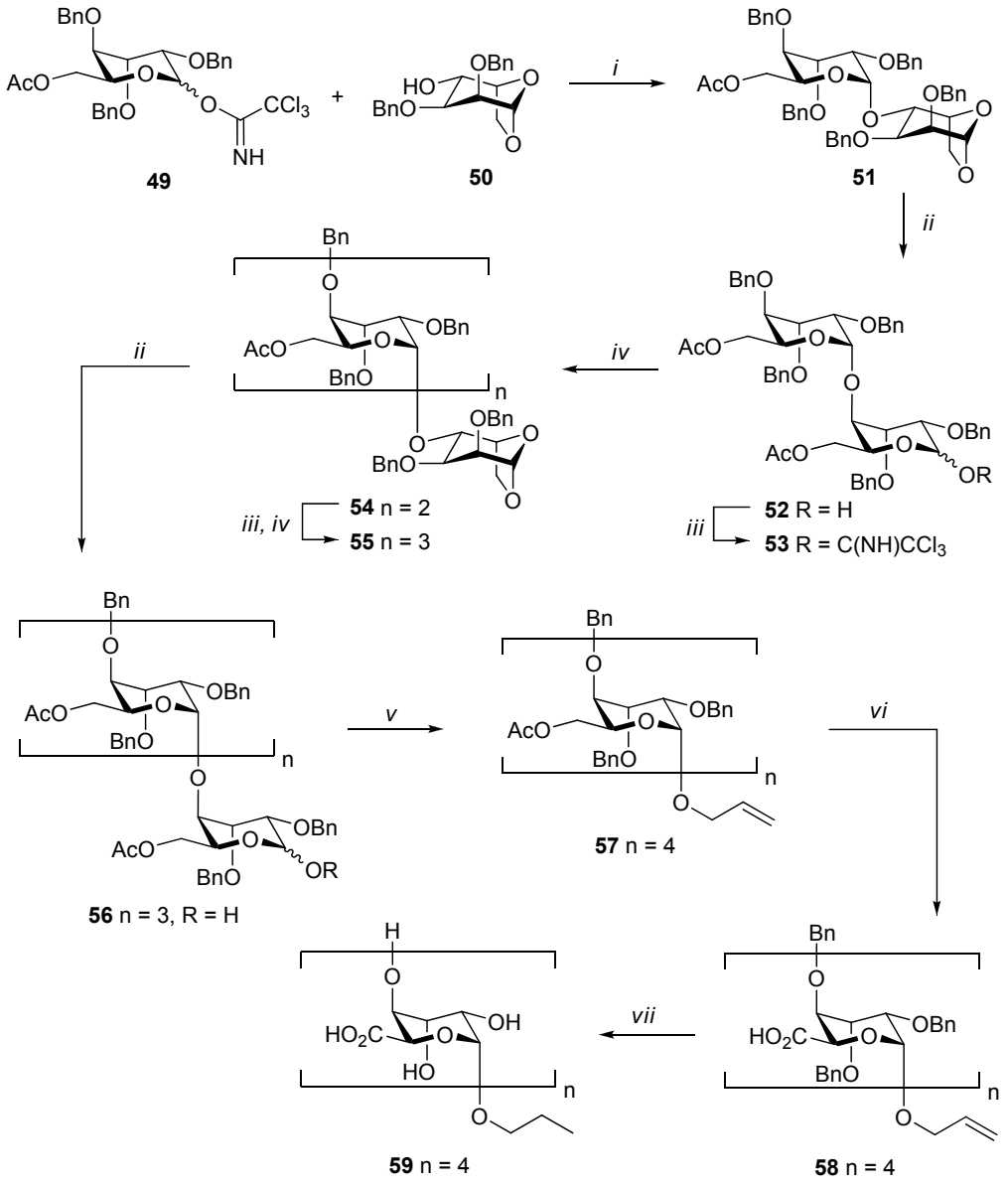
Scheme 5



Synthesis of a dodecasaccharide alginate. *Reagents and conditions:* (*i*) 12 times: (1) **45**, TfOH, CH_2Cl_2, -40°C; (2) H_2NNH_2·HOAc, pyridine, AcOH; (*ii*) Grubbs 1 catalyst, H_2CCH_2; (*iii*) KOH, THF, H_2O; (*iv*) H_2, Pd/C, THF, H_2O, *t*BuOH.

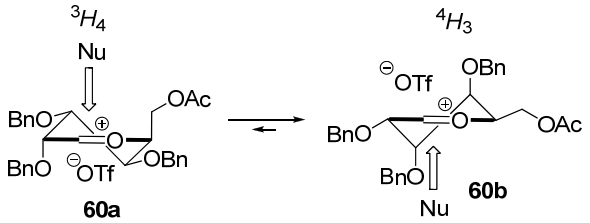
alkoxide and the lone-pair electrons of O-2, in a 1,2-*cis* constellation. Cleavage of the acetyl groups in **57** unmasked the primary alcohols which were oxidized to carboxylic acids with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy free radical) employing BAIB (bis-acetyloxyiodobenzene) as a co-oxidant to give partially protected tetramer **58**. A hydrogenolysis step completed the synthesis of the all-*cis*-linked guluronic acid tetramer **59**.

Scheme 6



Synthesis of a guluronic acid containing alginate tetrasaccharide. *Reagents and conditions:* (i) cat. TMSOTf, CH_2Cl_2, -86°C, 1 h, 70% (**51α**), 17% (**51β**); (ii) 1.TFA, Ac_2O, 0°C, 16 h; 2. H_2NNH_2·AcOH, DMF, 0°C→ rT, 6 h, 79% (**52**), 72% (toward **55**), 66% (**56**) in two steps; (iii) CCl_3CN, K_2CO_3, CH_2Cl_2, rT, 5 h, 89% (**53**), 89% (toward **55**); (iv) **50**, cat. TMSOTf, CH_2Cl_2, -86°C, 3 h, 78% (**54**), 68% (**55**); (v) tBuOK, H_2C=$CHCH_2Br$, tBuOH, 0°C→rT, 2 h, 71%; (vi) 1. NaOMe, MeOH, rT, 2 h; 2. TEMPO, BAIB, CH_2Cl_2, H_2O, rT, 1 h, 51% in two steps; (vii) H_2, 10% Pd/C, MeOH, H_2O, AcOH, rT, 12 h, 93%.

Scheme 7



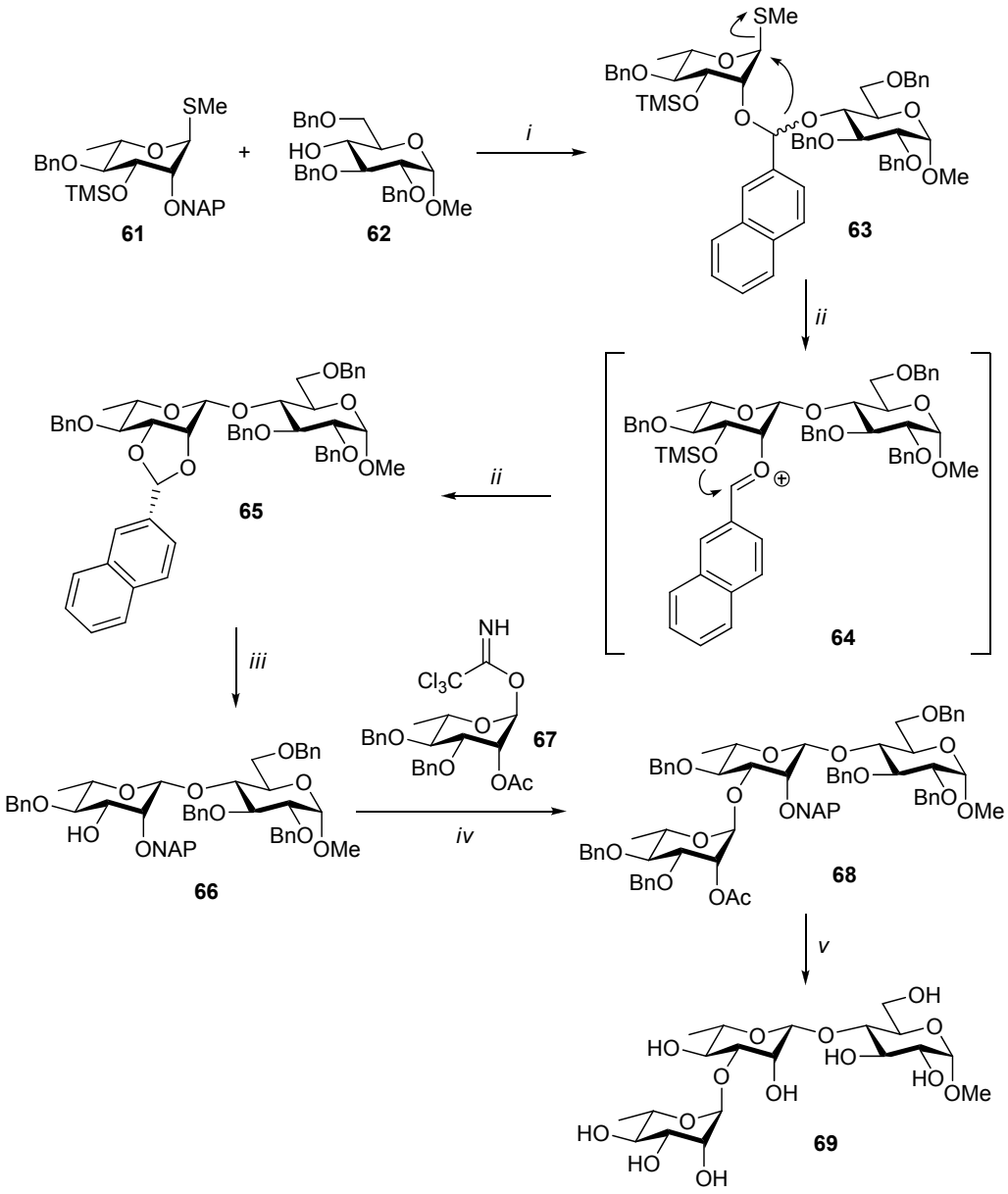
Gulose oxocarbenium ion conformations.

The same factors that render the stereoselective introduction of 1,2-*cis* mannosidic and the aforementioned *manno*-heptopyranosidic linkages difficult have to be dealt with in the synthesis of β-rhamnosides. Crich and Li recently reported a solution to this problem with an adaptation of their benzylidene mannoside strategy. In this approach the C-6 oxygen was replaced by a C-6-sulfur atom to giva a benzylidene-thio acetal, which provided the necessary -directing effect and allowed for the straightforward installation of the rhamnosyl C-5 methyl functionality by Raney nickel reduction of the thioether. An alternative approach to 1,2-*cis* rhamnoside linkages has been reported by Ito and co-workers who made use of an intramolecular aglycon delivery (IAD) strategy. This method, originally developed by Hindsgaul[19] in 1991 for the introduction of β-mannosidic linkages, entails the tethering of a glycosyl acceptor to the C-2 hydroxyl of a donor. In a subsequent intramolecular glycosylation step the acceptor is delivered from the same face of the donor as the C-2 hydroxyl, yielding a 1,2-*cis* linkage. The IAD method initially employed a dimethyl acetal for tethering, but nowadays, different acetal and ketal groups have been developed and the methodology has been shown to be compatible with different anomeric leaving groups and glycosylation conditions. In addition to β-mannosides other anomeric linkages have been synthesized by IAD, including α-glucosides, α-glucofuranosides and β-arabinofuranosides.[20] Ito and co-workers used an IAD approach to construct the β-rhamnose bond in their synthesis of a trimeric substructure of a polysaccharide from *Sphaerotilus natans* as depicted in Scheme 8.[21]

A mixed naphthylmethylidene linkage was formed between alcohol **62** and C-2-*O*-naphthylmethyl donor **61** under oxidative conditions. Next, activation of the resulting thiomethylglycoside **63** with MeOTf afforded disaccharide **65** via an IAD pathway and subsequent trapping of the benzylic cation by the neighboring silyl ether. Regioselective reductive opening of the naphthylmethylidene gave acceptor **66** in 87% yield. Straightforward introduction of an α-rhamnose linkage employing 2-*O*-acetyl donor **67** led to a fully protected trisaccharide **68**. Global deprotection was done in two steps, basic deacetylation and hydrogenation, to give target **69**.

As described above, mannuronic acid donors have been employed in an automated solid phase setting for the introduction of 1,2-*cis* mannosidic linkages on-resin. Boons and co-workers have recently reported on the stereoselective construction of 1,2-*cis*- glucosyl and

Scheme 8

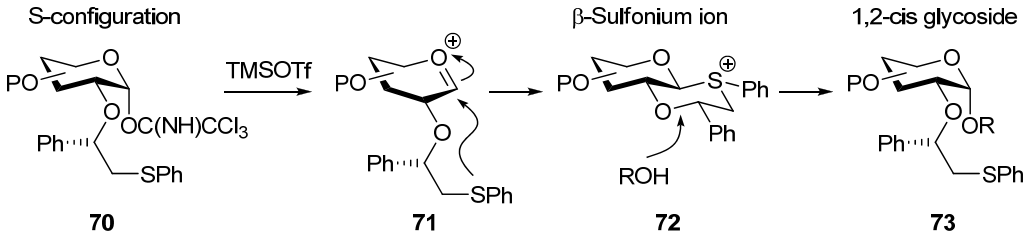


Synthesis of a tetrasaccharide subunit from *Plesimonas shigelloides*. *Reagents and conditions:* (*i*) DDQ, CH_2Cl_2, 93%; (*ii*) MeOTf, DTBMP, $(CH_2Cl)_2$; (*iii*) DIBAL-H, toluene, 87%; (*iv*) TMSOTf, Et_2O, -30°C, 3h, 95%; (*v*) (1) NaOMe, MeOH, CH_2Cl_2, 98%; (2) H_2, $Pd(OH)_2$/C, MeOH, AcOH, 96%.

1,2-*cis*-galactosyl linkages on-resin. Boons' stereoselective induction of 1,2-*cis* linkages is based on the use of a (S)-(phenylthiomethyl)benzyl chiral auxiliary at the C-2-OH.[22] Upon activation of the anomeric leaving group the auxiliary forms a *trans*-decalin β-

sulfonium ion with the phenyl substituent placed in an equatorial position. The α-sulfonium ion would possess an axially oriented phenyl group that would suffer from sterically unfavorable interactions with H-3. Electron-withdrawing acyl functionalities on the remaining alcohol groups are needed to promote the formation of a sulfonium ion intermediate through suppression of oxocarbenium ion generation. Substitution by alcohols of the β-sulfonium species occurs in an S_N2-like manner leading to the desired 1,2-*cis* stereochemistry (Scheme 9).

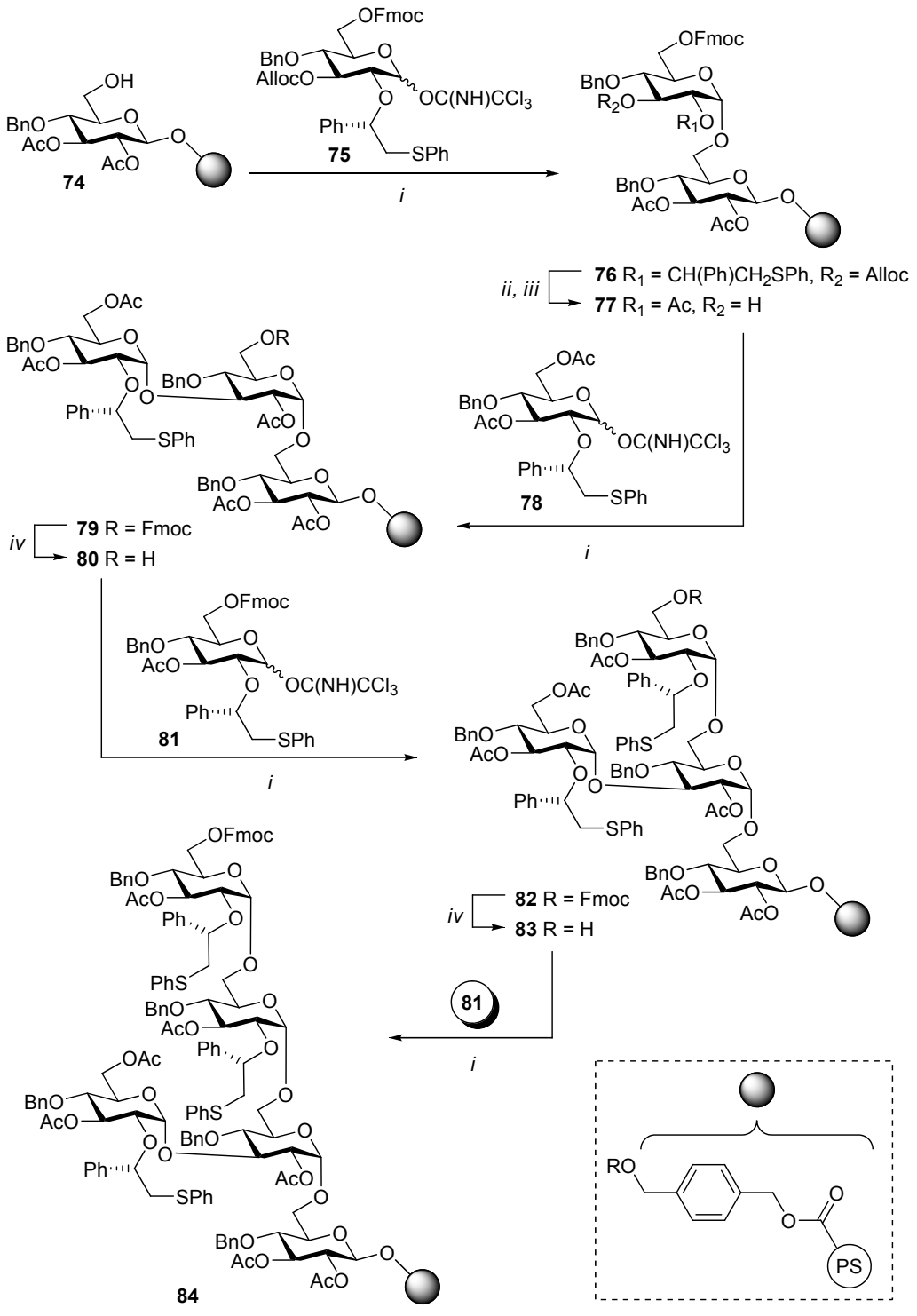
Scheme 9

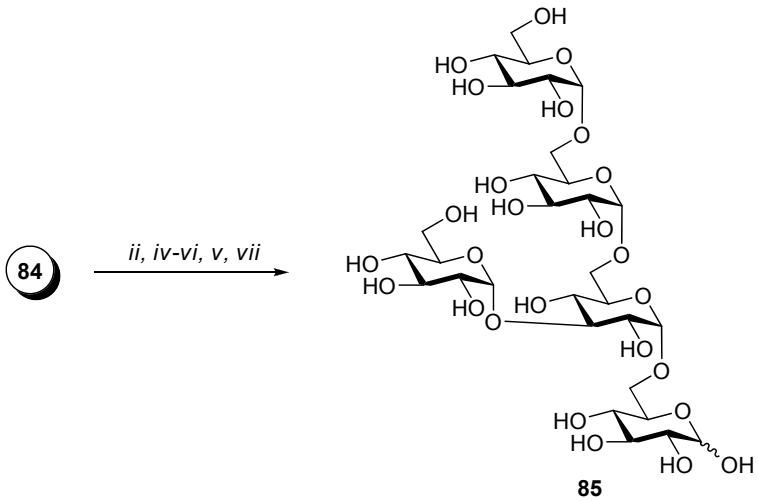


Anchimeric assistance by Boons' (S)-(phenylthiomethyl)benzyl chiral auxiliary.

This method was applied in the assembly of an α-glucan pentasaccharide repeating unit found in *A. carmichaeli*.[23] The synthesis is shown in Scheme 10 and commenced with the TMSOTf catalyzed union of polystyrene resin-bound alcohol **74** and donor **75**. The glycosylation was carried out by pre-activation of the donor with a stoichiometric amount of TMSOTf at -40°C. The formed intermediate sulfonium ion was added to the resin bound acceptor. Alloc deprotection of the resulting disaccharide furnished the C-3-OH acceptor, which proved to be rather inreactive because of significant steric shielding, as revealed in model studies. Therefore, the (S)-(phenylthiomethyl)benzyl group was converted to an acetyl function with Ac_2O and $BF_3 \bullet OEt_2$ prior to the Alloc removal and ensuing glycosylation event, in which pre-activated donor **78** was condensed with resin bound dimer **77**. After Fmoc deprotection, the same glycosylation protocol was followed using donor **81** to construct the third α–glycosidic bond. Again removal of the Fmoc preceded the final coupling toward the fully protected resin-bound branched pentaglucan **84**. Conversion of the chiral auxiliaries to acetyl functions, Fmoc deprotection, release of the glucan from the resin under Zemplén conditions and reacetylation gave, after size exclusion chromatography, a pentasaccharide as the major product with its mono-debenzylated counterpart as a side product. From this mixture the stereochemical integrity of the introduced glycosidic linkages could be determined and no anomeric β-isomers were detected. After 13 steps on resin the overall yield was 25%, corresponding to a yield of 90% per step. Finally, deacetylation and hydrogenation gave the target pentamer **85**. In addition, the authors showed that the same methodology could be used to construct a galactose containing analogue of pentasaccharide **85**.

Scheme 10


OFmoc
BnO
AllocO
OC(NH)CCl3
Ph
SPh
75
OH
BnO
AcO
AcO
74
i
OFmoc
BnO
R2O
R1O
BnO
AcO
AcO
ii, iii
76 R1 = CH(Ph)CH2SPh, R2 = Alloc
77 R1 = Ac, R2 = H
OAc
OR
BnO
AcO
Ph
SPh
78
iv
79 R = Fmoc
80 R = H
81
PhS
82 R = Fmoc
83 R = H
84
RO
O
PS

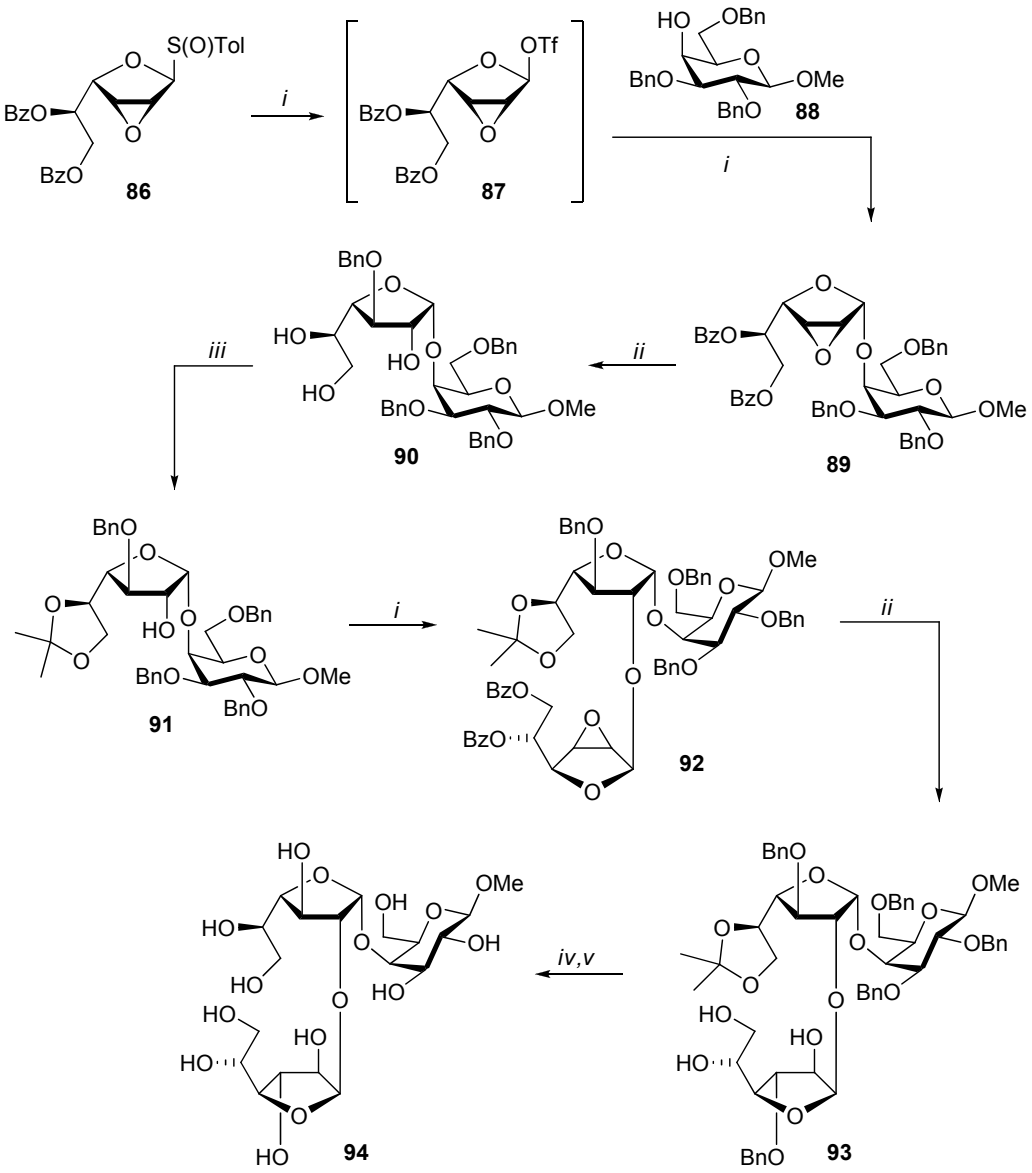


Solid supported synthesis of an α-glucan pentasaccharide repeating unit found in *A. carmichaeli.* *Reagents and conditions:* (*i*) **75**, **78** or **81**, TMSOTf, CH_2Cl_2, MS 4 Å, 15 min, -40°C then added to **74**, **77** or **80**, DTBMP, CH_2Cl_2, MS 4 Å, 16 h, -40°C → rT; (*ii*) $BF_3 \bullet Et_2O$, Ac_2O, CH_2Cl_2; (*iii*) $Pd(PPh_3)_4$ (40 mol%), THF, AcOH; (*iv*) piperidine, DMF; (*v*) NaOMe, MeOH, CH_2Cl_2; (*vi*) Ac_2O, pyridine; (*vii*) $Pd(OH)_2$/C (20 wt%), H_2, EtOH/H_2O (1/1, v/v); PS, polystyrene.

Recently several methods have been introduced for the stereoselective formation of furanosyl 1,2-*cis*-linkages. For example, the group of Lowary has found that 2,3-anhydropentosyl thioglycosides and sulfoxides can be used as stereoselective 1,2-*cis* directing donors.[24] The mechanistic principle behind the selectivity was addressed through computational chemistry and low-temperature NMR spectroscopy, which identified anomeric triflates as glycosylating species.[25] Following glycosylation, the epoxide can be opened to provide the desired *cis*-furanoside. A recent and illustrative example of this approach is the synthesis of trisaccharide **94** from 2,3-anhydro-D-gulofuranosyl sulfoxides, as depicted in Scheme 11.[26] This trisaccharide is structurally related to an antigenic polysaccharide from *Eubacterium saburreum* strain T19. By varying the protective group pattern on the key 2,3-anhydro-D-gulofuranosyl sulfoxide donor it was found that a benzoyl protected building block gave the best results in terms of stereoselective coupling and subsequent epoxide opening. Thus, the assembly of the target trisaccharide started with the coupling of anhydro donor **86** with acceptor **88**. This was done using conditions which ensured the intermediacy of triflate **87** and S_N2-like substitution of this intermediate gave dimer **89** with complete α-selectivity. Opening of the epoxide with LiOBn and (-)-sparteine and concomitant benzoyl deprotection gave triol **90** in 69% yield along with 5% of its regioisomer.

Although the mechanistic details underlying the regioselectivity the epoxide opening have not been determined, a specific lithium-sparteine-epoxide complex has been proposed to account for the observed regiochemistry. Acid-mediated installment of an isopropylidene acetal on dimer **90** gave alcohol **91**, which was subjected to the next *cis*-furanosylation event.

Scheme 11



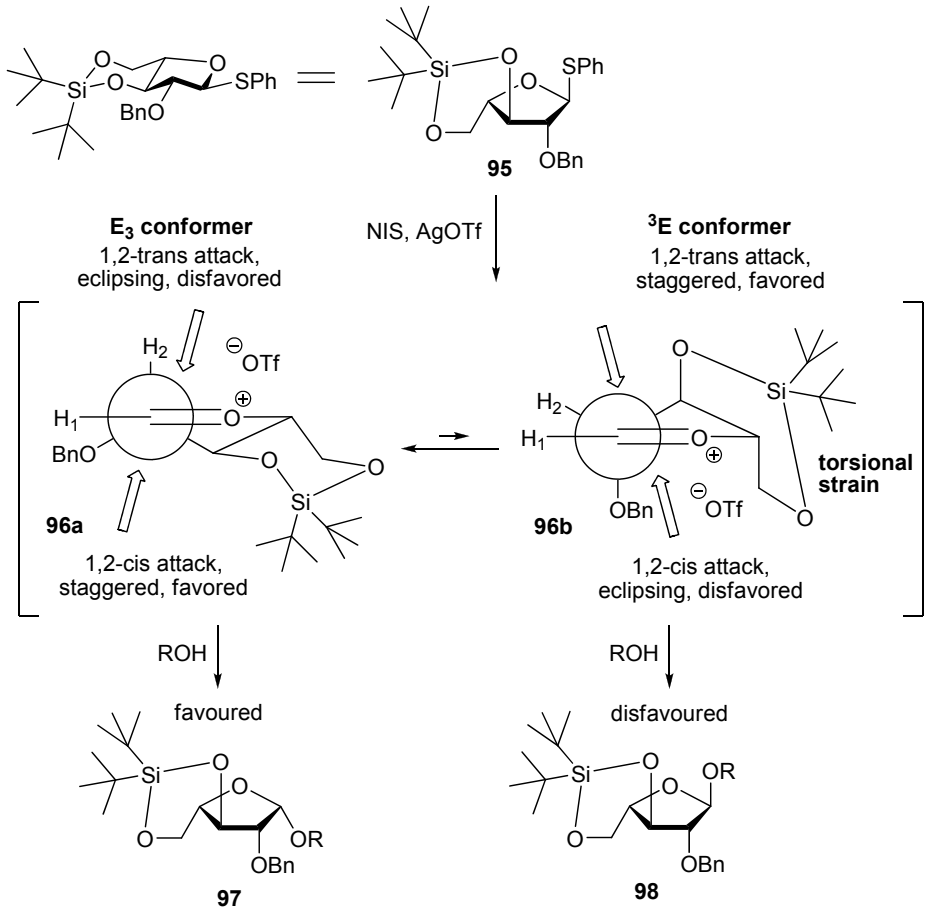
Synthesis of a trisaccharide related to *Eubacterium saburreum* strain T19. *Reagents and conditions:* (*i*) **86**, Tf_2O, DTBMP, CH_2Cl_2, -78°C 10 min, then -40 °C 20 min, then **88** or **91**, 30-60 min, 72% (**89**), 59% (**92**); (*ii*) LiOBn, (-)-sparteine, BnOH, 75°C, 69% (**90**), 61% (**93**); (*iii*) $(CH_3)_2C(OCH_3)_2$, acetone, *p*-TsOH, rt, 89%; (*iv*) AcOH, H_2O, 50 °C, 81%; (*v*) H_2, $Pd(OH)_2$/C, MeOH, rT, (quant.).

Prolonged reaction times were necessary for the glycosylation of acceptor **91**, which most probably is due to the sterically hindered nature of the acceptor. Opening of the epoxide in **92** gave triol **93** in 61% alongside 13% of the regioisomeric product. Acidic hydrolysis of the

acetal and catalytic hydrogenation took place uneventfully to afford the desired target trisaccharide **94**.

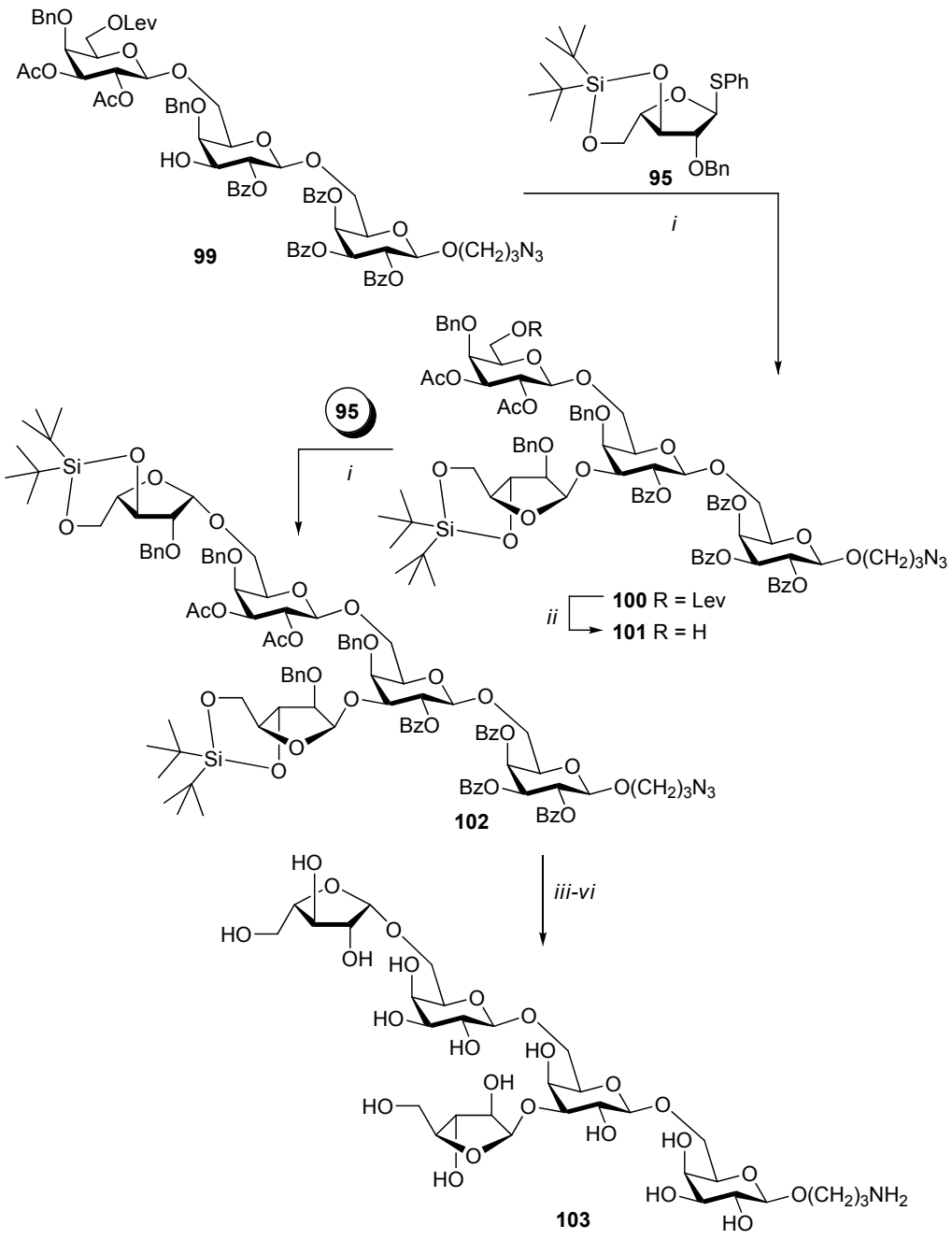
Besides stereospecific reactions on anomeric triflate intermediates, furanosyl oxocarbenium ions have also been exploited for the introduction of *cis*-furanosidic linkages.[27] Boons and co-workers described that L-arabinofuranosyl donors and the corresponding oxocarbenium ions can be locked in a E_3 conformation. A computational study revealed that the L-arabinofuranosyl oxocarbenium ion can take up two possible low-energy ion conformers ^3E and E_3 (Scheme 12). Attack on the ^3E conformer by a nucleophile proceeds preferably from the diastereotopic face that leads to 1,2-*trans* product. This is due to unfavorable interactions with the eclipsed C-2 substituent on the *Re*-face of the oxocarbenium ion and the presence of only staggered substituents on the *Si*-face.

Scheme 12



L-Arabinofuranosyl oxocarbenium low-energy ion conformers.

Scheme 13



Synthesis of a fragment of arabinogalactans. *Reagents and conditions:* (*i*) NIS, AgOTf, DCM, MS 4Å, -20 °C, **100** (67%), **102** (89%); (*ii*) H_2NNH_2, DCM/MeOH, 80%; (*iii*) TBAF, THF; (*iv*) NaOMa, MeOH, 50 °C; (*v*) Pd/C, H_2, pyridine; (*vi*) $Pd(OH)_2$, H_2, AcOH, H_2O, 34% (over 4 steps).

Through the same line of reasoning it becomes evident that attack of the E_3 conformer occurs preferably from the *Si*-face, giving the 1,2-*cis* product. To lock the arabinofuranosyl donor in the E_3 conformation, 3,5-*O*-di-tert-butylsilane protected thiodonor **95** was designed. The donor places C-5 and O-3 in pseudoequatorial positions, resulting in a perfect chair conformation of the protecting group. The efficiency of the methodology was illustrated by the synthesis of an arabinogalactan fragment, a constituent of the primary plant cell wall. A part of the synthesis is shown in Scheme 13. Trisaccharide **99** was constructed in 4 steps using thioglycoside donors and following an approach from the reducing to the non-reducing end. Introduction of the first arabinose moiety was accomplished by a NIS/AgOTf mediated coupling employing silylidene donor **95**. The tetrasaccharide product was obtained in 67% yield with complete β-selectivity. Liberation of the non-reducing end C-6-OH by levulinoyl deprotection afforded acceptor **101**. The second arabinose residue was coupled to this acceptor using as the same promoter system and pentamer **102** was obtained as a single diastereomer. Global deprotection of this product was achieved in four steps, entailing removal of the silylidene groups with TBAF, saponification of the acetyl and benzoyl esters under Zemplén conditions, reduction of the azide moiety to an amine and final catalytic hydrogenolysis of the benzyl ethers, giving the fully deprotected target pentasaccharide **103**. It is interesting to note that in the benzylidene mannopyranosyl system, a ketal functionality is used to favor formation of an anomeric triflate, whereas the silylidene ketal in donor **95** serves to promote the formation of a single oxocarbenium ion intermediate.

Conclusion

Glycosylation reactions can proceed via a multitude of pathways, passing through a variety of reactive intermediates. Because all these intermediates have their specific reactivity and associated selectivity, predicting and controlling the stereochemical course of glycosylation reaction can be a precarious undertaking. And although our understanding of the stereoelectronic effects, controlling the stereochemistry in the formation of the glycosidic bond, is continuously growing, optimization of a glycosylation reaction is often still a game of trial and error. This chapter has described some recent developments aimed at effecting stereoselective glycosylations in the context of complex carbohydrate synthesis. From the presented examples it becomes clear that there is a broad pallet of reaction intermediates that can be summoned to achieve this goal. The key to success in these approaches are to promote one reactive intermediate over another and the judicious tuning of the carbohydrate core.

Outline of this Thesis

As described above 2-acetamido-4-amino-2,4,6-trideoxy-D-galactose (AAT) is a rare carbohydrate residue present in polysaccharides of various infectious bacteria. To gain more

insight into the roles played by these polysaccharides in pathologic pathways, access to pure fragments of polysaccharides is of importance. Therefore the synthesis of these polysaccharides and AAT, as a consequence, has attracted quite some attention. One of the obstacles in these syntheses is presented by the procurement of sufficient amounts of an AAT-building block. **Chapter 2** describes the synthesis of an orthogonally protected AAT-building block on multigram-scale from D-glucosamine. A key feature of the synthetic strategy is the introduction of the C-4 amino substituent, which is accomplished by a one-pot three-step procedure, involving regioselective C-3-*O*-trichloroacetimidate formation, C-4-*O*-triflation, and intramolecular substitution. The constructed AAT-building block is used in syntheses of all possible trimer repeating units of the type 1 capsular polysaccharide of *Streptococcus pneumonia*, Sp1, which are described in **Chapter 3**. Key feature of all assemblies is the introduction of the required 1,2-*cis* galacturonic acid linkages by employing α-selective galacturonic acid-[3,6]-lactone building blocks. These synthons do not only perform well when used as donor galactosides, they also show to be reactive acceptor glycosides when equipped with a free hydroxyl function. All but one of the three frame-shifted trimer repeats was constructed via highly stereoselective glycosylation reactions. The epimeric mixture of trisaccharides, formed in the unselective glycosylation event, could be readily separated after global deprotection using high performance anion-exchange chromatography (HPEAC). An investigation of both the reactivity and the stereoselectivity of the used galacturonic acid-3,6-lactone thioglycosides is described in **Chapter 4**. Herein a series of competitive glycosylation experiments using different thiophilic activator systems are described and it is shown that the relative reactivity of different thioglycosides depends significantly on the activator system used. With respect to the stereoselectivity of the studied galacturonic acid-3,6-lactone thioglycoside donor, it was found that a pre-activation based glycosylation system gives rise to an α-selective glycosylation process, whereas an *in-situ* activation protocol leads to the formation of the β-product with good selectivity. **Chapter 5a** describes the assembly of mannosyl donors, equipped with different thio ether linkages at C-6. Activation of these donors leads to the formation of bicyclic sulfonium ions, which serve as a reservoir for their more reactive monocyclic oxocarbenium ion counterparts. Nucleophilic attack of these species preferentially gives 1,2-*cis* linked products. This finding is exploited in **Chapter 5b**, where a synthesis of a tetrasaccharide found in *Xanthomonas campestris* is described. In addition to the stereoselective formation of 1,2-*cis* glycosidic linkages the synthesis features the reduction of C-6 thio ethers to gain access to rhamnosides.

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Chapter 2

Multigram-scale Synthesis of an Orthogonally Protected 2-Acetamido-4-Amino-2,4,6-Trideoxy-D-Galactose (AAT) Building Block[1]

Introduction

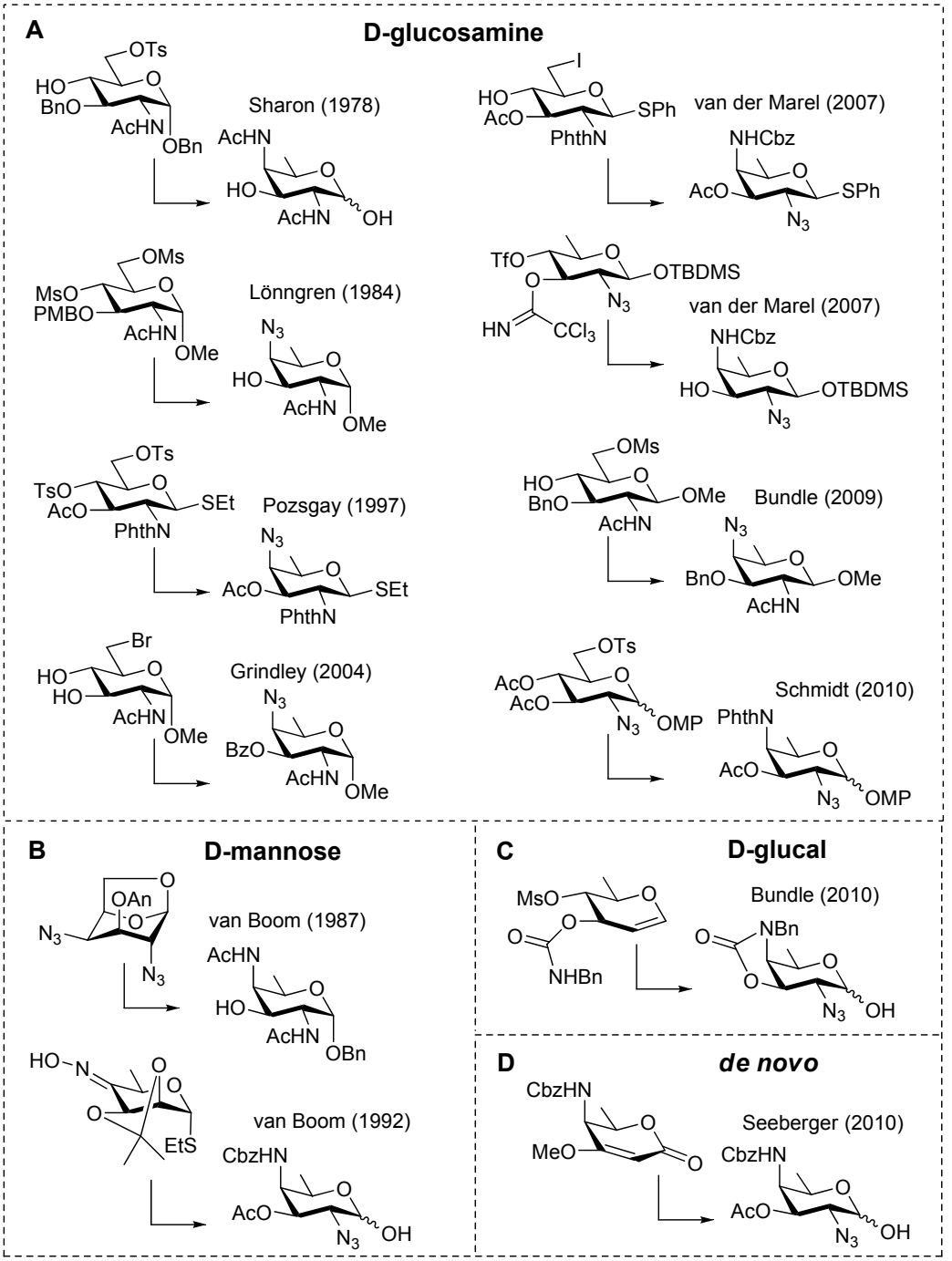
2-Acetamido-4-amino-2,4,6-trideoxy-D-galactose (AAT)[2] is a carbohydrate residue found in various polysaccharides, present in infectious bacteria, such as *Shigella sonnei*,[3] *Streptococcus pneumonia*,[4] *Bacteroides fragilis*,[5] *Streptococcus mitis*[6] and *Proteus vulgaris*.[7] AAT represents an important constituent of many zwitterionic polysaccharides (ZPs), which are capable of eliciting a T-cell dependent immune response.[8] Key to this activity is the presence of both negative and positive charges on the polysaccharide backbone. The negative charges in these polysaccharides originate from either uronic acid constituents or pyruvate moieties, whereas the positive charge is often found on the C-4 amino function of the AAT-residues. To gain insight into the role of these AAT-containing polysaccharides in bacterial pathogenicity and immunogenicity, the availability of (fragments of) pure polysaccharides is of importance and therefore the synthesis of these polysaccharides has attracted ample attention.[9,10,11,12] In these syntheses one of the obstacles is presented by the procurement of sufficient amounts of a suitable AAT-building block. Over the years several

syntheses have been reported, most of which start from a glucosamine precursor, as summarized in Scheme 1. Transformation of the glucosamine core (Scheme 1A) into an AAT-building block requires deoxygenation of C-6 and introduction of the second amino functionality with concomitant inversion at C-4. Lönngren and co-workers employed a di-mesylate to accomplish these two steps in the first synthesis of an orthogonally protected AAT building block in 1984.[13] Other syntheses typically employ the installment of a C-6 tosylate, which is subsequently displaced by iodine prior to hydride substitution (Sharon 1974,[14] Pozsgay 1997,[15,9] Schmidt 2010[16]). Introduction of the C-4 amino functionality has most often been accomplished through the S_N2-type displacement of a C-4 mesylate,[13,14] tosylate[15] or triflate[9,10,16] with azide[17,18] or phthalimide.[16]

Syntheses starting from different precursors have also been developed, as exemplified by the synthetic efforts of van Boom and co-workers, who started from D-mannose (Scheme 1B).[19] Recently, Bundle reported an elegant procedure starting from d-glucal (Scheme 1C).[20] Deoxygenation of C-6 was followed by the regioselective introduction of a C-3 benzyl carbamate. Intramolecular displacement of the subsequently installed C-4 mesylate led to a C-4-amino galactal, protected with a cyclic carbamate, which was subjected to azidonitration to install the required C-2 azide functionality. Seeberger and co-workers employed a conceptually different approach and used Cbz-protected L-threonine as a precursor to generate a Cbz-protected C-4-amino galactal intermediate in a *de novo* strategy (Scheme 1D).[21] The use of an intramolecular displacement strategy to obtain a suitably protected AAT-building block, featuring a non-participating azide group at C-2, has previously been reported by van den Bos.[9] This strategy is based on the regioselective installment of a C-3-*O*-imidate functionality, followed by the introduction of a C-4-triflate and subsequent oxazoline formation.[22]

In this chapter, an optimized synthetic route for the multi-gram synthesis of AAT building block **9** is described, using this approach. The synthesis started from glucosamine hydrochloride **1**, as depicted in Scheme 2. Introduction of the required C-2 azide was accomplished by an azidotransfer reaction using imidazole-1-sulfonyl azide·HCl, introduced by Goddard-Borger and Stick.[23] Global acetylation was then followed by liberation of the anomeric hydroxyl by a treatment with piperidine in THF. In a previous synthesis of an AAT building block (see Scheme 1A) a *tert*-butyldimethylsilyl group was employed to mask the anomeric hydroxyl.[9] It was found, however, that this silyl ether was not completely stable to the acidic reaction conditions employed later on in the synthesis to cleave the intermediate oxazoline and therefore a switch to the use of the more acid stable *tert*-butyldiphenylsilyl (TBDPS) ether was made.[24] Introduction of the anomeric TBDPS ether using TBDPS-Cl and imidazole in DCM led to the fully protected crystalline glucosazide **2**, which was obtained in 60% yield over the four steps without a chromatographic purification (300 mmol scale). Next, the three acetyl groups were removed and a tosylate was regioselectively installed at the C-6-OH. Substitution of the tosylate by iodide then set the stage for the crucial deoxygenation step, which required substantial optimization. It was found that the use of $NaBH_4$ as a redu-

Scheme 1

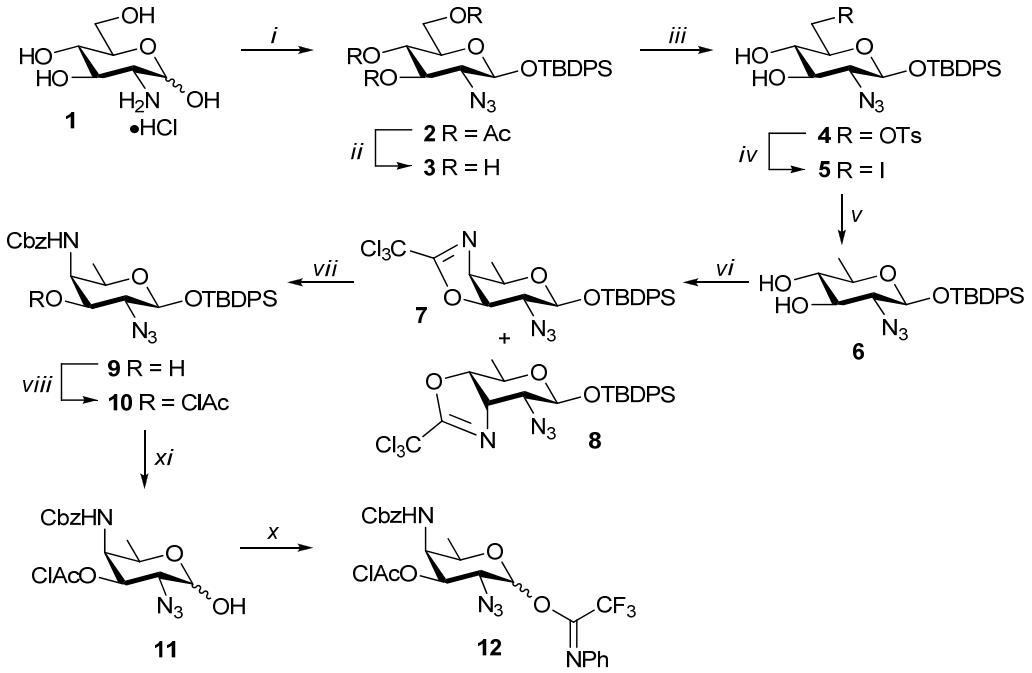


Previous syntheses of AAT-building blocks.

cing agent in DMSO led to partial reduction of the azide functionality and therefore the milder reducing agent $NaCNBH_3$ was used at elevated temperature. It was found that diethylene glycol was the optimal solvent for the reaction and at reflux temperature iodide **5** was uneventfully reduced to give key intermediate **6** in 88% yield. The required C-4 amino group was installed using an intramolecular displacement strategy.[22] Thus, in a one-pot three step procedure diol **6** was treated with trichloroacetonitrile and a catalytic amount of DBU to give the intermediate C-3-*O*-imidate. Next, triflic anhydride and pyridine (5 equiv.) were added to the reaction mixture to form the C-4 trifluoromethanesulfonyl ester. Finally, treatment of this species with an excess DiPEA furnished oxazoline **7**,[25] which was isolated in 63% yield. The *allo*-configured oxazoline **8**, formed from the regioisomeric imidate, by C-3-*O*-triflation and intramolecular substitution, was also isolated in 23% yield. Hydrolysis of the oxazoline moiety in **7** with acetic acid and water gave an intermediate amino alcohol, which was directly transformed into benzyl carbamate **9**. As anticipated, the anomeric TBDPS ether was unaffected during cleavage of the oxazoline moiety. *tert*-Butyldiphenylsilyl 4-(*N*-benzyloxycarbonyl)-amino-2-azido-2,4,6-trideoxy-β-D-galactopyranoside **9** was obtained in 19% yield from D-glucosamine in 14 steps, requiring 5 chromatographic purifications. AAT building block **9** was further converted into 1-hydoxyl donor **11** by installation of a chloroacetyl ester at the C-3-OH and subsequent removal of the anomeric silyl group using $HF{\cdot}Et_3N$ (98% over two steps). Imidate donor **12** was obtained from this lactol by treatment with *N*-phenyltrifluoroacetamidoyl chloride in acetone in the presence of Cs_2CO_3 and a few drops of water.

In conclusion, an optimized synthetic route for the multi-gram synthesis of orthogonally protected AAT-building blocks has been described starting from d-glucosamine. Key steps in the synthesis include the deoxygenation of a C-6-iodo glucosazide and the subsequent one-pot three step tethered nucleophilic inversion procedure to introduce the C-4 amino functionality. The usefulness of AAT synthons 9, 11, 12 in the construction of (fragments of) zwitterionic polysaccharides shall be demonstrated in the following chapter.

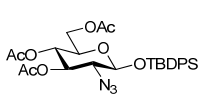
Scheme 2



Reagents and conditions: (i) (1) imidazole-1-sulfonyl azide·HCl, MeOH, $CuSO_4$ (cat.); (2) pyridine, Ac_2O; (3) piperidine, THF; (4) t-BuPh_2SiCl, imidazole, DMF (60%, 4 steps); *(ii)* NaOMe (cat.), MeOH, DCM (quant.); *(iii)* tosyl chloride, pyridine (83%); *(iv)* NaI, butanone (92%); *(v)* $NaCNBH_3$, diethylene glycol diethyl ether, reflux (88%); *(vi)* Cl_3CCN, DBU, DCM, -13°C then Tf_2O, pyridine then DiPEA (**7**: 63%, **8**: 24%); *(vii)* (1) AcOH, H_2O, EtOAc; (2) *N*-(benzyloxycarbonyloxy)succinimide, triethylamine, DCM (75%); *(viii)* $(ClAc)_2O$, pyridine, DCM, (quant.); *(ix)* triethylamine·3HF, THF, (98%); *(x)* $ClC(=NPh)CF_3$, Cs_2CO_3, H_2O, acetone, (83%, α/β 1:3).

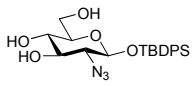
Experimental section

General Procedures: All chemicals were used as received. Trifluoromethanesulfonic anhydride (Tf_2O) was distilled from P_2O_5 and stored in a Schlenk flask. TLC analysis was conducted on silica gel-coated aluminum TLC sheets (Merck, silica gel 60, F_{245}). Compounds were visualized by UV absorption (245 nm), by spraying with 20% H_2SO_4 in ethanol or with a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ 25 g/L, $(NH_4)_4Ce(SO_4)_4\cdot 2H_2O$ 10 g/L, 10% H_2SO_4 in H_2O followed by charring at ~140 °C. Flash chromatography was performed on silica gel (Screening Devices, 40-63 µm 60Å, www.screeningdevices.com) using technical grade, distilled solvents. NMR spectra were recorded on a Bruker AV400. For solutions in $CDCl_3$ chemical shifts (δ) are reported relative to tetramethylsilane (^1H) or $CDCl_3$ (^{13}C). Peak assignments were made based on HH-COSY and HSQC measurements. Optical rotation was measured using a Propol automatic polarimeter. The IR absorbance was recorded using a Shimadzu FTIR-83000 spectrometer. Mass analysis was performed using a PE/SCIEX API 165 with an Electrospray Interface (Perkin-Elmer).

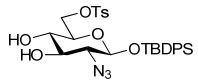


***Tert*-butyldiphenylsilyl 3,4,6-tri-*O*-acyl-2-azido-2-deoxy-β-D-glucopyranoside (2):** To a mixture of 107.8 g D-glucosamine·HCl (500 mmol, 1 equiv.) in 2L MeOH

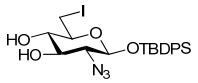
was added 174 mL triethylamine (1.25 mol, 2.5 equiv.), 1.25 g $CuSO_4 \cdot H_2O$ (5 mmol, 0.01 equiv.) and 125.8 g imidazole-1-sulfonyl azide·HCl[22] (600 mmol, 1.2 equiv.). The reaction was stirred for 1.5 hours and the solvents were evaporated. The crude material was coevaporated with pyridine and subsequently stirred overnight in 2L pyridine/Ac_2O (4/1 v/v). The solvent was evaporated and the residue was partitioned between H_2O and EtOAc. The organic layer was washed with aq. 1 M HCl solution, sat. aq. $NaHCO_3$ solution and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. To a mixture of the crude product in 1L THF was added 117 mL piperidine (1.19 mol, 2.4 equiv.) and the reaction was run for 2.5 hours. The mixture was diluted with 1.5 L EtOAc and washed with aq. 1 M HCl solution, sat. aq. $NaHCO_3$ solution and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude hemiacetal was coevaporated with toluene and dissolved in 700 mL DMF. To this solution 47.5 g imidazole (697 mmol, 1.4 equiv.) and 135.6 mL t-BuPh_2SiCl (523 mmol, 1.05 equiv.) were added and the mixture was stirred for 2 hours at 60°C. Next, 1.5L H_2O was added and the mixture was extracted with EtOAc. The combined organic layers were washed with aq. 1 M HCl solution, sat. aq. $NaHCO_3$ solution and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Crystallization from EtOH yielded 171.9 g of the title compound (**2**) (302.0 mmol, 60% over 4 steps). Spectral data were in accordance with those reported in literature.[26]



***Tert*-butyldiphenylsilyl 2-azido-2-deoxy-β-D-glucopyranoside (3):** To a solution of 66.11 g tert-butyldiphenylsilyl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-β-D-glucopyranoside **2** (116.1 mmol, 1 equiv.) in 500 ml methanol/DCM (9/1 v/v) was added 1.27 g NaOMe (23.6 mmol, 0.2 equiv.). The mixture was stirred until TLC indicated complete conversion of the starting material to a single lower running spot. The mixture was neutralized with Amberlite H^+ resin and filtered. The filtrate was evaporated to dryness yielding 51.4 g of the title compound (115.8 mmol, quant.). R*f* 0.25 (EtOAc/PE, 3/2, v/v); IR (neat, cm^{-1}) 3370 (br), 2932, 2860, 2110, 1428, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.66 (m, 4H, H_{arom}), 7.46 – 7.32 (m, 6H, H_{arom}), 4.51 (d, *J* = 7.7 Hz, 1H, H-1), 4.22 (s, 2H, OH), 3.49 – 3.36 (m, 3H, H-6, H-4), 3.30 (dd, *J* = 10.0, 7.7 Hz, 1H, H-2), 3.19 (br t, *J* = 9.4 Hz, 1H, H-3), 2.85 – 2.78 (m, 1H, H-5), 1.90 (s, 1H, OH), 1.11 (s, 9H, CH3 *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7 (CH_{arom}), 133.6, 132.4 (C_q), 130.1, 129.9, 127.7, 127.4 (CH_{arom}), 96.9 (C-1), 75.0 (C-5), 74.6 (C-3), 69.6 (C-4), 68.6 (C-2), 61.4 (C-6), 26.7 (CH_3 *t*-Bu), 19.0 (C_q *t*-Bu); $[\alpha]_D^{22}$ +25 (c 1.0, $CHCl_3$); HRMS $[M+Na]^+$ calcd for $C_{22}H_{29}N_3O_5SiNa$, 466.17687 found 466.17659.

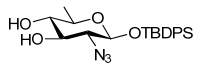


***Tert*-butyldiphenylsilyl 2-azido-2-deoxy-6-*O*-tosyl-β-D-glucopyranoside (4):** 8.45 g Tosylchloride (44.3 mmol, 3.0 equiv.) was added to an ice-cooled solution of 6.55 g tert-butyldiphenylsilyl 2-azido-2-deoxy-β-D-glucopyranoside (**3**) (14.8 mmol, 1.0 equiv.) in 75 mL pyridine. The mixture was stirred for 2 hours at 0°C and quenched by the addition of MeOH. After evaporation of the solvents the crude mixture was partitioned between EtOAc and water and the organic layer was washed with aq. 1 M HCl solution, sat. aq. $NaHCO_3$ solution and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography using EtOAc/ PE (3/7 → 2/3) gave 7.31 g (12.2 mmol, 83%) of the title compound (**4**) as a colorless oil. R*f* 0.29 (EtOAc/PE, 2/3, v/v); $[\alpha]_D^{22}$ +11 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3400 (br), 2932, 2858, 2110, 1174, 812; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.68-7.62 (m, 6H, H_{arom}), 7.44 – 7.21 (m, 8H, H_{arom}), 4.36 (d, J = 7.6 Hz, 1H, H-1), 4.05 (dd, J = 10.5, 4.5 Hz, 1H, H-6), 3.85 (d, J = 10.5 Hz, 1H, H6), 3.77 (s, 1H, OH), 3.67 (s, 1H, OH), 3.46 (t, J = 9.2 Hz, 1H, H-4), 3.30 (dd, 1H, J = 9.2, 7.6 Hz, H-2), 3.20 (t, J = 9.3 Hz, 1H, H-3), 2.99 (dd, J = 9.7, 4.2 Hz, 1H, H-5), 2.41 (s, 3H, CH_3 Ts), 1.08 (s, 9H, CH_3 t-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 144.9 (C_q Ts), 135.8, 135.7 (CH_{arom}), 132.8, 132.4, 132.2 (C_q Ph), 129.9, 129.8, 129.7, 127.9, 127.5, 127.4 (CH_{arom}), 96.7 (C-1), 74.5 (C-3), 73.0 (C-5), 69.3 (C-4), 68.3 (C-2), 68.1 (C-6), 26.7 (CH_3 t-Bu), 21.6 (CH_3 Ts), 19.0 (C_q t-Bu); HRMS $[M+Na]^+$ calcd for $C_{29}H_{35}N_3O_7SSiNa$ 620.18572, found 620.18562.

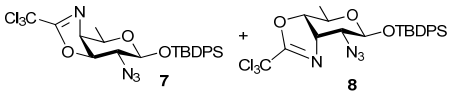


***Tert*-butyldiphenylsilyl 2-azido-2,6-dideoxy-6-iodo-β-D-glucopyranoside (5):** Tosylate **4** (7.22 g, 12.1 mmol, 1 equiv.) was refluxed for 6 hours in 60 mL

butanone together with 3.98 g NaI (26.6 mmol, 2.2 equiv.). After cooling to room temperature EtOAc was added and the mixture was washed with aq. 1M $Na_2S_2O_3$ solution and H_2O. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography using EtOAc/PE (1/4 → 3/7) afforded 6.12 g of the title compound **5** (11.1 mmol, 92%) as a yellow oil. Rf 0.46 (EtOAc/PE, 2/3, v/v); $[\alpha]_D^{22}$ +8 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3400, 2858, 2110, 1078, 812; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.79 – 7.69 (m, 4H, H_{arom}), 7.45 – 7.34 (m, 6H, H_{arom}), 4.49 (d, J = 7.6 Hz, 1H, H-1), 3.51 (s, 1H, OH), 3.41 (s, 1H, OH), 3.40 (t, J = 8.8 Hz, 1H, H-4), 3.37(dd, J = 9.6, 7.6, Hz, 1H, H-2), 3.28 (dd, J = 9.6, 8.8 Hz, 1H, H-3), 3.24 (dd, J = 10.8, 4.8 Hz, 1H, H6), 3.15 (dd, J = 10.8, 2.8 Hz, 1H, H-6), 2.62 – 2.53 (m, 1H, H-5), 1.13 (s, 9H, CH_3 t-Bu). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 136.1, 135.9 (CH_{arom}), 132.8, 132.5 (C_q Ph), 130.0, 129.7, 127.6, 127.5, 127.4, 127.3 (CH_{arom}), 96.4 (C-1), 74.3 (C-3), 73.6 (C-4), 73.1 (C-5), 68.6 (C-2), 26.8 (CH_3 t-Bu), 19.1 (C_q t-Bu), 5.8 (C-6); HRMS $[M+Na]^+$ calcd for $C_{22}H_{28}IN_3O_4SiNa$ 576.07860, found 576.07845.



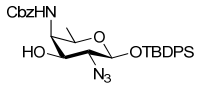
***Tert*-butyldiphenylsilyl 2-azido-2,6-dideoxy-β-D-glucopyranoside (6)**: To a solution of 10.56 g (19.1 mmol, 1 equiv.) *tert*-butyldiphenylsilyl 2-azido-2,6-dideoxy-6-iodo-β-D-glucopyranoside in 110 mL diethylene glycol diethyl ether was added 11.9 g (190 mmol, 10 equiv.) of $NaCNBH_3$ and the mixture was refluxed for 7 hours. After cooling to room temperature, the mixture was diluted with 1L of EtOAc, washed with water and brine. dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography using EtOAc/PE (1/4 v/v) afforded 7.2 g of the title compound **6** (16.8 mmol, 88%). Rf 0.38 (EtOAc/PE, 2/3, v/v); $[\alpha]_D^{22}$ +22 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3364, 2932, 2862, 2361, 2114, 1111, 1072, 818; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.70 (t, J = 7.9 Hz, 4H, H_{arom}), 7.42 – 7.31 (m, 6H, H_{arom}), 4.38 (d, J = 7.9 Hz, 1H, H-1), 4.11 (s, 1H, OH), 3.83 (s, 1H, OH), 3.27 (t, J = 8.5 Hz, 1H, H-2), 3.14 – 3.02 (m, 2H, H-3, H-4), 2.88 – 2.81 (m, 1H, H-5), 1.12 (s, 9H, CH_3 t-Bu), 1.02 (d, J = 6.9 Hz, 3H, H-6). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 135.9, 135.8 (CH_{arom}), 133.2 , 132.7 (C_q Ph), 129.8, 129.7, 127.5, 127.3 (CH_{arom}), 96.5 (C-1), 75.4 (C-4), 74.7 (C-3), 71.4 (C-5), 68.9 (C-2), 26.8 (CH_3 t-Bu), 19.1 (C_q t-Bu), 17.1 (C-6); HRMS $[M+Na]^+$ calcd for $C_{22}H_{31}N_3O_4SiNa$ 450.18195, found 450.18171.



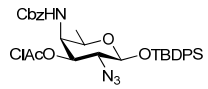
7 **8**

2-Trichloromethyl-4,5-dihydro-(2-azido-2,4,6-trideoxy-1-*O*-*tert*-butyldiphenylsilyl-β-D-galactopyranoso)[4,3-d]-1,3-oxazole (7) and **2-trichloromethyl-4,5-dihydro-(2-azido-2,4,6-trideoxy-1-*O*-*tert*-butyldiphenylsilyl-β-D-allopyranoso)[3,4-d]-1,3-oxazole (8):** Diol (**6**) (3.49 g, 8.18 mmol, 1 equiv.) and 984 µL Cl_3CCN (9.82 mmol, 1.2 equiv.) were dissolved in 80 mL DCM, stirred over activated 3Å molecular sieves and cooled to -13°C. After addition of 122 µL DBU (818 µmol, 0.1 equiv.) the reaction mixture was allowed to stir for 1h. Then 3.30 mL pyridine (40.9 mmol, 5 equiv.) and 1.64 mL triflic anhydride (9.82 mmol, 1.2 equiv.) were added at -30°C and the reaction mixture was allowed to warm to ambient temperature. 2 Hours later 13.52 mL DiPEA (81.8 mmol, 10 equiv.) was injected and the mixture was stirred overnight. H_2O was added and the organic layer was separated from the aqueous phase, which was extracted with DCM. Drying over $MgSO_4$, filtration and concentration under reduced pressure, filtration over celite (eluent: EtOAc/PE 1/99) and again removal of the solvents gave a crude mixture. Purification was done by flash column chromatography (silica was pretreated with triethylamine/PE (1/19 → 0/1)) using Et_2O/PE (0/1 → 5/95) as eluent to furnish the title compounds (**8**) (1.07 g, 1.94 mmol, 24%) Rf 0.80 (EtOAc/PE, 1/9, v/v); $[\alpha]_D^{22}$ -27 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2932, 2860, 2108, 1653, 1427, 978, 698; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.72 – 7.65 (m, 4H, H_{arom}), 7.45 – 7.33 (m, 6H, H_{arom}), 4.87 (d, J = 5.8 Hz, 1H, H-1), 4.75 (dd, J = 8.5, 5.7 Hz, 1H, H-3), 4.59 (t, J = 8.8 Hz, 1H, H-4), 3.93 (t, J = 5.7 Hz, 1H, H-2), 3.43 – 3.36 (m, 1H, H-5), 1.14 (d, J = 6.2 Hz, 3H, H-6), 1.11 (s, 9H, CH_3 t-Bu). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 163.7 (C=N), 135.7, 135.6 (CH_{arom}), 132.8, 132.5(C_q Ph), 130.0, 129.8, 127.8, 127.7, 127.4 (CH_{arom}), 94.6 (C-1), 84.0 (C-4), 68.8 (C-5), 66.5 (C-3), 61.4 (C-2), 26.7 (CH_3 t-Bu), 19.0 (C_q t-Bu), 18.9 (C-6); HRMS $[M+H]^+$ calcd for $C_{24}H_{28}Cl_3N_4O_3Si$ 553.09908, found 553.09909; and (**7**) (2.83 g, 5.13 mmol, 63%) Rf 0.58 (EtOAc/PE, 1/9, v/v); $[\alpha]_D^{22}$ +42 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2860, 2116, 1655, 1427, 1063, 700; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY,

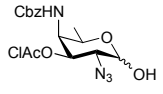
HSQC) δ 7.83 – 7.61 (m, 4H, H_{arom}), 7.50 – 7.32 (m, 6H, H_{arom}), 4.64 (t, J = 8.1 Hz, 1H, H-4), 4.31 (d, J = 8.1 Hz, 1H, H-1), 3.90 (dd, J = 8.3, 3.2 Hz, 1H, H-4), 3.44 – 3.38 (m, 1H, H-5), 3.38 (t, J = 8.0 Hz, 1H, H-2), 1.32 (d, J = 6.3 Hz, 3H, H-6), 1.13 (s, 9H, CH_3 t-Bu). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 162.3 (C=N), 135.9, 135.8 (CH_{arom}), 132.8, 132.5 (C_q Ph), 130.0, 129.8, 127.6, 127.4 (CH_{arom}), 95.4 (C-1), 84.5 (C-3), 69.9 (C-5), 67.0 (C-4), 66.6 (C-2), 26.7 (CH_3 t-Bu), 19.1 (C_q t-Bu), 17.3 (C-6); HRMS $[M+H]^+$ calcd for $C_{24}H_{28}Cl_3N_4O_3Si$ 553.09908, found 553.09892.



***Tert*-butyldiphenylsilyl 4-(*N*-benzyloxycarbonyl)-amino-2-azido-2,4,6-trideoxy-β-D-galactopyranoside (9):** 1.61 g Dihydro-oxazole (**7**) (2.92 mmol, 1 equiv.) was stirred overnight in 18 mL AcOH/H_2O/EtOAc (4/1/1). The solvents were removed and the residue was coevaporated with toluene. The crude amine was dissolved in 15 mL of DCM and 526 µL triethylamine (3.79 mmol, 1.3 equiv.) and 800 mg *N*-(benzyloxycarbonyloxy)succinimide (3.21 mmol, 1.1 equiv.) were added. Stirring was allowed for 45 minutes followed by quenching with MeOH. Product **9** (1.22 g, 2.19 mmol, 75%) was obtained in pure form by flash column chromatography using EtOAc/PE (1/4 → 1/3). Rf 0.59 (EtOAc/PE, 7/13, v/v); $[\alpha]_D^{22}$ +19 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3410 (br), 2939, 2862, 2114, 1705, 1512, 1111, 1065; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.71 – 7.68 (m, 4H, H_{arom}), 7.44 – 7.31 (m, 11H, H_{arom}), 5.17 – 5.06 (m, 2H, CH_2 Cbz), 4.97 (d, J = 9.4 Hz, 1H, NH), 4.37 (d, J = 7.8 Hz, 1H, H1), 3.83 (dd, J = 9.3, 3.4 Hz, 1H, H-4), 3.51 (dd, J = 10.0, 2.8 Hz, 1H, H-3), 3.31 – 3.20 (m, 2H, H-2, H-5), 3.17 (s, 1H, OH), 1.10 (s, 9H, CH_3 t-Bu), 0.96 (d, J = 6.4 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 157.8 (C=O Cbz), 135.9 (C_q Ph), 135.8, 135.7 (CH_{arom}), 133.2, 132.7 (C_q Ph), 129.8, 129.7, 128.5, 128.2, 128.1, 127.4, 127.3 (CH_{arom}), 97.0 (C-1), 72.2 (C-3), 69.3 (C-5), 67.3 (CH_2 Cbz), 66.8 (C-2), 54.8 (C-4), 26.7 (CH_3 t-Bu), 19.0 (C_q t-Bu), 16.1 (C-6). HRMS $[M+H]^+$ calcd for $C_{30}H_{37}N_4O_5Si$ 561.25277, found 561.25250.

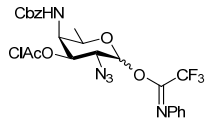


***Tert*-butyldiphenylsilyl 4-(*N*-benzyloxycarbonyl)-amino-2-azido-3-*O*-chloroacetyl-2,4,6-trideoxy-β-D-galactopyranoside (10):** To a mixture of alcohol **9** (860 mg, 1.54 mmol, 1 equiv.), 5 mL DCM and 607 µL pyridine (7.68 mmol, 5 equiv.) was added 525 mg chloroacetic anhydride (3.07 mmol, 2 equiv.). After 1 hour, 500 µL H_2O was added and the mixture was stirred for another 15 minutes. After evaporation the residue was taken up in EtOAc and washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and evaporated to dryness yielding title compound **10** (984 mg, 1.54 mmol, quant.). Rf 0.79 (EtOAc/PE, 1/3, v/v); $[\alpha]_D^{22}$ -9 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2114, 1713, 1504, 1165, 1057, 733. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.71 – 7.68 (m, 4H, H_{arom}), 7.46 – 7.25 (m, 11H, H_{arom}), 5.14 (d, J = 12.2 Hz, 1H, CH_2 Cbz), 5.02 (d, J = 12.2 Hz, 1H, CH_2 Cbz), 4.93 (d, J = 9.5 Hz, 1H, NH), 4.64 (dd, J = 10.7, 3.7 Hz, 1H, H-3), 4.44 (d, J = 7.7 Hz, 1H, H-1), 4.00 (dd, J = 9.5, 3.4 Hz, 1H, H-4), 3.95 – 3.81 (m, 2H, CH_2, ClAc), 3.48 (dd, J = 10.4, 8.0 Hz, 1H, H-2), 3.36 (q, J = 6.2 Hz, 1H, H-5), 1.11 (s, 9H, CH_3 t-Bu), 0.97 (d, J = 6.3 Hz, 3H, H-6). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 166.5, 156.45 (C=O), 136.2 (C_q Ph), 135.7 (CH_{arom}), 132.9, 132.4 (C_q Ph),, 129.9, 128.5, 128.3, 128.1, 127.5, 127.4 (CH_{arom}), 97.0 (C-1), 74.6 (C-3), 68.9 (C-5), 67.1 (CH_2 Cbz), 63.5 (C-2), 51.6 (C-4), 40.5 (CH_2 ClAc), 26.7 (CH_3 t-Bu), 19.0, (C_q t-Bu), 16.0 (C-6); HRMS $[M+Na]^+$ calcd for $C_{32}H_{37}ClN_4O_6SiNa$ 659.20631, found 659.20672.



4-(*N*-Benzyloxycarbonyl)-amino-2-azido-3-*O*-chloroacetyl-2,4,6-trideoxy-D-galactopyranose (11): 1.03 g galactosazide **10** (1.62 mmol, 1 equiv.) in 10 mL THF was treated with 527 µL $N_3Et{\cdot}3HF$ (3.23 mmol, 2 equiv.) and the mixture was stirred at 70ºC for 30 minutes. When the reaction mixture had cooled to ambient temperature EtOAc was added and the organic mixture was washed with sat. aq. $NaHCO_3$. The aqueous layer was extracted with DCM and the combined organic layers were dried over $MgSO_4$, filtered and evaporated. Purification by flash column chromatography using EtOAc/PE (1/3 → 3/7) yielded galactopyranose **11** (632 mg, 1.58 mmol, 98%, α/β 1:2) with a minor unidentified side-product. Rf 0.42 (EtOAc/PE, 2/3, v/v); IR (neat, cm^{-1}) 3356 (br), 2361, 2114, 1701, 1526, 1061; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.42 – 7.29 (m, 5H, H_{arom}), 5.44 (d, J = 9.6 Hz, 0.7H, NH-α), 5.35 – 5.28 (m, 0.6H, H-

1α, H-3α), 5.17 - 5.04 (m, 2H, CH_2 Cbz-α, CH_2 Cbz-β), 4.75 (dt, J = 13.2, 6.6 Hz, 0.7H, H-3β), 4.63 (d, J = 8.0 Hz, 0.7H, H-1β), 4.52 – 4.47 (m, 0.3H, H-5α), 4.33 (s, 0.7H, OH-β), 4.26 – 4.22 (m, 0.3H, H-4α), 4.18 – 4.12 (m, 0.7H, H-4β), 3.96 – 3.86 (m, 2H, CH_2 ClAc), 3.81 – 3.74 (m, 0.7H, H-5β), 3.56 (dd, J = 11.1, 3.7 Hz, 0.3H, H-2α), 3.50 (dd, J = 10.8, 8.0 Hz, 0.7H, H-2β), 3.42 (s, 0.3H, OH-α), 1.24 (d, J = 6.4 Hz, 0.7H, H-6β), 1.18 (d, J = 6.5 Hz, 0.3H, H-6α). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 166.9, 157.1, 157.0 (C=O), 136.1, 136.0 (C_q Ph), 128.6, 128.5, 128.3, 128.1, 127.9 (CH_{arom}), 96.2 (C-1β) , 91.8 (C-1α), 74.6 (C-3β), 72.2 (C-3α), 69.2 (C-5β), 67.3, 67.2 (CH_2 Cbz), 64.1 (C-5α), 61.8 (C-2β), 58.0 (C-2α), 52.5 (C-4α), 51.8 (C-4β), 40.6, 40.5 (CH_2 ClAc), 16.4 (C-6β), 16.3 (C-6α); HRMS $[M+H]^+$ calcd for $C_{16}H_{20}ClN_4O_6$ 399.10659, found 399.10647.



4-(*N*-Benzyloxycarbonyl)-amino-2-azido-3-*O*-chloroacetyl-2,4,6-trideoxy-α/β-D-galactopyranosyl (*N*-phenyl)trifluoroacetimidate (**12**): To a solution of 511 mg hemiacetal **11** (1.28 mmol, 1 equiv.) in 6.1 mL acetone and 0.3 mL H_2O were added 460 mg Cs_2CO_3 (1.41 mmol, 1.1 equiv.) and 532 mg $ClC(C=NPh)CF_3$ (2.56 mmol, 2 equiv.). When TLC analysis showed complete consumption of the starting material, the mixture was coevaporated with toluene. Purification by flash column chromatography using EtOAc/PE (1/9 → 3/7) yielded 606 mg of imidate **12** (1.06 mmol, 83%, anomers α/β 1:3). Rf 0.54 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 2116, 1717, 1524, 1211, 1163, 1072, 696; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) (T=333K) δ 7.41 – 7.23 (m, 9.3H, H_{arom}), 7.09 (m, 1.4H, H_{arom}), 6.83 (m, 2.7H, H_{arom}), 6.35 (s, 0.3H, H-1α), 5.49 (d, J = 7.5 Hz, 1H, H-1β), 5.28 (dd, J = 11.1, 3.5 Hz, 0.3H, H-3α), 5.20 – 4.96 (m, 4H, CH_2 Cbz, NH), 4.81 (dd, J = 10.7, 3.9 Hz, 1H, H-3β), 4.38 – 4.26 (m, 0.7H, H-4α, H-5α), 4.16 (dd, J = 9.7, 3.1 Hz, 1H, H-4β), 3.89 (s, 2.7H, CH_2 ClAc), 3.81 (dd, J = 10.9, 3.9 Hz, 0.3H, H-2α), 3.75 – 3.59 (m, 2H, H-2β, H-5β), 1.20 (m, 4H, H-6). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) (T=333K) δ 166.4, 156.7 (C=O), 143.1, 143.0, 136.3 (C_q Ph), 128.8, 128.6, 128.3, 128.0, 124.7, 124.6, 119.3, 119.2 (CH_{arom}), 95.9 (C-1β), 93.7 (C-1α), 74.6 (C-3β), 72.2 (C-3α), 70.6 (C-5β), 67.5 (C-5α), 67.4 (CH_2 Cbz), 60.2 (C-2β), 57.2 (C-2α), 52.4 (C-4α), 51.8 (C-4β), 40.3 (CH_2 ClAc), 16.2 (C-6); HRMS $[M-(C(N=Ph)CF_3)+H+Na]^+$ calcd for $C_{16}H_{19}ClN_4O_6$ 421.08853, found 421.08845.

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Chapter 3

Galacturonic Acid Lactones in the Synthesis of all Trisaccharide Repeating Units of the Zwitterionic Polysaccharide Sp1[1]

Introduction

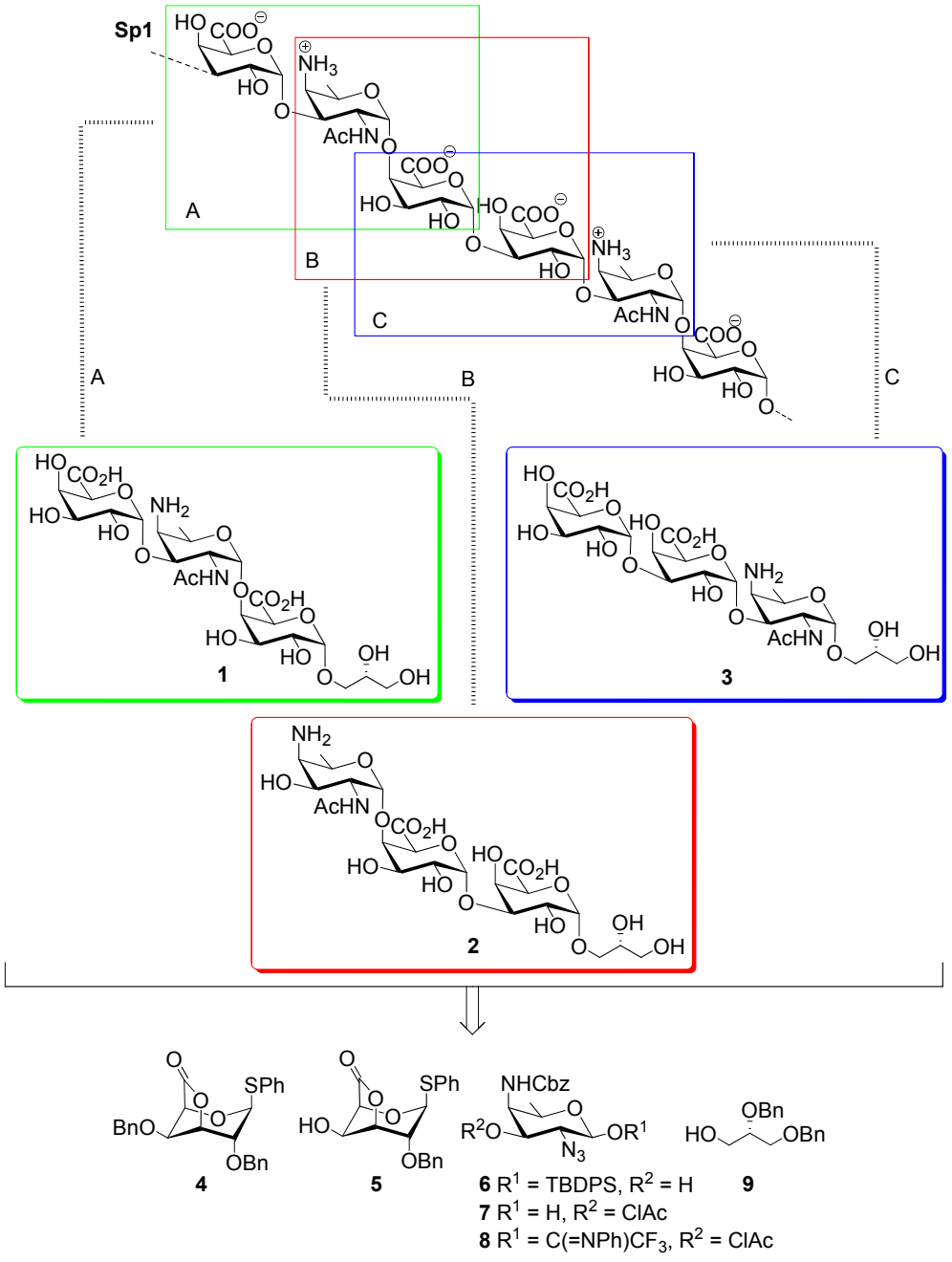
Zwitterionic polysaccharides (ZPs) present an unique class of polysaccharides from both a structural and a biological perspective.[2,3] These bacterial polysaccharides contain both basic amino functions and acidic carboxylate groups and feature a zwitterionic character at physiological pH. ZPs are the only known class of polysaccharides that is capable of eliciting a T-cell dependent immune response, a mode of action that was long thought to be confined to peptides.[1,2] Indeed, the sole manner in which regular polysaccharides could be applied in effective vaccine formulations has been through conjugation to immunostimulatory carrier proteins.[4] Without these proteins, capsular polysaccharides are processed by antigen presenting cells but not presented by MHC class II proteins to T-cells, a key step in the realization of adaptive immune responses. In contrast, ZPs are capable of stimulating CD-4+ T-cell proliferation through presentation by MHC-II molecules.[3,5,6] In addition, ZPs have also been shown to stimulate the innate immune system through interaction with Toll-like receptor 2 (TLR2).[7] To elucidate the mode of action of the zwitterionic polysaccharide at the

molecular level, well-defined ZPs fragments can serve as valuable tools.[8] *Streptococcus pneumonia* is the causative agent of pneumonia, bacteremia, otitis media, meningitis and peritonitis[9] and one of its capsular polysaccharides, Sp1, is a prominent member of the ZPs family.[5,10] Sp1 is an overall anionic polysaccharide build up from non-branching [→3)-α-2,4,6-trideoxy-4-amino-D-GalNAc-(1→4)-α-D-GalA*p*-(1→3)-α-D-GalA*p*-(1→]^{11} trisaccharide repeats, as depicted in Figure 1. The trimer repeat contains two α-D-galacturonic acids in addition to the α-2,4,6-trideoxy-4-amino-2-acetamido-D-galactose moiety. In this chapter the assembly of all three possible spacer containing Sp1 repeating units **1**, **2**, and **3** is reported (Figure 1).

Results and discussion

The synthesis of (fragments of) the Sp1 oligosaccharide contains several challenges, including the presence of the uronic acid moieties and the 2,4,6-trideoxy-4-amino-D-GalNAc monosaccharide,[8,12] that are interconnected through 1,2-*cis*-glycosidic bonds. Different approaches have been pursued for the introduction of uronic acids in oligosaccharide chains.[13] These can be introduced at the monosaccharide level in a pre-glycosylation oxidation strategy, which uses glycuronic acid building blocks as donor and acceptor in the construction of the target oligomer. Alternatively, a post-glycosylation oxidation approach can be followed in which the oligosaccharide backbone is built up prior to the installment of the carboxylate functions. Galacturonic acids are generally considered to be relatively poor glycosyl donors,[14,15] because of the electron withdrawing effect of the C-5 carboxylic acid ester (also see Chapter 4). Similarly, the C-5 carboxylate also exerts a deactivating effect on the nucleophilicity of the proximal hydroxyl functions, and the C-4 hydroxyl group in galacturonic acid acceptors has been regarded as a poor nucleophile.[16] In the first synthesis of two Sp1-oligomers Bundle and co-workers therefore resorted to the use of non-oxidized galactose building blocks in a post-glycosylation oxidation approach (see Chapter 1).[17] For the synthesis of all three frame-shifted repeating units of the Sp1 saccharide, a modular strategy in which monomeric building blocks can be combined in a flexible manner was chosen, as retrosynthetically depicted in Figure 1. To limit the amount of synthetic transformations at the oligosaccharide stage, and especially avoid the late-stage multiple oxidation step, the use of C-5 oxidized galactosyl building blocks was explored. It has been described previously that conformationally locked 1-thio galacturonic acid lactone donors show excellent reactivity[18,19] as well as anomeric selectivity in glycosidations, to provide α-linked galacturonides in excellent yield.[20] This makes them attractive donor glycosides in the assembly of the target Sp1-oligomers. Additionally, the inverted $^{1}C_{4}$- chair conformation of the galacturonic acid-[3,6]-lactones positions the C4-OH equatorially, as opposed to the less accessible axial orientation in the normal $^{4}C_{1}$-chair.[21] In the synthesis of L-guluronate alginate oligomers, Hung and co-workers have shown that changing the orientation of the C4-OH of a gulosyl acceptor from an axial to an equatorial position, by locking the L-gulosyl ring in a $^{4}C_{1}$-conformation with an 1,6-anhydro bridge, increases the nucleophilicity of the C4-OH.[22] It was

Figure 1



The Sp1 polysaccharide and the retrosynthetic strategy towards the three frame-shifted trimer repeats **1**, **2**, and **3**.

reasoned that the inversion of the galacturonic acid chair conformation in the lactone synthons can have a similar beneficial effect on the galacturonic acid C4-hydroxyl. Thus, for the assembly of the Sp1-repeating units two galacturonic acid lactones were envisaged: fully protected lactone thiodonor **4** and acceptor lactone **5**. These can be combined with suitably protected 2,4,6-trideoxy-4-amino-D-galactosamine building blocks **6** and **7**, bearing a non-participating azide functionality at C2 and a benzyloxycarbonyl (Z)-protected amine at C4 (Figure 1). In this synthetic plan, the reducing ends of the trimer repeating units are capped with a diol spacer.

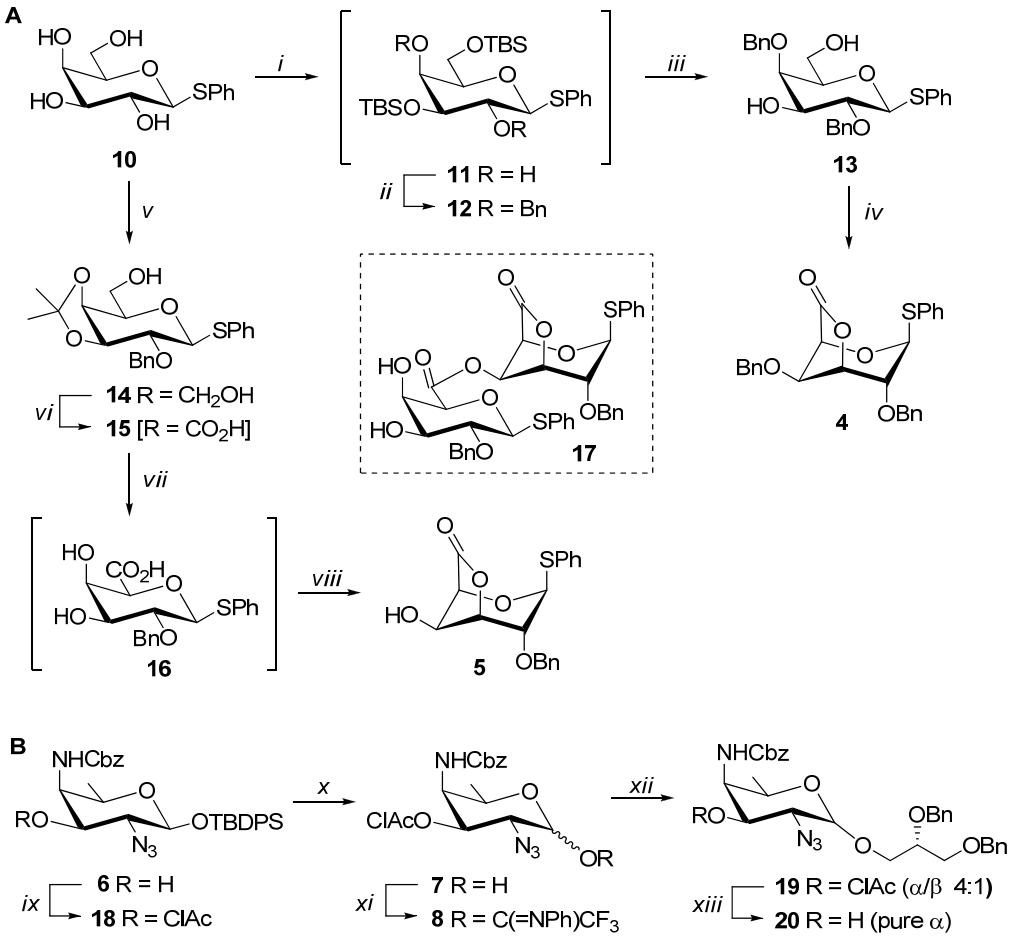
The synthesis of the required building blocks is depicted in Scheme 1. The assembly of the galacturonic acid lactone building blocks **4** and **5** started from known β-1-thiogalactose **10** (Scheme 1A).[23] Selective silylation of the 3 and 6 hydroxyls in **10** led to diol **11**,[24] which was used without purification in the ensuing benzylation step to provide the fully protected galactoside **12**. Desilylation of crude **12** using tetrabutylammonium fluoride in THF led to the isolation of diol **13** in 80% yield over three steps. TEMPO/BAIB-mediated oxidation[25,26] of the primary alcohol in **13** was followed by *in situ* lactone formation to provide the target galacturonic acid lactone **4** in one step, as described by Van den Bos *et al*.[20]

To construct galacturonic acid lactone acceptor **5**, β-1-thiogalactose **10** was transformed into partially protected **14** following a one-pot procedure reported by Sinaÿ and co-workers.[32] TEMPO/BAIB-mediated oxidation of the primary hydroxyl and subsequent acidic hydrolysis of the acetonide gave crude acid **16**.[27] Lactonization of the acid was accomplished using ethylchloroformate to generate the mixed anhydride, which cyclized to give **5** in 62% yield over the last 3 steps.[28] The concentration at which this lactonization step was performed turned out to be of vital importance to the outcome of the reaction. Insufficiently diluted conditions afforded **17** as a side product, providing an indication that the equatorially oriented hydroxyl function in lactone acceptor **5** is a reactive nucleophile. The structure of the lactone building blocks **4** and **5** was fully ascertained by NMR spectroscopy. Because of the spatial arrangement of the sugar protons in the rigid bicyclic systems full assignment of the ^{1}H NMR signals was not trivial[29] and ^{1}H, ^{13}C, ^{1}H-^{1}H COSY and ^{1}H-^{13}C HSQC data were required to prove the structures of the lactones (Figure 2).

A vicinal coupling of H-4 with 4-OH in **5** pointed out the H-4 proton signal in the spectrum of **5**. The resonance of H-3 was assigned based on its relatively large chemical shift. Because the ^{1}H-NMR spectrum of **5** showed a coupling of H-3 with both H-2 and H-5,[30] the latter two protons were distinguished by a long range ^{1}H-^{13}C HMBC NMR experiment, in which a clear cross peak between H-2 and the benzylic carbon was revealed. In this experiment a crosspeak between C-6 and H-3 was also observed. Chemical shift similarities in the spectra of **4** and **5**, in combination with a ^{1}H-^{13}C HMBC NMR experiment, which revealed a crosspeak between H-4 of **4** and a benzylic carbon, led to the full assignment of the resonance sets belonging to lactone **4**.

The required 2,4,6-trideoxy-4-amino-D-galactosamine[8,12,31] building blocks **6**, **7** and **8** were constructed as described in the previous chapter. Acceptor **19** was obtained as outlined in Scheme 1B. Imidate **8** was condensed with glycerol acceptor **9**, accessible from solketal fol-

Scheme 1

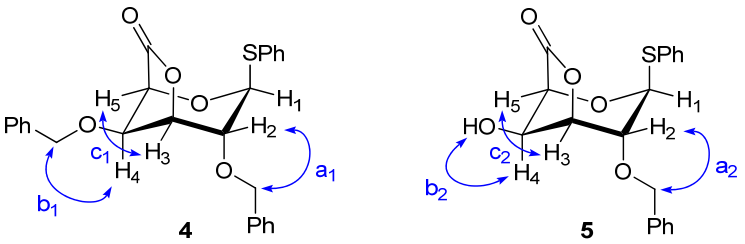


Reagents and conditions: (*i*) TBDMSCl, imidazole, DMF; (*ii*) BnBr, NaH, DMF, 0°C; (*iii*) TBAF, THF, 80% (over 3 steps); (*iv*) TEMPO, BAIB, DCM, H_2O, 75%; (*v*) ref 32; (*vi*) TEMPO, BAIB, DCM, H_2O; (*vii*) AcOH/H_2O (4/1 v/v), 60°C; (*viii*) ethylchloroformate, DiPEA, THF, 62% (over 3 steps); (*ix*) cat. TfOH, DCM/Et_2O (1/1 v/v), 0°C, quant. (α/β 4:1); (*x*) thiourea, EtOH, pyridine, 65°C, 78% for **19**, 18% for the β-anomer.

lowing literature procedures,[33] under the agency of a catalytic amount of TfOH in dichloromethane to provide **18** as a 1 : 1 mixture of inseparable anomers. Although the use of a DCM/Et_2O solvent system in this glycosylation event led to the preferential formation of the α-anomer,[34] the anomers remained inseparable at this stage. Fortunately, after dechloroacetylation of **18**, the epimers were separable by flash column chromatography and 2,4,6-trideoxy-4-amino-D-galactosamine building block **19** was obtained in 78%, alongside 18% of its C1-epimer.

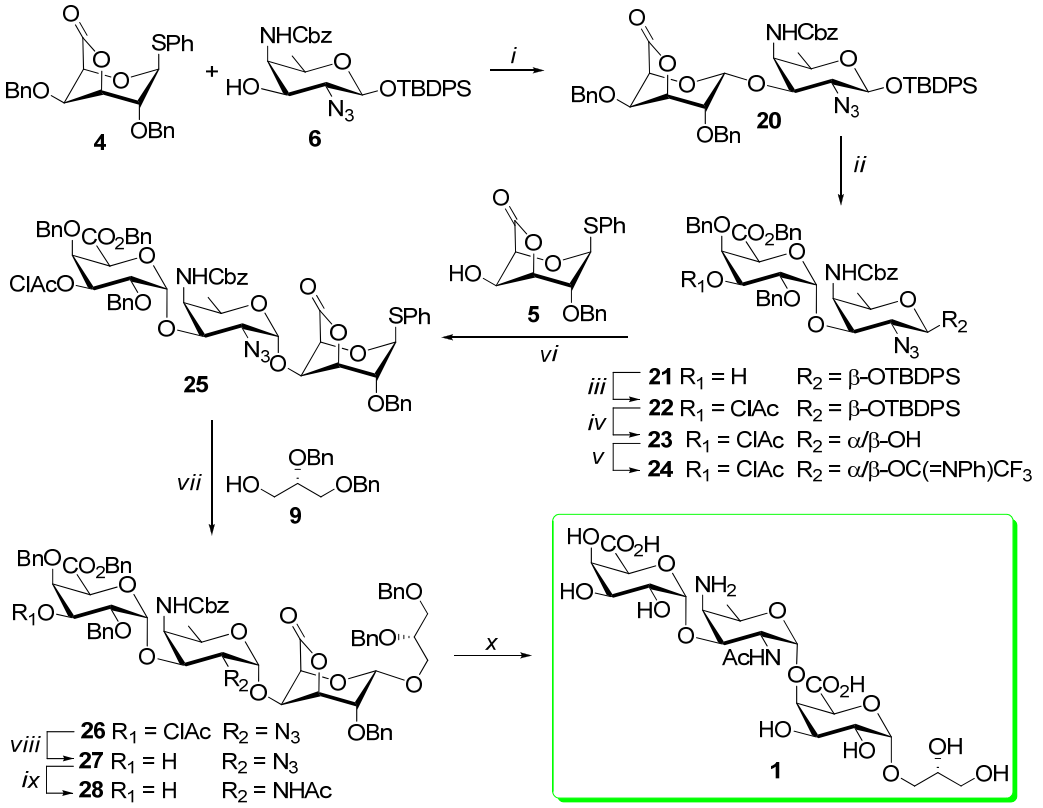
With all monomeric building blocks in hand, the assembly of the three target frame-shifted trimer repeats **1**, **2**, and **3** was started. The synthesis of trisaccharide **1** (Scheme 2)

Figure 2



Schematic representation of observed crosspeaks from 2D NMR experiments with lactone building blocks **4** (a1: H2-CH_2 Bn (HMBC), b1: H4-CH_2 Bn (HMBC), c1: H3-H5 (COSY)) and **5** (a2: H2-CH_2 Bn (HMBC), b2: H4-CH_2 Bn (HMBC), c2: H3-H5 (COSY)) where upon the assignment of peaks was based.

Scheme 2



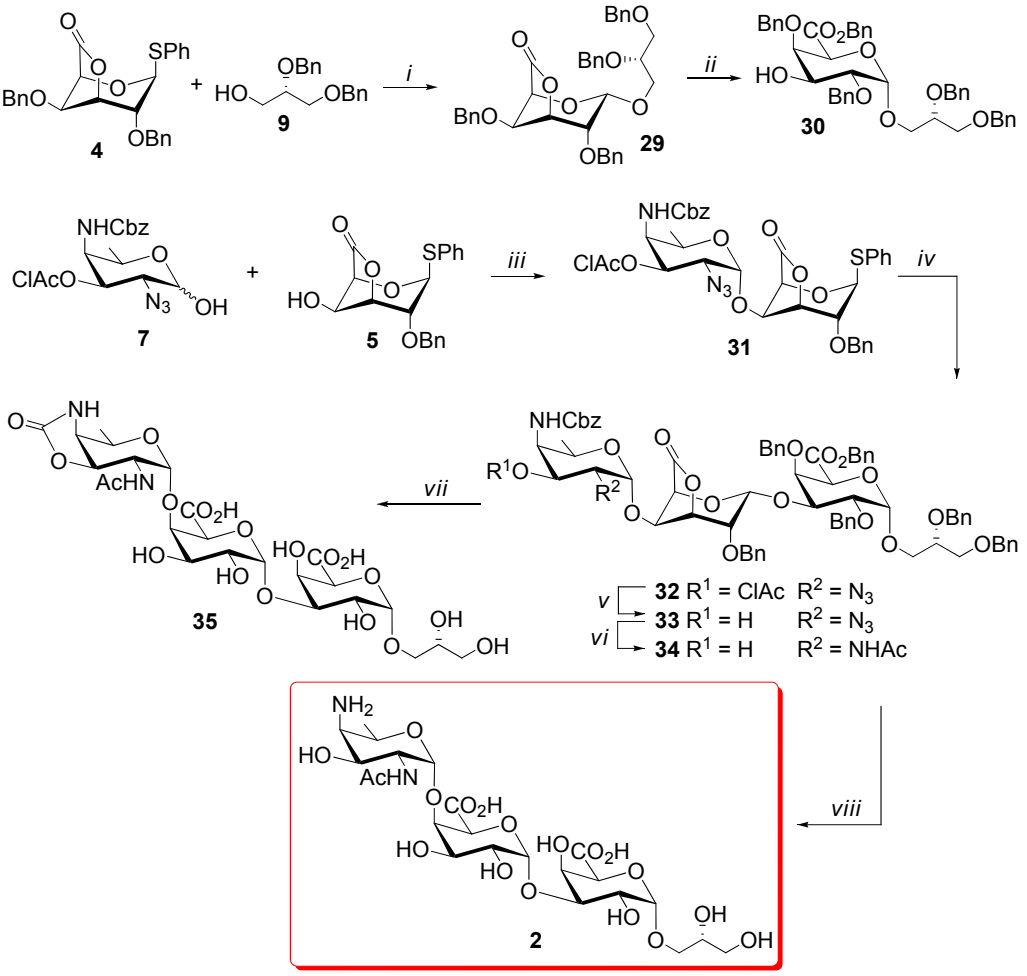
Reagents and conditions: (*i*) **4**, Ph_2SO, Tf_2O, DCM, TTBP, -60°C then acceptor **6**, 75%; (*ii*) BnOH, AcCl, 50°C, overnight, quant.; (*iii*) $(ClAc)_2O$, 86%; (*iv*) EtN_3•3HF, THF, 84%; (α/β 1:4); (*v*) ClC(=NPh)CF_3, Cs_2CO_3, H_2O, acetone, 85%; (*vi*) cat. TfOH, DCM, 81% (α/β 8:1); (*vii*) **25**, Ph_2SO, Tf_2O, DCM, TTBP, -60°C then acceptor **9**, 81%; (*viii*) thiourea, EtOH, pyridine, 65°C, 76%; (*ix*) AcSH/pyridine (1/1 v/v), 94%; (*x*) TMSONa, DCM, then H_2/Pd(C), *t*BuOH, H_2O, HCl, 52% over 2 steps.

began with the coupling of lactone **4** and 2,4,6-trideoxy-4-amino-D-galactosazide **6**. To this end, donor **4** was pre-activated using *in situ* generated diphenylsulfonium bistriflate[35] and subsequently treated with acceptor **6** to give disaccharide **20** in good yield and excellent stereoselectivity. Opening of the lactone ring using benzyl alcohol under acidic conditions20 afforded benzylester **21** quantitatively. Chloroacetylation of the liberated hydroxyl functionality, anomeric desilylation and installment of the *N*-phenyltrifluoro imidate function then led to dimeric glycosyl donor **24**. Coupling of this donor with lactone acceptor **5** employing TfOH as a promoter gave *S*-phenyl trimer **25** in 81% yield and 8:1 α/β selectivity, showcasing the apt nucleophilicity of lactone acceptor **5**. Next, thiodonor **25** and glycerol acceptor **9** were condensed in a Ph_2SO/Tf_2O-mediated pre-activation glycosylation event furnishing the fully protected glycerol capped trisaccharide **26** as the sole anomer. Global deprotection started with removal of the chloroacetylgroup to give alcohol **27**. Reduction of the azide in **27** with either PMe_3 or dithiothreitol and ensuing acetylation of the amine and free C3''-OH gave only low yields of the desired product. The use of freshly distilled thiolacetic acid and pyridine on the other hand, gave acetamide **28** in 94% yield,[36] with the alcohol functionality still intact. Studies to open the lactone ring in compound **29** (*vide infra*) led to the use of TMSONa as a nucleophilic reagent to hydrolyze the lactone functionality in **28**.[37] Hydrogenolysis of the remaining benzyl ester, benzyloxy carbamate and benzyl groups then furnished the first target trisaccharide **1** in 52% yield over the last two steps.

For the construction of trisaccharide **2**, lactone donor **4** was converted into glycerol capped galacturonic acid ester acceptor **30** (Scheme 3). To this end, lactone donor **4** was coupled with acceptor **9** in a Ph_2SO/Tf_2O-mediated glycosylation to yield **29** with excellent anomeric selectivity (α/β = 10:1). Unfortunately, the acid catalyzed opening of lactone **29** in benzyl alcohol as described above did not lead to the anticipated product. A product resulting from the endocyclic opening of the galactopyranosyl core was observed. Use of Bu_2SnO[38] in BnOH did give the desired product, but only in low yields. Finally, the lactone ring was successfully opened using TMSONa, to afford the free acid, which was subsequently treated with benzyl bromide and Cs_2CO_3 providing the reducing end galacturonic acid acceptor **30** in 75% yield.

Next, hemiacetal donor **7** and lactone acceptor **5** were coupled under the agency of Ph_2SO and Tf_2O to stereoselectively form the α-linked dimer **31** in 84% yield. The generated thiodonor **31** was engaged in a next glycosylation event with spacer capped galacturonic acid ester acceptor **30** to produce the fully protected trisaccharide **32**, again with complete α-selectivity. To deliver target compound **2** the same global deprotection strategy was envisioned as used previously for the fully protected trisaccharide **26**. Thus, dechloroacetylation with thiourea was followed by reduction of the azide group using AcSH and simultaneous N-acetylation to produce acetamide **34**. Unfortunately, treatment of **34** with TMSONa in dichloromethane and ensuing hydrogenolysis did not afford the anticipated trisaccharide **2**. Instead, oxazolidinone **35** was obtained, resulting from intramolecular nucleophilic attack of the 3''-OH onto the nearby benzyl carbamate during the TMSONa

Scheme 3



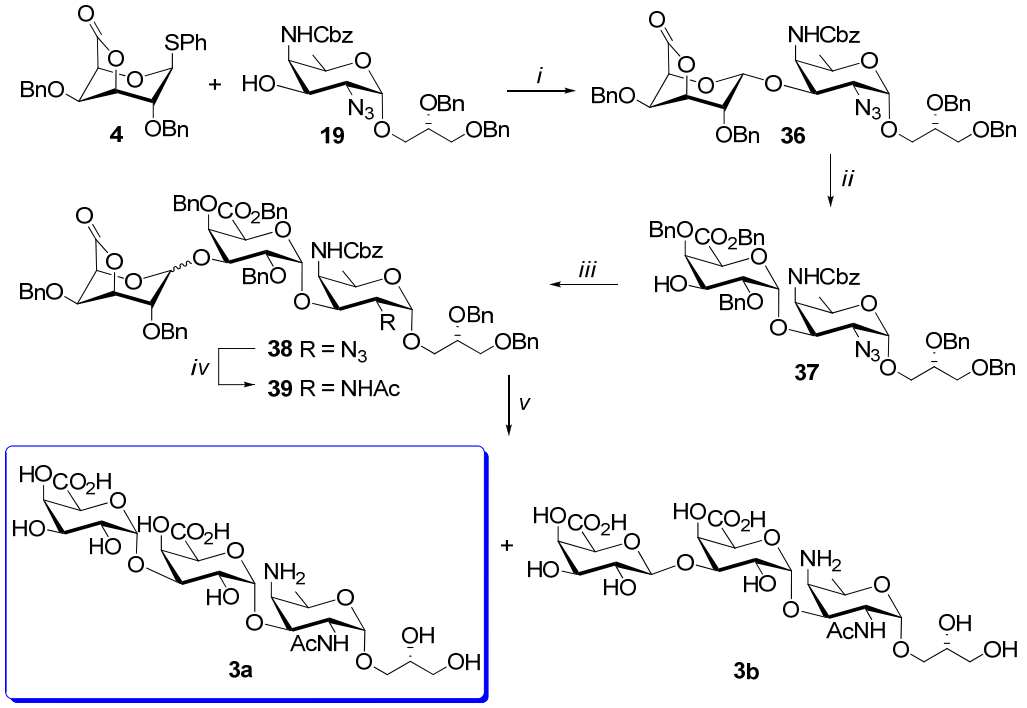
Reagents and conditions: (*i*) **4**, Ph_2SO, Tf_2O, DCM, TTBP, -60°C then acceptor **9**, 93% (α/β 10:1); (*ii*) (1) TMSONa, DCM; (2) BnBr, Cs_2CO_3, DMF, 75% (2 steps); (*iii*) **7**, Ph_2SO, Tf_2O, DCM, TTBP, -60°C then acceptor **5**, 84%; (*iv*) **31**, Ph_2SO, Tf_2O, DCM, TTBP, -60°C then acceptor **30**, 60%; (v) thiourea, EtOH, pyridine, 65°C, 51%; (*vi*) thiolacetic acid/pyridine (1/1 v/v), 62%; (*vii*) TMSONa, DCM, then H_2/Pd(C), *t*BuOH, H_2O, HCl, 38%; (*viii*) H_2/Pd(C), *t*BuOH, H_2O, HCl, then H_2O, HCl, 38%.

treatment. The formation of the oxazolidinone could be circumvented by reversal of the lactone ring opening and reduction steps. Hydrogenolysis of acetamide **34** under mildly acidic conditions provided the crude trimer lactone. The ^{1}H NMR spectrum of the crude lactone recorded directly after hydrogenolysis already showed partial hydrolysis of the lactone ring, and therefore the crude lactone was further subjected to mild acidic hydrolysis conditions to provide the target trimer **2** in 38% over the last two steps.

The assembly of the third and last trisaccharide **3** commenced with the sulfonium bistriflate-mediated condensation of lactone donor **4** and acceptor **19**. As depicted in Scheme

4, disaccharide **36** was produced in a completely α-selective fashion in 70% yield. TMSONa opening of the lactone functionality in **36** and subsequent benzyl ester installment set the stage for the next glycosylation event, in which key lactone donor **4** was employed again. The coupling of **4** and **37**, proceeded without any selectivity and trisaccharide **38** was isolated as an inseparable 1 : 1 mixture in 78% yield. Changing the solvent system to either toluene or acetonitrile in dichloromethane did not significantly alter the stereochemical outcome of the glycosylation. In light of the excellent α-selectivity of all previous condensations using the galacturonic acid-[3,6]-lactone donors, and especially the coupling of **31** with galacturonic acid acceptor **30**, the lack of selectivity in the condensation of **4** and **37** is surprising and it was decided to investigate the stereochemical behavior of donor **4** at a later stage (see Chapter 4).

Scheme 4

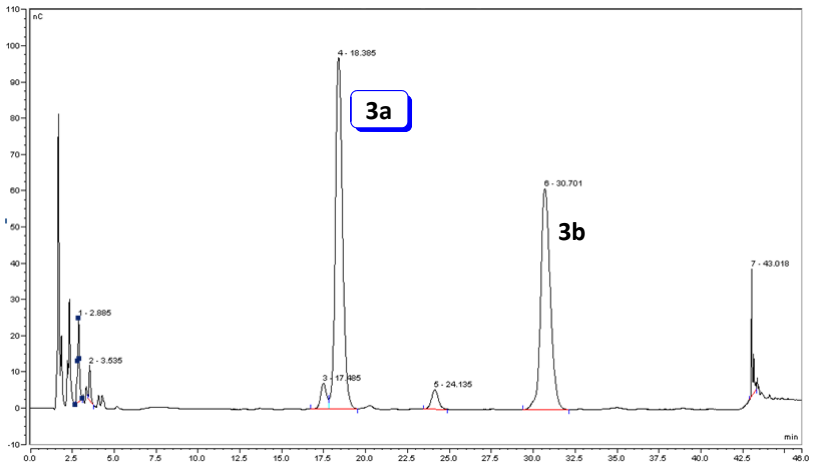


Reagents and conditions: (*i*) **4**, Ph_2SO, Tf_2O, DCM, TTBP, -60°C then acceptor **19**, 70%; (*ii*) (1) TMSONa, DCM; (2) BnBr, Cs_2CO_3, DMF, 74% over 2 steps; (*iii*) **4**, Ph_2SO, Tf_2O, DCM, TTBP, -60°C then acceptor **37**, 78%; (*iv*) AcSH, pyridine, 40%; (*v*) TMSONa, DCM, then H_2/Pd(C), *t*BuOH, H_2O, HCl.

Global deprotection of the epimeric mixture was accomplished by reduction of the azide in **38** and concomitant acetylation to give acetamide **39** in moderate yield. Then, TMSONa-mediated lactone hydrolysis and ensuing reduction of the remaining protective groups gave a crude epimeric mixture of fully deprotected trisaccharides. The two anomers

could be separated by high performance anion-exchange chromatography (HPAEC).[39] The use of a gradient of 30 mM to 80 mM NaOAc in 100 mM NaOH led to the elution of the α- and β-epimers with a retention time difference of over 10 minutes, as depicted in Figure 3. Preparative ion exchange chromatography gave target C-1''-α-configured trisaccharide **3a** (28% over the last two steps), and its β-epimer **3b** (17% over the last two steps) in pure form. The structures of the trisaccharides were corroborated by NMR spectroscopy. The heteronuclear one-bond coupling constant of C-1" and H-1" in **3a** ($^1J_{C\text{-}H}$ = 170.3 Hz) and **3b** ($^1J_{C\text{-}H}$ = 161.5 Hz) unambiguously confirmed the α-anomeric configuration for the former and the β-anomeric configuration for the latter trisaccharide.

Figure 3



Dionex HPAEC (high performance anion-exchange chromatography) trace of the epimeric mixture obtained after hydrogenation of **39** under acidic conditions, showing a retention time difference of 12.32 minutes between both epimers. Recovery: 28% for **3a** and 17% for **3b** (over 2 steps from **39**).

Conclusion

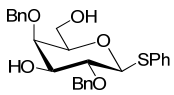
In summary, the synthesis of all three frame-shifted trisaccharide repeats of the zwitterionic polysaccharide Sp1 of *Streptococcus pneumonia*, exploiting the use of 1-thio galacturonic acid lactones as key donor and acceptor building blocks, has been described. The galacturonic acid-[3,6]-lactones proved to be efficient donor galactosides for the construction of the galacturonic acid target compounds. The yields of the glycosylations using the lactone donors were good to excellent and in all but one of the galacturonylations very high α-selectivities were observed. The unexpected lack of α-selectivity in the condensation of key lactone donor **4** and dimer acceptor **37** has raised questions concerning generality of the preference of this donor to form 1,2-*cis* bonds in glycosylation reactions. This matter shall be addressed in the following chapter. In addition to being adequate donor glycosides, the galacturonic acid lactones were also shown to be excellent nucleophiles when

equipped with a free C4-hydroxyl function. The $^1C_4$-chair conformation of lactone **5** places the C4-hydroxyl in an equatorial position which makes it significantly more reactive towards incoming electrophiles. It is envisaged that this strategy can also be applied to other glycuronic acid acceptors. Finally, HPAEC proved to be a powerful purification technique for this class of compounds as the difference in one stereochemical center led to a significant difference in retention time, allowing the separation of the two epimers **3a** and **3b**.

Experimental section

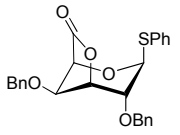
General Procedures: All chemicals were used as received. Trifluoromethanesulfonic anhydride (Tf_2O) was distilled from P_2O_5 and stored in a Schlenk flask. TLC analysis was conducted on silica gel-coated aluminum TLC sheets (Merck, silica gel 60, F_{245}). Compounds were visualized by UV absorption (245 nm), by spraying with 20% H_2SO_4 in ethanol or with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ 25 g/L, $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ 10 g/L, 10% H_2SO_4 in H_2O followed by charring at ~140 °C. Flash chromatography was performed on silica gel (Screening Devices, 40-63 µm 60Å, www.screeningdevices.com) using technical grade, distilled solvents. NMR spectra were recorded on a Bruker AV400. For solutions in $CDCl_3$ chemical shifts (δ) are reported relative to tetramethylsilane (^1H) or $CDCl_3$ (^{13}C). Peak assignments were made based on HH-COSY and HSQC measurements. Optical rotation was measured using a Propol automatic polarimeter. The IR absorbance was recorded using a Shimadzu FTIR-83000 spectrometer. Mass analysis was performed using a PE/SCIEX API 165 with an Electrospray Interface (Perkin-Elmer).

General Procedure for Glycosylations using Ph_2SO/Tf_2O: A solution of donor (1 equiv.), diphenyl sulfoxide (1.1 equiv.) and tri-*tert*-butylpyrimidine (1.5 equiv.) in DCM (0.05M) was stirred over activated molsieves (3Å) for 30 min. The mixture was cooled to -60°C before triflic acid anhydride (1.1 equiv.) was added. The mixture was allowed to warm to -45°C and was subsequently recooled to -60°C before a mixture (dried over 3Å molsieves) of acceptor (1.5 equiv.) and tri-*tert*-butylpyrimidine (1.0 equiv.) in little DCM was added. Stirring was continued and the reaction mixture was allowed to warm to -10°C. The reaction mixture was quenched with triethylamine (5.0 equiv.), diluted with DCM and washed with sat. aq. $NaHCO_3$. The aqueous phase was extracted with DCM and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography and removal of the eluent afforded the coupled product.

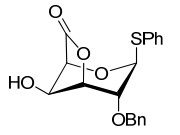


Phenyl 2,4-di-*O*-benzyl-1-thio-β-D-galactopyranoside (13). To a mixture of 10.0 g phenyl-1-thio-galactopyranose in 150 mL DMF (36.8 mmol, 1 equiv.) was added 8.77 g imidazole (128.8 mmol, 3.5 equiv.) and 16.64 g TBSCl (110.4 mmol, 3 equiv.). After 2 hours of stirring, TLC analysis showed complete consumption of the starting material. The reaction was quenched by the addition of 3 mL of MeOH. The mixture was partitioned between H_2O and Et_2O and the aqeous layer was extracted. The combined organic phases were washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated. The crude product was dissolved in 150 mL DMF and to this solution were added 13.2 mL BnBr (110.4 mmol, 3 equiv.) and 4.42 g NaH (60% in mineral oil, 110.4 mmol, 3 equiv) at 0ºC. After stirring at ambient temperature overnight, the reaction was quenched with MeOH at 0ºC, taken up in Et_2O and washed with 5% aq. LiCl and brine. After drying over $MgSO_4$, filtration and concentration under reduced pressure, the residue was dissolved in 40 mL THF and treated with 146.8 mL 1.0 M TBAF (in THF, 146.8 mmol, 4 equiv.). The mixture was stirred for 3 hours and subsequently taken up in EtOAc and H_2O. The water layer was further extracted with EtOAc and the combined organic layers were dried ($MgSO_4$) , filtered and evaporated. Purification by flash column chromatography using EtOAc/PE (7/13 → 9/11)

afforded the target compound **13** (13.4 g, 29.6 mmol, 80% over 3 steps) Rf 0.27 (EtOAc/PE, 1/1, v/v); $[\alpha]_D^{22}$ +1 (c 1.4, $CHCl_3$); IR (neat, cm^{-1}) 1311, 1049, 1018, 871, 732, 640, 694; ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.53 (m, 2H, H_{arom}), 7.43 – 7.09 (m, 13H, H_{arom}), 4.90 (d, J = 10.8 Hz, 1H, CH_2 Bn), 4.76 (d, J = 11.6 Hz, 1H, CH_2 Bn), 4.68 – 4.54 (m, 3H, CH_2 Bn, H-1), 3.84 (dd, J = 11.0, 7.4 Hz, 1H, H-6), 3.75 (s, 1H, H-4), 3.74 – 3.65 (m, 2H, H-2, H-3), 3.56 (dd, J = 11.2, 4.5 Hz, 1H, H-6), 3.49 – 3.42 (m, 1H, H-5), 2.41 (bs, 1H, OH), 2.03 (bs, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 138.0, 137.9, 133.9 (C_q Ph), 131.2, 128.9, 128.5, 128.4, 128.3, 128.0, 127.9, 127.2 (CH_{arom}), 87.1 (C-1), 79.0 (C-5), 78.1 (C-2), 75.8, 75.7 (C-3, C-4), 75.2, 74.7 (CH_2 Bn), 62.1 (C-6); HRMS $[M+Na]^+$ calcd for $C_{26}H_{28}N_3O_5SNa$ 475.15497, found 475.15567.

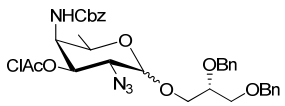


Phenyl 2,4-di-*O*-benzyl-1-thio-β-D-galactopyranosidurono-3,6-lactone (4). The thiodonor lactone was synthesized as reported previously and all physical and spectroscopic data were in accordance with the published data.[25] ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.63 – 7.09 (m, 15H, H_{arom}), 5.41 (s, 1H, H-1), 4.80 (dd, *J* = 4.7, 1.3 Hz, 1H, H-3), 4.65 (d, *J* = 11.8 Hz, 1H, CH_2 Bn), 4.59 (s, 2H, CH_2 Bn), 4.54 (d, *J* = 11.8 Hz, 1H, CH_2 Bn), 4.39 (br s, 1H, H-4), 4.27 (d, *J* = 4.7 Hz, 1H, H-2), 4.04 (br s, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): δ 172.6 (C=O), 136.7, 136.5, 133.6 (C_q Ph), 132.7, 129.0, 128.7, 128.6, 128.5, 128.3, 128.1, 128.0, 127.8 (CH_{arom}), 85.8 (C-1), 78.9 (C-3), 78.6 (C-2), 76.0 (C-4), 73.0 (CH_2 Bn), 71.5 (CH_2 Bn), 70.8 (C-5).

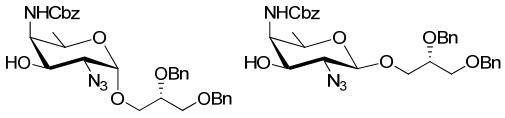


Phenyl 2-*O*-benzyl-1-thio-β-D-galactopyranosidurono-3,6-lactone (5). To a vigorously stirred solution of 3.59 g phenyl 2-*O*-benzyl-3,4-*O*-isopropylidene-1-thio-β-galactopyranoside (8.93 mmol, 1 equiv.) in 30 mL DCM and 15 mL H_2O was added 279 mg TEMPO (1.79 mmol, 0.2 equiv.) and 7.19 g BAIB (22.3 mmol, 2.5 equiv.). After 2 hours of stirring at room temperature, $Na_2S_2O_3$ solution (10% in H_2O) was added and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated. The crude acid was stirred at 65ºC in 20 mL AcOH/H_2O (4/1 v/v) until TLC analysis showed disappearance of the starting material. The mixture was concentrated in vacuo and coevaporated with toluene. The crude product was dissolved in 350 mL anhydrous DCM followed by addition of 1.77 mL Dipea (10.7 mmol, 1.2 equiv.) and 939 µL ethylchloroformate (9.82 mmol, 1.1 equiv.). After 3 hours of stirring at ambient temperature, the mixture was evaporated and lactone **5** was obtained in pure form after flash column chromatography using EtOAc/PE (1/4 → 1/3) (1.08 g, 3.0 mmol, 34% over 3 steps). Rf 0.26 (EtOAc/PE, 3/7, v/v); $[\alpha]_D^{22}$ – 223 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3440, 1794, 1095, 1055, 694; ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.45 – 7.23 (m, 10H, H_{arom}), 5.39 (s, 1H, H-1), 4.77 (dd, J = 4.7, 1.3 Hz, 1H, H-3), 4.62 – 4.50 (m, 3H, H-4, CH_2 Bn), 4.22 (d, J = 4.7 Hz, 1H, H-2), 3.98 (t, J = 1.3 Hz, 1H, H-5), 3.29 (s, 1H, OH) ; ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 174.1 (C=O), 136.4, 133.4 (C_q Ph), 132.5, 129.0, 128.6, 128.3, 128.1, 128.0 (CH_{arom}), 85.3 (C-1), 81.2 (C-3), 78.3 (C-2), 72.9 (CH_2 Bn), 72.5 (C-5), 69.5 (C-4).; HRMS $[M+Na]^+$ calcd for $C_{19}H_{18}O_5SNa$ 381.07672, found 381.07675. When lactonization of the crude acid diol **16** was executed at a 0.21 M concentration, lactone **5** was isolated in 26% along with 19% of **2-*O*-benzyl-1-thio- β-D-galactopyranosiduronyl-3,6-lactone) 2-*O*-benzyl-1-thio-β-D-galactopyranosyluronate (17).** Rf 0.41 (EtOAc/PE, 2/3, v/v); $[\alpha]_D^{22}$ -158 (c 2.0, CH_2Cl_2); IR (neat, cm^{-1}) 3470, 1806, 1774, 1101, 741, 692; 'a' designates signals belonging to the galacturonic acid ester, 'b' is used for signals stemming from the galacturonic acid lactone. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.0 Hz, 2H, H_{arom}), 7.48 – 7.20 (m, 18H, H_{arom}), 5.59 (s, 1H, H-4b), 5.44 (s, 1H, H-1b), 5.08 (d, *J* = 4.6 Hz, 1H, H-3b), 4.93 (d, *J* = 10.8 Hz, 1H, CH_2 Bn), 4.70 – 4.65 (m, 2H, CH_2 Bn), 4.62 – 4.54 (m, 2H, CH_2 Bn, H-1a), 4.35 (d, *J* = 4.8 Hz, 1H, H-2b), 4.20 – 4.16 (m, 2H, H-4a, H-5b), 4.09 (s, 1H, H-5a), 3.73 – 3.62 (m, 2H, H-3a, H-2a), 3.50 (d, *J* = 4.1 Hz, 1H, OH), 3.25 (d, *J* = 4.1 Hz, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 166.3 (C=O), 137.9, 136.3, 133.3 (C_q Ph), 133.0, 132.6, 132.4, 129.0, 128.6, 128.5, 128.3,

128.2, 128.1, 128.0, 127.9 (CH_{arom}), 87.6 (C-1a), 86.3 (C-1b), 78.4 (C-3b), 78.1 (C-2b), 77.2 (C-2a), 76.4 (C-5a), 75.4 (CH_2 Bn), 74.0 (C-3a), 72.9 (CH_2 Bn), 72.6 (C-4b), 70.0, 69.8 (C-4a, C-5b); HRMS $[M+Na]^+$ calcd for $C_{38}H_{36}O_{10}S_2Na$ 739.16421, found 739.16431.

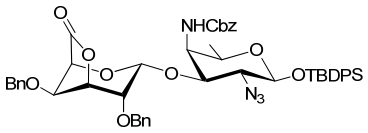


4-(*N*-Benzyloxycarbonyl)-amino-2-azido-3-*O*-chloroacetyl-2,4,6-trideoxy-α/β-D-galactopyranosyl-(1→3)-1,2-di-*O*-benzyl-sn-glycerol (18). A catalytic amount of triflic acid was added under anhydrous conditions to a mixture of 403 mg imidate **8** (707 µmol, 1 equiv.) and 578 mg alcohol **9** (2.21 mmol, 3 equiv.) in 7 mL DCM/Et_2O (1/1 v/v) at 0ºC. After 20 minutes of stirring, TLC analysis showed complete conversion of the starting material. The reaction was quenched by adding triethylamine and the solvents were removed in vacuo. Purification by size exclusion chromatography (DCM/MeOH 1/1 v/v) yielded the title compound as an anomeric mixture (460 mg, 704 µmol, α/β 4:1, quant.) Rf 0.81 (EtOAc/PE, 3/7, v/v); IR (neat, cm^{-1}) 2936, 2111, 1768, 1718, 1520, 1041, 698; ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.42 – 7.23 (m, 18.8H, H_{arom}), 5.25 (dd, J = 11.1, 3.7 Hz, 1H, H-3α), 5.13 (dd, J = 10.6, 7.5 Hz, 2.5H, CH_2 Cbz, NH), 5.01 (d, J = 12.3 Hz, 1,25H, CH_2 Cbz), 4.89 (d, J = 3.7 Hz, 1H, H-1α), 4.72 – 4.60 (m, 2.8H, CH_2 Bn, H-3β), 4.58 – 4.48 (m, 2.5H, CH_2 Bn), 4.28 (d, J = 8.0 Hz, 0.25H, H-1β), 4.18 – 4.04 (m, 2.25H, H-4α, H-5α, H-4β), 3.99 – 3.73 (m, 4.8H, CH_2 Gro, CH Gro, CH_2 ClAc), 3.63 – 3.57 (m, 4H, CH_2 Gro, H-5β), 3.45 – 3.35 (m, 1.3H, H-2β, H-2α), 1.19 (d, J = 6.3 Hz, 0.8H, H-6β), 1.04 (d, J = 6.4 Hz, 3H, H-6α).; ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 166.6, 156.6, 156.5 (C=O), 138.2, 137.9, 136.2 (C_q Ph), 128.5, 128.3, 128.2, 127.9, 127.6, 127.5 (CH_{arom}), 102.2 (C-1β), 97.9 (C-1α), 76.8 (CH Gro-β), 76.6 (CH Gro-α), 74.3 (C-3β), 73.3 (CH_2 Bn), 72.1, 72.0 (CH_2 Bn), 71.6 (C-3α), 69.5, 69.4, 69.2 (CH_2 Gro), 68.9 (C-5β), 67.9 (CH_2 Gro), 67.0 (CH_2 Cbz), 64.0 (C-5α), 60.8 (C-2β), 57.2 (C-2α), 52.3 (C-4α), 51.6 (C-4β), 40.5 (CH_2 ClAc), 16.3 (C-6β), 16.1 (C-6α); HRMS $[M+Na]^+$ calcd for $C_{33}H_{37}ClN_4O_8Na$ 675.21921, found 675.21973.

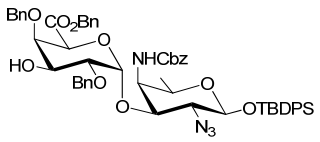


4-(*N*-Benzyloxycarbonyl)-amino-2-azido-2,4,6-trideoxy-α-D-galactopyranosyl-(1→3)-1,2-di-*O*-benzyl-sn-glycerol (19α) and 4-(*N*-benzyloxycarbonyl)-amino-2-azido-2,4,6-trideoxy-β-D-galactopyranosyl-(1→3)-1,2-di-*O*-benzyl-sn-glycerol (19β). A mixture of 460 mg azide **18** (704 µmol, 1 equiv.), 454 µl pyridine (5.63mmol, 8 equiv.), 161 mg thiourea (2.11 mmol, 3 equiv.) and 7 mL ethanol was stirred for 3 hours at 65ºC. The mixture was concentrated and the crude residue was taken up in EtOAc. The organic phase was washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated. Purification by flash column chromatography using EtOAc/PE (1/4 → 3/7) yielded 317 mg of **19**α (549 µmol, 78%) and 66 mg of **19**β (114 µmol, 16%). **19**α: Rf 0.3 (EtOAc/PE, 1/3, v/v); $[\alpha]_D^{22}$ +91 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3418, 2916, 2106, 1697, 1026, 725; ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.40 – 7.23 (m, 15H, H_{arom}), 5.17 – 5.06 (m, 3H, NH, CH_2 Cbz), 4.81 (d, J = 3.7 Hz, 1H, H-1), 4.71 – 4.62 (m, 2H, CH_2 Bn), 4.54 (dd, J = 12.0, 12.0 Hz, 2H, CH_2 Bn), 4.14 (dd, J = 10.7, 3.5 Hz, 1H, H-3), 4.08 (q, J = 6.5 Hz, 1H, H-5), 3.96 (dd, J = 8.8, 2.5 Hz, 1H, H-4), 3.83 – 3.76 (m, 2H, CH Gro, CH_2 Gro), 3.63 (d, J = 4.7 Hz, 2H, CH_2 Gro), 3.57 (dd, J = 9.4, 4.3 Hz, 1H, CH_2 Gro), 3.24 (s, 1H, OH), 3.12 (dd, J = 10.7, 3.6 Hz, 1H, H-2), 1.07 (d, J = 6.5 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 158.1 (C=O), 138.3, 138.0, 135.8 (C_q Ph), 128.6, 128.3, 128.1, 127.7, 127.6, 127.6 (CH_{arom}), 98.2 (C-1), 76.8 (CH Gro), 73.4 (CH_2 Bn), 72.1 (CH_2 Bn), 69.4 (CH_2 Gro), 68.5 (C-3), 67.6 (CH_2 Gro), 67.5 (CH_2 Cbz), 64.5 (C-5), 60.4 (C-2), 55.8 (C-4), 16.4 (C-6); HRMS $[M+Na]^+$ calcd for $C_{31}H_{36}N_4O_7Na$ 599.24762, found 599.24731; **19**β: Rf 0.16 (EtOAc/PE, 1/3, v/v); $[\alpha]_D^{22}$ -13 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3348, 2870, 2106, 1705, 1049, 741; ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.47 – 7.17 (m, 15H, H_{arom}), 5.29 – 5.03 (m, 3H, NH, CH_2 Cbz), 4.67 (s, 2H, CH_2 Bn), 4.54 (s, 2H, CH_2 Bn), 4.22 (d, J = 8.0 Hz, 1H, H-1), 3.99 – 3.91 (m, 2H, CH_2 Gro, H-4), 3.83 – 3.78 (m, 1H, CH Gro), 3.72 (dd, J = 10.2, 5.2 Hz, 1H, CH_2 Gro), 3.63 (dd, J = 4.9, 1.5 Hz, 2H, CH_2 Gro), 3.60 – 3.53 (m, 2H, H-3, H-5), 3.22 (dd, J = 10.0, 8.2 Hz, 1H, H-2), 3.16 (d, J = 2.3 Hz, 1H, OH), 1.19 (d, J = 6.2 Hz, 3H, H-6). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 158.0 (C=O), 138.6, 138.2, 136.0 (C_q Ph), 128.6, -128.4, 128.3, 128.1, 127.7, 127.6 (CH_{arom}), 102.5 (C-1), 77.0 (CH Gro), 73.5 (CH_2 Bn), 72.5 (C-3), 72.3 (CH_2 Bn), 69.8

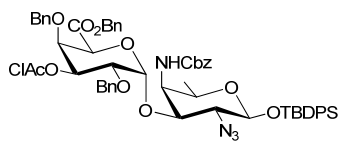
(CH_2 Gro), 69.5 (C-5) (CH_2 Gro), 67.5 (CH_2 Cbz), 64.5 (C-2), 54.9 (C-4), 16.6 (C-6); HRMS $[M+H]^+$ calcd for $C_{31}H_{36}N_4O_7$ 577.26568, found 577.26583.



2,4-di-*O*-benzyl-α-D-galactopyranosiduronyl-3,6-lactone-(1→3)-Tert-butyldiphenylsilyl 4-(*N*-benzyloxycarbonyl)-amino-2-azido-2,4,6-trideoxy-β-D-galactopyranoside (20). Lactone **4** (338 mg) was coupled to alcohol **6** (0.77 equiv. instead of 1.5 equiv) according to the general procedure for glycosidations using Ph_2SO/Tf_2O. The reaction was quenched using triethylamine (5 equiv.) and the title compound **20** was obtained in 75% yield (391 mg, 435 µmol). Flash column chromatography eluent: EtOAc/toluene (0/1 → 1/49). Rf 0.78 (EtOAc/Toluene, 1/4, v/v); $[\alpha]_D^{22}$ 27 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2860, 2361, 2114, 1800, 1717, 1506, 1061; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.79 – 7.08 (m, 25H, H_{arom}), 5.13 – 5.00 (m, 3H, CH_2 Cbz, H-1'), 4.92 (d, J = 9.7 Hz, 1H, NH), 4.79 (d, J = 11.6 Hz, 1H, CH_2 Bn), 4.71 (d, J = 3.8 Hz, 1H, H-3'), 4.62 – 4.52 (m, 2H, CH_2 Bn), 4.50 (s, 1H, H-4'), 4.36 (d, J = 7.8 Hz, 1H, H-1), 4.27 (d, J = 11.6 Hz, 1H, CH_2 Bn), 4.18 (s, 1H, H-5'), 4.05 (dd, J = 4.9, 2.1 Hz, 1H, H-2'), 3.92 (dd, J = 10.0, 3.7 Hz, 1H, H-4), 3.68 (dd, J = 10.5, 4.0 Hz, 1H, H-3), 3.30 – 3.23 (m, 2H, H-2, H-5), 1.10 (s, 9H, CH_3 t-Bu), 1.00 (d, J = 6.3 Hz, 3H, H-6). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 171.8 (C=O), 156.5 (C=O Cbz), 138.0, 136.8 (C_q Ph), 135.8 (CH_{arom}), 133.1, 132.5 (C_q Ph), 129.9, 129.8, 128.6, 128.5, 128.4, 128.3, 128.1, 127.8, 127.7, 127.5, 127.4 (CH_{arom}), 96.9 (C-1), 95.6 (C-1'), 80.4 (C-3'), 77.1 (C-3), 75.8 (C-4'), 75.0 (C-2'), 74.3 (CH_2 Bn), 72.2 (C-5'), 71.5 (CH_2 Bn), 69.0 (C-5), 67.2 (CH_2 Cbz), 64.8 (C-2), 50.9 (C-4), 26.8 (CH_3 t-Bu), 19.1 (C_q t-Bu), 16.3 (C-6); HRMS $[M+Na]^+$ calcd for $C_{50}H_{54}N_4O_{10}SiNa$ 921.35014, found 921.35091.

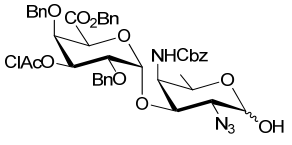


Benzyl 2,4-di-*O*-benzyl-α-D-galactopyranosyluronate-(1→3)-*tert*-butyldiphenylsilyl 4-(*N*-benzyloxycarbonyl)-amino-2-azido-2,4,6-trideoxy-β-D-galactopyranoside (21). After adding a catalytic amount of AcCl to a solution of 412 mg lactone **20** (367 µmol) in 2 mL BnOH, the mixture was allowed to stir overnight at 50°C. Following neutralization using triethylamine, the mixture was diluted with EtOAc, washed with sat. aq. $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. Size exclusion chromatography (DCM/MeOH 1/1 v/v) followed by flash column chromatography using EtOAc/ Toluene (1/19→1/9) gave 370 mg (367 µmol, quant.) of the title compound **21**. Rf 0.51 (EtOAc/Toluene, 1/4, v/v); $[\alpha]_D^{22}$ +34 (c 0.39, CH_2Cl_2); IR (neat, cm^{-1}) 3500, 2932, 2112, 1761, 1719, 1508, 1107, 1059; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.75 – 7.60 (m, 4H, H_{arom}), 7.49 – 7.16 (m, 24H, H_{arom}), 7.14 – 7.03 (m, 2H, H_{arom}), 5.54 (d, J = 3.3 Hz, 1H, H-1'), 5.14 (d, J = 12.2 Hz, 1H, CH_2 Bn), 5.06 (m, 2H, CH_2 Bn), 4.91 (d, J = 10.4 Hz, 1H, NH), 4.76 (d, J = 12.2 Hz, 1H, CH_2 Bn), 4.68 – 4.61 (m, 3H, H-5', CH_2 Bn), 4.42 – 4.36 (m, 3H, H-1, CH_2 Bn), 4.30 (s, 1H, H-4'), 4.21 (dd, J = 10.0, 3.2 Hz, 1H, H-3'), 4.09 (dd, J = 10.1, 3.5 Hz, 1H, H-4), 3.90 (dd, J = 10.1, 3.3 Hz, 1H, H-2'), 3.57 (dd, J = 10.8, 4.2 Hz, 1H, H-3), 3.38 (dd, J = 10.9, 7.7 Hz, 1H, H-2), 3.23 (q, J = 6.1 Hz, 1H, H-5), 2.12 (s, 1H, OH), 1.09 (s, 9H, CH_3 t-Bu), 0.92 (d, J = 6.3 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 168.3 (C=O), 156.7 (C=O Cbz), 138.2, 137.8, 136.0 (C_q Ph), 135.8, 135.7 (CH_{arom}), 135.1, 133.2, 132.8 (C_q Ph), 129.9, 129.8, 128.5, 128.4, 128.2, 128.0, 127.9, 127.6, 127.5, 127.4 (CH_{arom}), 97.2 (C-1), 92.1 (C-1'), 77.6 (C-4'), 74.9 (CH_2 Bn), 74.8 (C-2'), 72.3 (C-3), 72.0 (CH_2 Bn), 70.6 (C-5'), 69.8 (C-5), 69.3 (C-3'), 67.0 (CH_2 Cbz, CH_2 Bn), 65.3 (C-2), 49.9 (C-4), 26.8 (CH_3 t-Bu), 19.1 (C_q t-Bu), 16.0 (C-6).; HRMS $[M+Na]^+$ calcd for $C_{57}H_{62}N_4O_{11}SiNa$ 1029.40766, found 1029.40828.

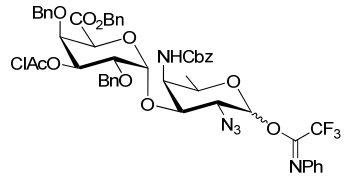


Benzyl 2,4-di-*O*-benzyl-3-*O*-chloroacetyl-α-D-galactopyranosyluronate-(1→3)-*tert*-butyldiphenylsilyl 4-(*N*-benzyloxycarbonyl)-amino-2-azido-2,4,6-trideoxy-β-D-galactopyranoside (22). 2.10 g of alcohol **21** (2.09 mmol, 1 equiv.) was coevaporated with toluene and dissolved in 10 mL DCM. 1.68

mL (20.9 mmol, 10 equiv.) of pyridine and 1.07 g of $(ClAc)_2O$ (6.3 mmol, 3 equiv.) were added at 0°C and the mixture was stirred at ambient temperature for 2.5 hours. Next, H_2O and EtOAc were added and the organic phase was washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered and evaporated. Purification by flash column chromatography using EtOAc/Tol (0/1 → 1/19) yielded 2.11 g of chloroacetate **22** (1.94 mmol, 93%). Rf 0.81 (EtOAc/Toluene, 1/4, v/v); $[\alpha]_D^{22}$ +78 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2936, 2112, 1760, 1718, 1508, 1063, 696; ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.68 (dd, J = 7.0, 3.4 Hz, 4H, H_{arom}), 7.46 – 7.12 (m, 24H, H_{arom}), 7.08 – 6.97 (m, 2H, H_{arom}), 5.53 (d, J = 3.3 Hz, 1H, H-1'), 5.41 (dd, J = 10.5, 2.9 Hz, 1H, 3'), 5.15 (dd, J = 12.1, 12.1 Hz, 2H, CH_2 Bn), 5.03 (d, J = 12.2 Hz, 1H, CH_2 Bn), 4.89 (d, J = 10.4 Hz, 1H, NH), 4.78 (s, 1H, 5'), 4.67 (dd, J = 12.4, 12.4 Hz, 2H, CH_2 Bn), 4.44 – 4.37 (m, 3H, H-4', H-1, CH_2 Bn), 4.31 (dd, J = 11.8, 11.8 Hz, 2H, CH_2 Bn), 4.14 – 4.02 (m, 2H, H-2', H-4), 3.63 (d, J = 14.9 Hz, 1H, CH_2 ClAc), 3.58 (dd, J = 10.8, 4.1 Hz, 1H, H-3), 3.51 (d, J = 14.9 Hz, 1H, CH_2 ClAc), 3.42 (dd, J = 10.7, 7.7 Hz, 1H, H-2), 3.23 (q, J = 6.1 Hz, 1H, H-5), 1.10 (s, 9H, CH_3 t-Bu), 0.91 (d, J = 6.3 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 167.8, 166.4 (C=O), 156.6 (C=O Cbz), 138.0, 137.7, 136.0 (C_q Ph), 135.8, 135.7 (CH_{arom}), 134.9, 133.2, 132.8 (C_q Ph), 129.9, 129.8, 128.8, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4 (CH_{arom}), 97.3 (C-1), 92.7 (C-1'), 76.8 (C-4'), 75.0 (CH_2 Bn), 72.9 (C-3'), 72.6 (C-3, CH_2 Bn), 72.2 (C-2'), 70.2 (C-5'), 69.7 (C-5), 67.2, 66.9 (CH_2 Bn), 65.1 (C-2), 49.9 (C-4), 40.3 (CH_2 ClAc), 26.8 (CH_3 t-Bu), 19.1 (C_q t-Bu), 16.0 (C-6); HRMS $[M+Na]^+$ calcd for $C_{59}H_{63}ClN_4O_{12}SiNa$ 1105.37925, found 1105.38018.

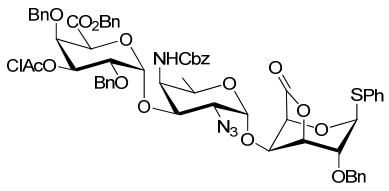


Benzyl 2,4-di-*O*-benzyl-3-*O*-chloroacetyl-α-D-galactopyranosyluronate-(1→3)-4-(*N*-benzyloxycarbonyl)-amino-2-azido-2,4,6-trideoxy-D-galactopyranose (23). A mixture of 2.05 g dimer **22** (1.89 mmol, 1 equiv.), 20 mL THF and 2.47 mL triethylamine·3HF (15.13 mmol, 8 equiv.) was stirred overnight at 70ºC. The solvent was removed using a rotary evaporator and the crude anomers were purified by flash column chromatography using EtOAc/PE (7/13→9/11). 1.35 g (1.60 mmol, 84%, α/β 1:4) of the title compound **23** was obtained. Data of major anomer (β): Rf 0.24 (EtOAc/PE, 2/3, v/v); IR (neat, cm^{-1}) 3425, 2108, 1763, 1717, 1541, 1244, 1036; ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.38 – 7.15 (m, 18H, H_{arom}), 7.08 – 7.00 (m, 2H, H_{arom}), 5.54 (d, J = 3.3 Hz, 1H, H-1'), 5.43 – 5.36 (m, 2H, H-3', NH), 5.21 – 5.10 (m, 2H, CH_2 Bn), 5.06 (d, J = 12.3 Hz, 1H, CH_2 Cbz or CH_2 CO_2Bn), 4.85 (s, 1H, H-5'), 4.67 (m, 2H, CH_2 Bn), 4.55 (d, J = 7.0 Hz, 1H, H-1), 4.44 – 4.37 (m, 2H, CH_2 Bn, H-4'), 4.36 – 4.28 (m, 2H, CH_2 Bn), 4.20 (dd, J = 10.4, 4.3 Hz, 1H, H-4), 4.11 (dd, J = 10.5, 3.3 Hz, 1H, H-2'), 3.70 (dd, J = 10.8, 4.2 Hz, 1H, H-3), 3.66 – 3.44 (m, 4H, CH_2 ClAc, H-5, H-2), 1.19 (d, J = 6.3 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 167.8, 166.3 (C=O), 156.9 (C=O Cbz), 137.7, 137.6, 136.0, 134.7 (C_q Ph), 128.9, 128.7, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4 (CH_{arom}), 96.5 (C-1), 92.5 (C-1'), 76.7 (C-4'), 74.9 (CH_2 Cbz or CH_2 CO_2Bn), 72.8, (C-3'), 72.5 (CH_2 Cbz or CH_2 CO_2Bn), 72.4 (C-3), 72.2 (C-2'), 70.1 (C-5'), 69.8 (C-5), 67.2, 66.7 (CH_2 Bn), 63.1 (C-2), 49.9 (C-4), 40.2 (CH_2 ClAc), 16.4 (C-6); HRMS $[M+Na]^+$ calcd for $C_{16}H_{19}ClN_4O_6Na$ 867.26147, found 867.26183.

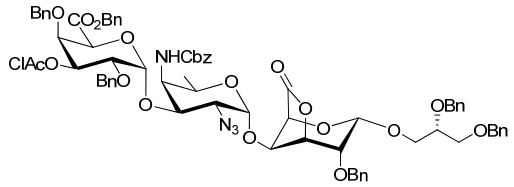


Benzyl 2,4-di-*O*-benzyl-3-*O*-chloroacetyl-α-D-galactopyranosyluronate-(1→3)-4-(*N*-benzyloxycarbonyl)-amino-2-azido-2,4,6-trideoxy-D-galactopyranosyl (*N*-phenyl)trifluoroacetimidate (24). To a solution of 666 mg hemiacetal **23** (0.787 mmol, 1 equiv.) in 15 mL acetone/H_2O (19/1) were added 282 mg Cs_2CO_3 (0.866 mmol, 1.1 equiv.) and 327 mg ClC(C=NPh)CF_3 (1.57 mmol, 2.0 equiv.). The mixture was stirred overnight at ambient temperature and evaporated to dryness after the addtion of 328 µL triethylamine (2.36 mmol, 3.0 equiv.). Flash column chromatography of the crude product using EtOAc/PE (3/7) with 1% triethyamine as eluent afforded 680 mg (669 µmol, 85%) of the title imidate as one of the two possible epimers. Rf 0.64 (EtOAc/Toluene, 1/4, v/v); IR (neat, cm^{-1}) 2112, 1759, 1717, 1516, 1209, 1078, 696; ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.39 – 7.18 (m, 20H, H_{arom}), 7.13 (t, J = 7.5 Hz, 1H, H_{arom}), 7.08 – 7.00 (m, 2H, H_{arom}), 6.84 (d, J = 7.8 Hz, 2H, H_{arom}), 5.57 (d, J = 2.8 Hz, 1H, H-

1'), 5.41 (dd, J = 10.6, 2.9 Hz, 1H, H-3'), 5.23 – 5.03 (m, 4H, NH, CH_2 Cbz or CH_2 CO_2Bn), 4.79 (s, 1H, H-5'), 4.74 – 4.64 (m, 2H, CH_2 Cbz or CH_2 CO_2Bn, CH_2 Bn), 4.46 – 4.38 (m, 2H, CH_2 Bn, H-4'), 4.37 – 4.22 (m, 3H, CH_2 Bn, H-4), 4.13 (dd, J = 10.5, 3.4 Hz, 1H, H-2'), 3.82 – 3.73 (m, 1H, H-5), 3.73 – 3.66 (m, 1H, H-2), 3.63 (d, J = 14.9 Hz, 1H, CH_2 ClAc), 3.52 (d, J = 14.9 Hz, 1H, CH_2 ClAc), 1.22 (d, J = 6.9 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 167.6, 166.4 (C=O), 156.6 (C=O Cbz), 142.9, 137.8, 137.6, 135.8, 134.8 (C_q Ph), 128.8, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 124.6, 119.2 (CH_{arom}), 92.9 (C-1'), 76.8 (C-4'), 75.1 (CH_2 Cbz or CH_2 CO_2Bn), 72.8 (C-3'), 72.7 (CH_2 Cbz or CH_2 CO_2Bn), 72.6 (C-3 or C-5), 72.1 (C-2'), 71.2 (C-3 or C-5), 70.3 (C-5'), 67.3, 67.0 (CH_2 Bn), 61.3 (C-2), 49.7 (C-4), 40.3 (CH_2 ClAc), 16.3 (C-6); HRMS $[M-(C(N=Ph)CF_3)+H+Na]^+$ calcd for $C_{43}H_{45}ClN_4O_{12}Na$ 867.26147, found 867.26164.

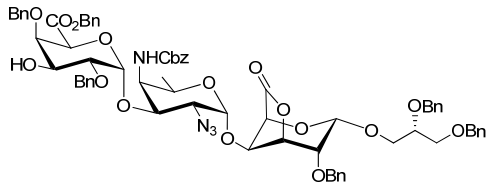


Benzyl 2,4-di-*O*-benzyl-3-*O*-chloroacetyl-α-D-galactopyranosyluronate-(1→3)-4-(*N*-benzyloxycarbonyl)-amino-2-azido-2,4,6-trideoxy-D-galactopyranosyl-(1→4)-phenyl 2-*O*-benzyl-1-thio-β-D-galactopyranosiduruno-3,6-lactone (25). Imidate donor (X) (600mg, 590 µmol, 1 equiv) and 391 mg lactone acceptor 5 (1.09 mmol, 1.85 equiv.) were coevaporated with toluene and stirred over activated 3Å molecular sieves in 6 mL DCM for 30 minutes. The mixture was cooled to 0ºC before 5 µL triflic acid (59 µmol, 0.1 equiv.) was added. After 30 minutes of stirring, the reaction was quenched by the addition of 41 µL triethylamine (295µmol, 0.5 equiv.). The mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$. The aqueous phase was extracted with DCM and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Size exclusion chromatography (DCM/MeOH 1/1 v/v) and flash column chromatography (eluent: EtOAc/PE 1/3 → 9/11) afforded the α-coupled product **25** (450mg, 379 µmol, 64%). Rf 0.57 (EtOAc/Toluene, 1/4, v/v); $[\alpha]_D^{22}$ +62 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2106, 1805, 1759, 1720, 1520, 1242, 1034; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.50 – 7.43 (m, 2H, H_{arom}), 7.41 – 7.14 (m, 26H, H_{arom}), 7.07 – 7.00 (m, 2H, H_{arom}), 5.54 (s, 1H, H-1''), 5.42 (s, 1H, H-1), 5.39 (dd, J = 10.7, 2.7 Hz, 1H, H-3''), 5.18 (s, 2H, CH_2), 5.09 – 4.96 (m, 3H, CH_2, H-1', NH), 4.86 (d, J = 4.7 Hz, 1H, H-2), 4.69 – 4.63 (m, 4H, CH_2 Bn, H-5''), 4.58 – 4.55 (m, 2H, H-4, CH_2), 4.40 – 4.37 (m, 2H, H-4'', CH_2 Bn), 4.35 – 4.25 (m, 4H, H-4', H-3, CH_2 Bn), 4.18 (dd, J = 10.6, 3.9 Hz, 1H, H-3'), 4.14 – 4.05 (m, 3H, H-2'', H-5', H-5), 3.56 (d, J = 14.9 Hz, 1H, CH_2 ClAc), 3.46 (d, J = 14.9 Hz, 1H, CH_2 ClAc), 3.39 (dd, J = 11.0, 3.9 Hz, 1H, H-2'), 1.13 (d, J = 6.2 Hz, 3H, H-6'); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 171.7, 167.5, 166.4 (C=O), 156.7 (C=O Cbz), 138.0, 137.7, 136.3, 135.9, 134.9, 133.3 (C_q Ph), 132.8, 129.0, 128.8, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6 (CH_{arom}), 97.7 (C-1'), 93.1 (C-1''), 85.7 (C-1), 79.1 (C-2), 78.4 (C-3), 76.8 (C-4''), 76.3 (C-4), 75.1, 73.2 (CH_2 Bn), 72.8 (C-3'', CH_2 Bn), 72.3 (C-2''), 70.4 (C-5''), 70.2 (C-5'), 69.9 (C-3'), 67.4, 67.0 (CH_2), 66.5 (C-5), 58.8 (C-2'), 50.7 (C-4'), 40.3 (CH_2 ClAc), 16.3 (C-6');

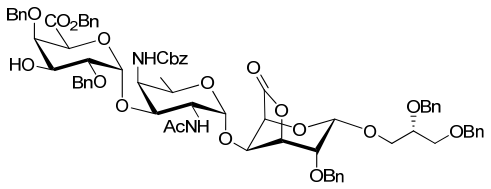


Benzyl 2,4-di-*O*-benzyl-3-*O*-chloroacetyl-α-D-galactopyranosyluronate-(1→3)-4-(*N*-benzyloxycarbonyl)-amino-2-azido-2,4,6-trideoxy-D-galactopyranosyl-(1→4)-2-*O*-benzyl-α-D-galactopyranosiduronyl-3,6-lactone-(1→3)-sn-glycerol (26). Thiodonor **25** (328 mg) was coupled to glycerol acceptor **9** (4.0 equiv. instead of 1.5 equiv) according to the general procedure for glycosylations using Ph_2SO/Tf_2O. The reaction was quenched with triethylamine (5 equiv.) and the title compound **26** was purified using size exclusion chromatography. Yield: 81% (302 mg, 224 µmol). Rf 0.59 (EtOAc/PE, 2/3, v/v); $[\alpha]_D^{22}$ +99 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2874, 2108, 1803, 1761, 1719, 1028, 696; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.39 – 7.16 (m, 33H, H_{arom}), 7.06 – 6.99 (m, 2H, H_{arom}), 5.53 (d, J = 2.5 Hz, 1H, H-1''), 5.38 (dd, J = 10.6, 2.7 Hz, 1H, H-3''), 5.25 – 5.12 (m, 2H, CH_2 Bn), 5.05 (d, J = 12.2 Hz, 1H, CH_2 Bn), 4.99 – 4.97 (m, 2H, NH, H-1'), 4.90 – 4.86 (m, 2H, H-1, CH_2 Bn), 4.74 – 4.61 (m, 7H, H-4, H-3, H-5'', CH_2 Bn), 4.58 –

4.45 (m, 3H, CH_2 Bn), 4.40 – 4.37 (m, 2H, CH_2 Bn, H-4''), 4.34 – 4.26 (m, 3H, H-4', CH_2 Bn), 4.21 – 4.14 (m, 2H, H-5, H-3'), 4.13 – 4.08 (m, 2H, CH_2 Gro, H-2''), 4.02 (q, J = 6.3 Hz, 1H, H-5'), 3.89 (dd, J = 5.0, 2.2 Hz, 1H, H-2), 3.87 – 3.82 (m, 1H, CH Gro), 3.70 (dd, J = 10.7, 6.9 Hz, 1H, CH_2 Gro), 3.59 – 3.52 (m, 3H, CH_2 Gro, CH_2 ClAc), 3.45 (d, J = 14.9 Hz, 1H, CH_2 ClAc), 3.38 (dd, J = 10.9, 3.9 Hz, 1H, H-2'), 1.11 (d, J = 6.3 Hz, 3H, H-6'). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 170.7, 167.5, 166.3 (C=O), 156.7 (C=O Cbz), 138.3, 137.9, 137.6, 137.4, 135.9, 134.9 (C_q Ph), 128.9, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6 (CH_{arom}), 99.3 (C-1), 97.5 (C-1'), 93.0 (C-1''), 80.6 (C-3), 77.2 (CH Gro), 76.8 (C-4''), 75.5 (C-4), 75.1 (CH_2 Bn), 74.5 (CH_2 Bn), 74.3 (C-2), 73.4 (CH_2 Bn), 72.8 (CH_2 Bn, C-3), 72.3 (CH_2 Bn, C-2''), 71.4 (C-5), 71.1 (CH_2 Gro), 70.4 (C-5''), 69.8 (C-3'), 69.5 (CH_2 Gro), 67.4, 67.0 (CH_2), 66.2 (C-5'), 58.7 (C-2'), 50.6 (C-4'), 40.3 (CH_2 ClAc), 16.2 (C-6'); HRMS $[M+Na]^+$ calcd for $C_{73}H_{75}ClN_4O_{19}Na$ 1369.46062, found 1369.46265.

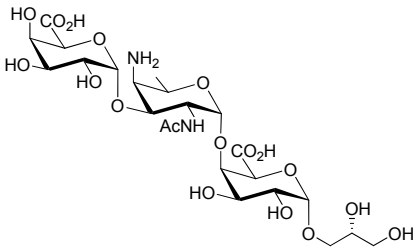


Benzyl 2,4-di-*O*-benzyl-α-D-galactopyranosyluronate-(1→3)-4-(*N*-benzyloxycarbonyl)-amino-2-azido-2,4,6-trideoxy-D-galactopyranosyl-(1→4)-2-*O*-benzyl-α-D-galactopyranosiduronyl-3,6-lactone-(1→3)-1,2-di-*O*-benzyl-sn-glycerol (27). A solution of 302 mg compound **26** (224 µmol, 1 equiv.), 145 µL pyridine (1.79 mmol, 8 equiv.) and 51 mg thiourea (672 µmol, 3 equiv.) in 4 mL EtOH was stirred at 65ºC for 3 hours. The mixture was concentrated under reduced pressure, diluted with EtOAc and washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography using EtOAc/toluene (1/4→1/3) gave 218 mg (171 µmol, 76%) of the title compound **27**. Rf 0.62 (EtOAc/PE, 2/3, v/v); $[\alpha]_D^{22}$ +95 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2924, 2106, 1805, 1759, 1713, 1535, 1034; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.39 – 7.12 (m, 33H, H_{arom}), 7.11 – 7.05 (m, 2H, H_{arom}), 5.55 (d, J = 2.2 Hz, 1H, H-1''), 5.15 (m, 2H, CH_2 Bn), 5.09 – 5.05 (m, 2H, NH, CH_2 Bn), 4.92 (d, J = 4.2 Hz, 1H, H-1'), 4.89 – 4.83 (m, 2H, H-1, CH_2 Bn), 4.74 – 4.58 (m, 7H, H-4, H-3, CH_2 Bn, CH_2), 4.55 (s, 1H, H-5''), 4.54 – 4.44 (m, 3H, CH_2 Bn), 4.43 – 4.28 (m, 3H, CH_2 Bn, H-4'), 4.24 (s, 1H, H-4''), 4.20 – 4.11 (m, 3H, H-5, H-3'', H-3'), 4.09 (dd, J = 10.7, 3.5 Hz, 1H, CH_2 Gro), 4.00 (q, J = 6.2 Hz, 1H, H-5'), 3.92 – 3.81 (m, 3H, H-2'', H-2, CH Gro), 3.68 (dd, J = 10.7, 6.9 Hz, 1H, CH_2 Gro), 3.54 (d, J = 5.3 Hz, 2H, CH_2 Gro), 3.36 (dd, J = 11.0, 3.9 Hz, 1H, H-2'), 2.04 (s, 1H, OH), 1.10 (d, J = 6.2 Hz, 3H, H-6'); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 170.6, 168.0 (C=O), 156.7 (C=O Cbz), 138.2, 138.0, 137.8, 137.7, 137.2, 135.8, 134.9 (C_q Ph), 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4 (CH_{arom}), 99.2 (C-1), 97.3 (C-1'), 92.3 (C-1''), 80.5 (C-3), 77.6 (C-4''), 77.1 (CH Gro), 75.1 (C-4), 74.8 (CH_2 Bn), 74.6 (C-2''), 74.3 (CH_2 Bn), 74.2 (C-2), 73.3 (CH_2 Bn), 72.2 (CH_2 Bn), 72.0 (CH_2 Bn), 71.2 (C-5), 71.0 (CH_2 Gro), 70.6 (C-5''), 69.3 (CH_2 Gro, C-3'), 69.0 (C-3''), 67.0, 66.9 (CH_2), 66.2 (C-5'), 58.6 (C-2'), 50.5 (C-4'), 16.1 (C-6'); HRMS $[M+Na]^+$ calcd for $C_{71}H_{74}N_4O_{18}Na$ 1293.48903, found 1293.49043.

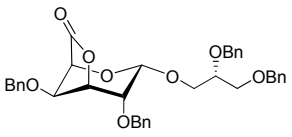


Benzyl 2,4-di-*O*-benzyl-α-D-galactopyranosyluronate-(1→3)-2-acetamido-4-(*N*-benzyloxycarbonyl)-amino-2,4,6-trideoxy-α-D-galactopyranosyl-(1→4)-2-*O*-benzyl-α-D-galactopyranosiduronyl-3,6-lactone-(1→3)-1,2-di-*O*-benzyl-sn-glycerol (28). To an ice cooled solution of 94 mg azide **27** (74 µmol) in 1 mL pyridine was added 1 mL of freshly distilled thiolacetic acid. The mixture was stirred at room temperature for 4 hours, concentrated under reduced pressure and coevaporated with toluene. Flash column chromatography using EtOAc/PE (1/1→3/2) afforded the title acetamide (89 mg, 69 µmol, 94%). Rf 0.41 (EtOAc/PE, 3/2, v/v); $[\alpha]_D^{22}$ +97 (c 0.7, CH_2Cl_2); IR (neat, cm^{-1}) 3368, 2924, 1801, 1718, 1668, 1028, 697; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.40 – 7.19 (m, 33H, H_{arom}), 7.13 (d, J = 6.7 Hz, 2H, H_{arom}), 5.43 (d, J = 8.9 Hz, 1H, NH), 5.24 (d, J = 9.9 Hz, 1H, NH), 5.19 – 5.12 (m, 2H, CH_2, H-

1''), 5.02 (d, J = 12.4 Hz, 1H, CH_2 Bn), 4.94 (d, J = 12.0 Hz, 1H, CH_2 Bn), 4.91 – 4.77 (m, 4H, CH_2 Bn, H-1', H-1), 4.73 – 4.59 (m, 6H, CH_2 Bn, H-4, H-3), 4.53 – 4.37 (m, 6H, CH_2 Bn, H-5''), 4.20 – 4.05 (m, 5H, H-4', H-4'', H-2', H-5, CH_2 Gro), 3.98 (dd, J = 9.9, 2.7 Hz, 1H, H-3''), 3.93 – 3.80 (m, 4H, H-2, H-5', CH Gro, H-2''), 3.75 – 3.65 (m, 2H, H-3', CH_2 Gro), 3.55 (dd, J = 5.0, 1.7 Hz, 2H, CH_2 Gro), 1.71 (s, 3H, CH_3 NHAc), 1.12 (d, J = 6.4 Hz, 3H, H-6'). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 171.2, 170.4, 168.3 (C=O), 156.9 (C=O Cbz), 138.3, 138.1, 137.9, 137.3, 136.4, 134.8 (C_q Ph), 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5 (CH_{arom}), 99.2 (C-1), 96.4 (C-1'), 96.0 (C-1''), 80.9 (C-3), 77.2 (C-4'', CH Gro), 75.4 (C-2''), 74.7, 74.5 (CH_2 Bn), 74.2 (C-2), 73.9 (C-4), 73.4 (CH_2 Bn), 73.3 (C-3'), 72.7, 72.3 (CH_2 Bn), 71.2 (C-5 or C-5''), 71.1 (CH_2 Gro, C-5 or C-5''), 69.4 (CH_2 Gro), 69.2 (C-3''), 67.2, 66.6 (CH_2 Bn), 66.4 (C-5'), 52.1 (C-4'), 48.3 (C-2'), 22.8 (CH_3 NHAc), 16.4 (C-6'); HRMS $[M+Na]^+$ calcd for $C_{73}H_{78}N_2O_{19}Na$ 1309.50910, found 1309.50940.

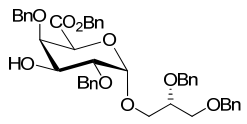


α-D-Galactopyranosyluronate-(1→3)-2-acetamido-4-amino-2,4,6-trideoxy-α-D-galactopyranosyl-(1→4)-α-D-galactopyranosyluronate-(1→3)-sn-glycerol (1). To a solution of 21 mg (16 µmol, 1 equiv.) of compound **28** in 1.5 mL DCM was added 8.0 mg TMSONa (71 µmol, 4.5 equiv.). The mixture was stirred for 2.5 hours, followed by the addition of 20 µL AcOH (355 µmol, 22.5 equiv.), evaporation and elution over a plug of silica (eluent: EtOAc, then EtOAc/MeOH/H_2O/AcOH 88/10/1/1). After removal of the eluent, the crude product was dissolved in 7 mL ^{t}BuOH/H_2O (5/2 v/v) and stirred under Argon atmosphere. A catalytic amount of palladium on activated charcoal and 125 µL of 1M aq. HCl were added and the mixture was allowed to stir for 2 days under hydrogen atmosphere. Filtration over Celite, gel filtration (HW-40, 0.15M Et_3NHOAc in H_2O) and subsequent lyophilisation afforded 5.2 mg of the pure title compound 1 (8.3 µmol, 52% over 2 steps). ^{1}H NMR (600 MHz, D_2O, HH-COSY, HSQC, HMBC, TOCSY, T= 290 K) δ 5.07 (d, J = 2.4 Hz, 1H, H-1''), 5.04 (d, J = 3.7 Hz, 1H, H-1), 4.98 (d, J = 4.0 Hz, 1H, H-1'), 4.79 (q, J = 6.7 Hz, 1H, H-5'), 4.37 (d, J = 2.7 Hz, 1H, H-4), 4.34 (s, 1H, H-5), 4.27 – 4.25 (m, 2H, H-4'', H-3'), 4.14 (s, 1H, H-5''), 4.11 (dd, J = 11.4, 4.0 Hz, 1H, H-2'), 4.07 (dd, J = 10.6, 3.1 Hz, 1H, H-3), 3.96 – 3.91 (m, 1H, CH Gro), 3.89 (dd, J = 10.6, 3.8 Hz, 1H, H-2), 3.85 (m, 2H, H-2'', H-3''), 3.84 – 3.78 (m, 2H, H-4', CH_2 Gro), 3.66 (dd, J = 11.8, 4.6 Hz, 1H, CH_2 Gro), 3.58 (dd, J = 11.8, 6.2 Hz, 1H, CH_2 Gro), 3.53 (dd, J = 10.6, 7.0 Hz, 1H, CH_2 Gro), 2.02 (s, 3H, CH_3 NHAc), 1.26 (d, J = 6.7 Hz, 3H, H-6'); ^{13}C NMR (151 MHz, D_2O, HH-COSY, HSQC, HMBC, TOCSY, T= 290 K) δ 175.6, 175.5, 174.7 (C=O), 99.6 (C-1), 99.1 (C-1'), 98.9 (C-1''), 80.0 (C-4), 73.3 (C-3'), 73.2 (C-5''), 71.5 (CH Gro), 71.3 (C-4'', C-5), 70.1 (C-3'', CH_2 Gro), 69.4 (C-3), 68.8 (C-2), 68.0 (C-2'), 63.7 (C-5'), 63.2 (CH_2 Gro), 53.5 (C-4'), 48.4 (C-2'), 23.0 (CH_3 NHAc), 16.3 (C-6'); ^{13}C-HMBC NMR (151 MHz, D_2O, T= 290 K) δ 99.6 ($J_{C1\text{-}H1}$ = 171.1 Hz, C-1), 99.1 ($J_{C1'\text{-}H1'}$ = 174.4 Hz, C-1'), 98.9 ($J_{C1''\text{-}H1''}$ = 171.1 Hz, C-1''); HRMS $[M+H]^+$ calcd for $C_{23}H_{39}N_2O_{18}$ 631.21924, found 631.21934.

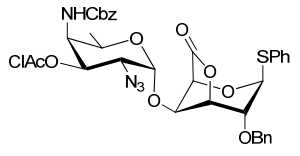


2,4-Di-*O*-benzyl-α-D-galactopyranosiduronyl-3,6-lactone-(1→3)-1,2-di-*O*-benzyl-sn-glycerol (29). 448 mg of lactone **4** was coupled to alcohol **9** according to the general procedure for glycosidations using Ph_2SO/Tf_2O, yielding 567 mg of the title compound **29** (928 µmol, α/β 10:1, 93%). Flash column chromatography gradient: EtOAc/PE (1/9 → 1/4). Rf 0.73 (EtOAc/Toluene, 1/5, v/v); IR (neat, cm^{-1}) 3030, 2868, 1798, 1454, 1057, 696; NMR assignment of the major anomer (α), ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.37 – 7.25 (m, 18H, H_{arom}), 7.19 (dd, J = 6.7, 2.7 Hz, 2H, H_{arom}), 4.86 – 4.83 (m, 2H, H-1, CH_2 Bn), 4.71 – 4.61 (m, 3H, H-3, CH_2 Bn), 4.56 (s, 2H, CH_2 Bn), 4.51 (d, J = 4.6 Hz, 2H, CH_2 Bn), 4.48 – 4.43 (m, 2H, H-4, CH_2 Bn), 4.14 (t, J = 1.6 Hz, 1H, H-5), 4.08 (dd, J = 10.7, 3.6 Hz, 1H, CH_2 Gro), 3.88 (dd, J = 5.0, 2.4 Hz, 1H, H-2), 3.86 – 3.81 (m, 1H, CH Gro), 3.67 (dd, J = 10.7, 6.9 Hz, 1H, CH_2 Gro), 3.54 (dd, J = 5.7, 4.7 Hz, 2H, CH_2 Gro); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 171.5 (C=O), 138.3, 137.8, 137.4, 136.6 (C_q Ph), 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.6, 127.5 (CH_{arom}), 99.2 (C-1), 80.1 (C-3), 77.1 (CH Gro), 75.4 (C-5), 74.3

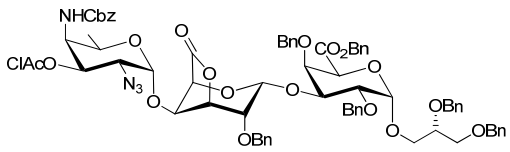
(C-2), 74.2 (CH_2 Bn), 73.2 (CH_2 Bn), 72.1 (CH_2 Bn), 71.8 (C-4), 71.3 (CH_2 Bn), 71.0 (CH_2 Gro), 69.4 (CH_2 Gro). HRMS $[M+Na]^+$ calcd for $C_{37}H_{38}O_8Na$ 633.24589, found 633.24698.



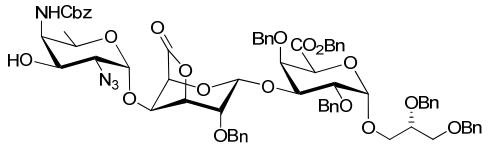
Benzyl 2,4-di-*O*-benzyl-α-D-galactopyranosyluronate-(1→3)-1,2-di-*O*-benzyl-sn-glycerol (30). To a solution of 831 mg lactone **29** (1.36 mmol, 1 equiv.) in 14 mL DCM was added 160 mg TMSONa (1.43 mmol, 1.05 equiv.). After 30 minutes TLC indicated complete consumption of the starting material and the mixture was evaporated, filtered through a plug of silica gel using EtOAc/Toluene/AcOH (20/79/1) as eluent. After removal of the eluent, the crude acid was dissolved in 14 mL DMF. Next, 154 µL BnBr (1.28 mmol, 1.1 equiv) and 418 mg Cs_2CO_3 (1.28 mmol, 1.1 equiv.) were added and the reaction was stirred for 2 hours. The mixture was diluted with EtOAc and washed with H_2O and brine. Drying over $MgSO_4$, filtration and concentration under reduced pressure gave the crude product, which was purified by flash column chromatography using EtOAc/PE (1/4 → 1/3) to give ester **30** (729 mg, 1.01 mmol, 75% over 2 steps). Rf 0.52 (EtOAc/Toluene, 1/3, v/v); $[\alpha]_D^{22}$ +44 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3030, 2870, 1759, 1454, 1107, 696; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.36 – 7.15 (m, 25H, H_{arom}), 5.09 – 4.95 (m, 3H, CH_2 Bn, H-1), 4.71 (d, J = 11.7 Hz, 1H, CH_2 Bn), 4.65 – 4.55 (m, 4H, CH_2 Bn), 4.49 (s, 3H, CH_2 Bn, H-5), 4.45 (d, J = 11.7 Hz, 1H, CH_2 Bn), 4.22 (dd, J = 3.1, 1.5 Hz, 1H, H-4), 4.11 – 4.05 (m, 1H, H-3), 3.88 – 3.80 (m, 2H, H-2, CH_2 Gro), 3.77 – 3.70 (m, 1H CH Gro), 3.58 (d, J = 5.0 Hz, 2H CH_2 Gro), 3.53 (dd, J = 10.4, 5.5 Hz, 1H, CH_2 Gro), 2.28 (d, J = 4.6 Hz, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 168.5 (C=O), 138.4, 138.3, 138.1, 138.0, 135.0 (C_q Ph), 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 127.9, 127.6, 127.5 (CH_{arom}), 97.4 (C-1), 78.0 (C-4), 76.7 (CH Gro), 76.6 (C-2), 74.9 (CH_2 Bn), 73.4 (CH_2 Bn), 72.6 (CH_2 Bn), 71.9 (CH_2 Bn), 70.4 (C-5), 69.7 (CH_2 Bn, C-3), 68.4 (CH_2 Gro), 66.9 (CH_2 COOBn); HRMS $[M+Na]^+$ calcd for $C_{44}H_{46}O_9Na$ 741.30340, found 741.30352.



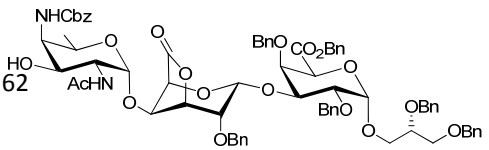
4-(*N*-Benzyloxycarbonyl)-amino-2-azido-3-*O*-chloroacetyl-2,4,6-trideoxy-D-galactopyranosyl-(1→4)-phenyl 2-*O*-benzyl-1-thio-β-D-galactopyranosidurono-3,6-lactone (31). A mixture of 441 mg hemiacetal **7** (1.11 mmol, 1 equiv), 559 mg diphenyl sulfoxide (2.76 mmol, 2.5 equiv.) and 330 mg tri-*tert*-butylpyrimidine (1.33 mmol, 1.2 equiv.) was coevaporated with toluene and stirred over activated molsieves (3Å) for 30 min in 10 mL DCM. The mixture was cooled to -60°C before 202 µL triflic acid anhydride (1.22 mmol, 1.1 equiv.) was added. The mixture was allowed to warm to -40°C before a mixture (dried over 3Å molsieves) of 792 mg acceptor **5** (2.21 mmol, 2 equiv.), 330 mg tri-*tert*-butylpyrimidine (1.33 mmol, 1.2 equiv.) in 2 mL DCM was added. Stirring was continued and the reaction mixture was allowed to warm to +4°C overnight. The reaction mixture was quenched with 769 µL triethylamine (5.53 mmol, 5.0 equiv.), diluted with DCM and washed with sat. aq. $NaHCO_3$. The aqueous phase was extracted with DCM and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by size exclusion chromatography (DCM/MeOH 1/1 v/v) and flash column chromatography (eluent: EtOAc/PE 1/4 → 3/7) gave the title compound **31** as a white foam (690 mg, 933 µmol, 84%). Rf 0.68 (EtOAc/PE, 2/3, v/v); $[\alpha]_D^{22}$ -38 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2112, 1805, 1717, 1514, 1042; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.48 – 7.27 (m, 15H, H_{arom}), 5.42 (s, 1H, H-1), 5.24 – 5.12 (m, 2H, H-3', CH_2 Cbz), 5.08 – 4.96 (m, 3H, CH_2 Cbz, NH, H-1'), 4.89 (dd, J = 4.9, 1.5 Hz, 1H, H-3), 4.69 (d, J = 11.8 Hz, 1H, CH_2 Bn), 4.63 – 4.54 (m, 2H, CH_2 Bn, H-4), 4.30 (d, J = 4.8 Hz, 1H, H-2), 4.27 – 4.20 (m, 2H, H-5', H-4'), 4.11 (s, 1H, H-5), 3.98 – 3.83 (m, 2H, CH_2 ClAc), 3.48 (dd, J = 11.1, 3.8 Hz, 1H, H-2'), 1.17 (d, J = 6.4 Hz, 3H, H-6'). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 171.7, 166.5 (C=O), 156.6 (C=O Cbz), 136.3, 136.1, 133.2 (C_q Ph), 132.8, 129.0, 128.8, 128.6, 128.4, 128.3, 128.1, 128.0 (CH_{arom}), 97.9 (C-1'), 85.7 (C-1), 79.1 (C-3), 78.4 (C-2), 76.6 (C-4), 73.2 (CH_2 Bn), 71.6 (C-3'), 70.2 (C-5), 67.3 (CH_2 Cbz), 65.7 (C-5'), 57.1 (C-2'), 52.2 (C-4'), 40.5 (CH_2 ClAc), 16.3 (C-6'); HRMS $[M+Na]^+$ calcd for $C_{35}H_{35}ClN_4O_{10}SNa$ 761.16546, found 761.16560.



4-(*N*-Benzyloxycarbonyl)-amino-2-azido-3-*O*-chloroacetyl-2,4,6-trideoxy-D-galactopyranosyl-(1→4)-phenyl 2-*O*-benzyl-α-D-galactopyranosiduronyl-3,6-lactone-(1→4)-benzyl 2,4-di-*O*-benzyl-α-D-galactopyranosyluronate-(1→3)-1,2-di-*O*-benzyl-sn-glycerol (32): Lactone **31** (538 mg) was coupled to alcohol **30** (2 equiv. instead of 1.5 equiv) according to the general procedure for glycosylations using Ph_2SO/Tf_2O. The reaction was quenched with triethylamine (5 equiv.) and the title compound **32** was obtained in 60% yield (590 mg, 438 µmol) after size exclusion chromatography (DCM/MeOH 1/1 v/v). Rf 0.58 (EtOAc/Toluene, 1/3, v/v); $[\alpha]_D^{22}$ +101 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2110, 1803, 1761, 1720, 1454, 1043; ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.43 – 7.01 (m, 35H, H_{arom}), 5.17 – 5.14 (m, 2H, H-3'', CH_2 Bn), 5.08 – 4.94 (m, 6H, CH_2 Bn, H-1', H-1, NH), 4.89 – 4.80 (m, 3H, H-1'', CH_2 Bn), 4.73 – 4.69 (m, 2H, H-4', H-3'), 4.66 – 4.59 (m, 2H, CH_2 Bn), 4.57 – 4.48 (m, 4H, CH_2 Bn), 4.46 (s, 1H, H-5), 4.41 – 4.33 (m, 3H, H-3, CH_2 Bn), 4.25 – 4.21 (m, 3H, H-4, H-5', H-4''), 4.18 (q, J = 6.6 Hz, 1H, H-5''), 3.99 (dd, J = 10.1, 3.5 Hz, 1H, H-2), 3.89 (d, J = 4.6 Hz, 2H, CH_2 ClAc), 3.88 – 3.80 (m, 2H, CH_2 Gro, H-2'), 3.80 – 3.74 (m, 1H, CH Gro), 3.65 – 3.57 (m, 3H, CH_2 Gro), 3.42 (dd, J = 11.2, 3.8 Hz, 1H, H-2''), 1.14 (d, J = 6.4 Hz, 3H, H-6''); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 170.7, 168.2, 166.5 (C=O), 156.5 (CH_2 Cbz), 138.6, 138.5, 138.2, 137.9, 137.1, 136.0, 134.8 (C_q Ph), 128.7, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.6, 127.5, 127.4, 127.2, 126.9 (CH_{arom}), 98.4 (C-1), 97.7 (C-1''), 94.9 (C-1'), 80.5 (C-3'), 76.5 (CH Gro), 75.7 (C-4), 75.5 (C-4'), 75.4 (C-3), 74.9 (C-2'), 74.7 (CH_2 Bn), 74.2 (CH_2 Bn), 73.9 (C-2), 73.3 (2 CH_2 Bn), 71.9 (CH_2 Bn), 71.5 (C-3''), 71.2 (C-5'), 70.1 (C-5), 69.7 (CH_2 Gro), 68.6 (CH_2 Gro), 67.3 (CH_2), 67.1 (CH_2), 65.4 (C-5''), 56.9 (C-2''), 52.1 (C-4''), 40.5 (CH_2 ClAc), 16.2 (C-6''); HRMS $[M+Na]^+$ calcd for $C_{73}H_{75}ClN_4O_{19}Na$ 1369.46062, found 1369.46158.

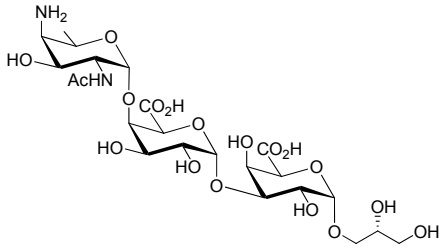


4-(*N*-Benzyloxycarbonyl)-amino-2-azido-2,4,6-trideoxy-D-galactopyranosyl-(1→4)-phenyl 2-*O*-benzyl-α-D-galactopyranosiduronyl-3,6-lactone-(1→4)-benzyl 2,4-di-*O*-benzyl-α-D-galactopyranosyluronate-(1→3)-1,2-di-*O*-benzyl-sn-glycerol (33). A solution of 76 mg compound **32** (56 µmol, 1 equiv.), 36 µL pyridine (451 µmol, 8 equiv.) and 13 mg (169 µmol, 3 equiv.) thiourea in 1 mL EtOH was stirred at 65ºC for 6 hours. The mixture was concentrated under reduced pressure, diluted with EtOAc and washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography using EtOAc/PE (7/13→9/11) gave 44 mg (34 µmol, 62%) of the title compound **33**. Rf 0.48 (EtOAc/PE, 3/7, v/v); $[\alpha]_D^{22}$ +97 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3400, 2874, 2110, 1081, 1717, 1705, 1028; ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.45 – 6.99 (m, 35H, H_{arom}), 5.12 (s, 2H, CH_2 Bn), 5.08 – 4.98 (m, 4H, NH, CH_2 Bn, H-1'), 4.96 (d, J = 3.6 Hz, 1H, H-1), 4.87 – 4.78 (m, 3H, CH_2, H-1''), 4.71 (dd, J = 4.9, 1.8 Hz, 1H, H-3'), 4.69 (s, 1H, H-4'), 4.67 – 4.59 (m, 2H, CH_2 Bn), 4.58 – 4.48 (m, 4H, CH_2 Bn), 4.46 (s, 1H, H-5), 4.42 – 4.32 (m, 3H, CH_2 Bn, H-3), 4.23 (s, 2H, H-4, H-5'), 4.09 (m, 2H, H-3'', H-5''), 4.03 – 3.96 (m, 2H, H-4'', H-2), 3.85 (dd, J = 10.4, 4.5 Hz, 1H, CH_2 Gro), 3.81 (dd, J = 4.6, 2.5 Hz, 1H, H-2'), 3.79 – 3.73 (m, 1H, CH Gro), 3.65 – 3.55 (m, 3H, CH Gro), 3.14 (dd, J = 10.7, 3.8 Hz, 1H, H-2''), 1.13 (d, J = 6.4 Hz, 3H, H-6''); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 171.1, 168.3 (C=O), 158.0 (CH_2 Cbz), 138.6, 138.5, 138.2, 137.9, 137.2, 135.7, 134.9 (C_q Ph), 128.7, 128.6, 128.5, 128.5, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.40, 127.2, 126.9 (CH_{arom}), 98.5 (C-1), 98.4 (C-1''), 94.9 (C-1'), 80.6 (C-3'), 76.6 (CH Gro), 75.9 (C-4'), 75.8 (C-4), 75.5 (C-3), 74.9 (C-2'), 74.7, 74.2 (CH_2 Bn), 73.9 (C-2), 73.4, 73.3, 71.9 (CH_2 Bn), 71.4 (C-5'), 70.1 (C-5), 69.7, 68.6 (CH_2 Gro), 68.4 (C-3''), 67.6, 67.1 (CH_2), 65.8 (C-5''), 59.9 (C-2''), 55.5 (C-4''), 16.4 (C-6''); HRMS $[M+Na]^+$ calcd for $C_{71}H_{74}N_4O_{18}Na$ 1293.48903, found 1293.48964.

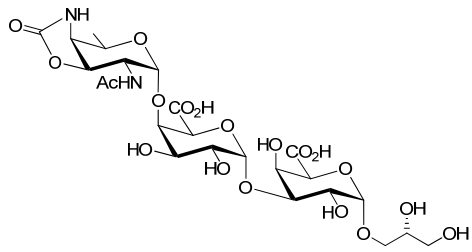


4-(*N*-Benzyloxycarbonyl)-amino-2-acetamido-2,4,6-trideoxy-D-galactopyranosyl-(1→4)-phenyl 2-

***O*-benzyl-α-D-galactopyranosiduronyl-3,6-lactone-(1→4)-benzyl 2,4-di-*O*-benzyl-α-D-galactopyranosyluronate-(1→3)-1,2-di-*O*-benzyl-sn-glycerol (34).** To an ice cooled solution of 281 mg azide **33** (221 µmol) in 5 mL pyridine was added 5 mL of freshly distilled thiolacetic acid. The mixture was stirred at room temperature for 2.5 hours, concentrated under reduced pressure and coevaporated with toluene. Flash column chromatography using EtOAc/PE (7/3→1/0) afforded the title acetamide (188 mg, 146 µmol, 66%). Rf 0.30 (EtOAc/PE, 3/1, v/v); $[\alpha]_D^{22}$ +83 (c 0.8, CH_2Cl_2); IR (neat, cm^{-1}) 3300, 2924, 1801, 1759, 1717, 1661, 1540, 1028; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.51 – 6.91 (m, 35H, H_{arom}), 5.67 (d, J = 8.4 Hz, 1H, NH), 5.40 (d, J = 9.7 Hz, 1H, NH), 5.18 – 4.99 (m, 5H, CH_2 Bn, H-1'), 4.95 (d, J = 3.5 Hz, 1H, H-1), 4.91 (d, J = 3.7 Hz, 1H, H-1''), 4.84 – 4.80 (m, 2H, CH_2 Bn), 4.69 (dd, J = 4.9, 1.5 Hz, 1H, H-3'), 4.66 (s, 1H, H-4'), 4.62 (m, 2H, CH_2 Bn), 4.59 – 4.48 (m, 4H, CH_2 Bn), 4.45 (s, 1H, H-5), 4.42 – 4.31 (m, 3H, CH_2 Bn, H-3), 4.22 (s, 1H, H-4), 4.12 (s, 1H, H-5'), 4.06 – 3.96 (m, 4H, H-2'', H-4'', H-5'', H-2), 3.86 – 3.73 (m, 4H, CH_2 Gro, H-3'', H-2', CH Gro), 3.65 – 3.56 (m, 3H, CH_2 Gro), 1.92 (s, 3H, CH_3 NHAc), 1.12 (d, J = 6.2 Hz, 3H, H-6''); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 171.5, 168.2 (C=O), 157.7 (CH_2 Cbz), 138.4, 138.3, 138.2, 137.8, 137.1, 136.0, 134.8 (C_q Ph), 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.6, 127.4, 127.3, 127.0, 126.7 (CH_{arom}), 98.4 (C-1), 97.5 (C-1''), 94.9 (C-1'), 80.9 (C-3'), 76.4 (CH Gro), 75.7 (C-4), 75.6 (C-3), 74.7, 74.6 (C-2', C-4', CH_2 Bn), 74.0 (CH_2 Bn), 73.7 (C-2), 73.4, 73.1, 71.7 (CH_2 Bn), 71.3 (C-5'), 70.0 (C-5), 69.6, 68.4 (CH_2 Gro), 67.7 (C-3''), 67.0, 66.9 (CH_2), 66.1 (C-5''), 55.2 (C-4''), 50.2 (C-2''), 22.9 (CH_3 NHAc), 16.4 (C-6''); HRMS $[M+Na]^+$ calcd for $C_{73}H_{78}N_2O_{19}Na$ 1309.50910, found 1309.50986.

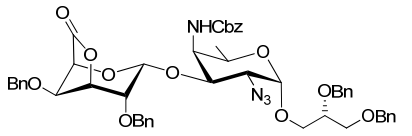


2-Acetamido-4-amino-2,4,6-trideoxy-α-D-galactopyranosyl-(1→4)-α-D-galactopyranosyluronate-(1→3)-α-D-galactopyranosyluronate-(1→3)-sn-glycerol (2). 54 mg (42 µmol, 1 equiv.) of compound **34** was dissolved in 7 mL ^{t}BuOH/H_2O (5/2 v/v) and stirred under Argon atmosphere. A catalytic amount of palladium on activated charcoal and 105 µL of 1M aq. HCl were added and the mixture was allowed to stir for 2 days under hydrogen atmosphere. Following filtration over Celite and removal of the eluent, the crude product was allowed to stir in a 0.04 M aq. HCl for two more days. Next, the mixture was concentrated in vacuo and purified by ion exchange column chromatography (30 mM NaOAc (aq) / 100 mM NaOH (aq) → 80 mM NaOAc (aq) / 100 mM NaOH (aq)) and filtration (HW-40, 0.15M Et_3NHOAc in H_2O) to afford 10 mg of the pure title compound **2** (16 µmol, 38%) after lyophilisation. ^{1}H NMR (600 MHz, D_2O, HH-COSY, HSQC, HMBC, TOCSY, T= 293 K) δ 5.32 (d, J = 3.8 Hz, 1H, H-1'), 5.08 (d, J = 3.8 Hz, 1H, H-1), 5.03 (d, J = 3.8 Hz, 1H, H-1''), 4.85 (q, J = 6.5 Hz, 1H, H-5''), 4.68 (s, 1H, H-5'), 4.60 (d, J = 1.9 Hz, 1H, H-4), 4.44 (d, J = 2.4 Hz, 1H, H-4'), 4.39 (s, 1H, H-5), 4.27 (dd, J = 11.3, 4.3 Hz, 1H, H-3''), 4.21 – 4.18 (m, 2H, H-3', H-3), 4.09 (dd, J = 11.3, 3.8 Hz, 1H, H-2''), 4.04 – 3.95 (m, 3H, H-2, CH Gro, H-2'), 3.88 (dd, J = 10.6, 3.6 Hz, 1H, CH_2 Gro), 3.74 (dd, J = 11.8, 4.5 Hz, 1H, CH_2 Gro), 3.70 (d, J = 3.7 Hz, 1H, H-4''), 3.66 (dd, J = 11.8, 6.2 Hz, 1H, CH_2 Gro), 3.57 (dd, J = 10.5, 7.1 Hz, 1H, CH_2 Gro), 2.17 (s, 3H, CH_3 NHAc), 1.33 (d, J = 6.7 Hz, 3H); ^{13}C NMR (151 MHz, D_2O, HH-COSY, HSQC, HMBC, TOCSY, T= 293 K) δ 176.1, 176.0, 175.3 (C=O), 99.7 (C-1'', C-1), 96.9 (C-1'), 81.0 (C-4'), 76.2 (C-3), 72.1, 72.0 (C-5, C-5'), 71.5 (CH Gro), 70.0 (CH_2 Gro), 69.4 (C-3'), 68.8 (C-2'), 68.5 (C-4), 67.5 (C-2), 65.5 (C-3''), 64.2 (C-5), 63.2 (CH_2 Gro), 56.2 (C-4''), 50.2 (C-2''), 23.2 (CH_3 NHAc), 16.3 (C-6''); ^{13}C-HMBC NMR (151 MHz, D_2O, T= 293 K) δ 99.7 ($J_{C1''-H1''}$ = 173.31 Hz, J_{C1-H1} = 170.6 Hz, C-1'', C-1), 96.9 ($J_{C1'-H1'}$ = 170.3 Hz, C-1'); HRMS $[M+H]^+$ calcd for $C_{23}H_{39}N_2O_{18}$ 631.21924, found 631.21928.

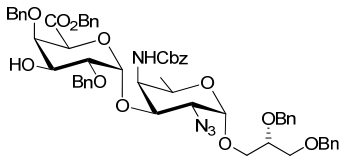


(1,3-Oxazolidino-2-one) [5,4-c]-2-acetamido-4-amino-2,4,6-trideoxy-α-D-galactopyranosyl-(1→4)-α-D-galactopyranosyluronate-(1→3)-α-D-galactopyranosyluronate-(1→3)-sn-glycerol (35). To a solution of 40.0 mg (31 µmol, 1 equiv.) of compound **34** in 1.5 mL DCM was added 14 mg

TMSONa (124 µmol, 4.0 equiv.). The mixture was stirred for one hour, followed by evaporation of the solvent and elution of the crude product over a plug of silica (eluent: EtOAc, then EtOAc/MeOH/H_2O/AcOH 93/5/1/1, then EtOAc/MeOH/H_2O/AcOH 88/10/1/1). After removal of the eluent, the crude product was dissolved in 5 mL $^tBuOH/H_2O$ (4/1 v/v) and stirred under argon atmosphere. A catalytic amount of palladium on activated charcoal and 190 µL of 1M aq. HCl were added and the mixture was allowed to stir overnight under hydrogen atmosphere. Filtration over Celite, followed by gel filtration (HW-40, 0.15M Et_3NHOAc in H_2O) and subsequent lyophilisation afforded 8.95 mg of the title compound **35** (11.8 µmol, 38% over 2 steps). ^1H NMR (600 MHz, D_2O, HH-COSY, HSQC, T= 306 K) δ 5.22 (d, *J* = 3.8 Hz, 1H, H-1'), 4.99 (d, *J* = 3.8 Hz, 1H, H-1), 4.95 (d, *J* = 3.8 Hz, 1H, H-1''), 4.79 (dd, *J* = 9.0, 7.2 Hz, 1H, H-3''), 4.70 – 4.61 (m, 2H, H-5', H-5''), 4.52 (d, *J* = 2.0 Hz, 1H, H-4), 4.40 – 4.33 (m, 2H, H-5, H-4'), 4.16 – 4.06 (m, 4H, H-4'', H-3', H-2'', H-3), 3.94 – 3.86 (m, 3H, H-2, CH Gro, H-2'), 3.78 (dd, *J* = 10.5, 3.7 Hz, 1H, CH_2 Gro), 3.64 (dd, *J* = 11.8, 4.6 Hz, 1H, CH_2 Gro), 3.56 (dd, *J* = 11.8, 6.2 Hz, 1H, CH_2 Gro), 3.49 (dd, *J* = 10.6, 7.0 Hz, 1H, CH_2 Gro), 3.19 (q, *J* = 7.3 Hz, 10H, CH_2 Et_3NHOAc), 2.07 (s, 3H, CH_3 NHAc), 1.28-1.24 (m, 18H, H-6'', CH_3 Et_3NHOAc). ^{13}C NMR (151 MHz, D_2O, HH-COSY, HSQC, T= 306 K) δ 175.5, 175.3, 174.8, 162.7 (C=O), 99.8 (C-1), 99.2 (C-1''), 96.9 (C-1'), 80.9 (C-4'), 76.7 (C-3''), 76.1 (C-3), 71.9, 71.8 (C-5, C-5'), 71.6 (CH Gro), 70.1 (CH_2 Gro), 69.5 (C-3'), 68.8 (C-2'), 68.4 (C-4), 67.5 (C-2), 63.3 (CH_2 Gro), 63.1 (C-5''), 56.9 (C-4''), 50.7 (C-2''), 47.6 (CH_2 Et_3NHOAc), 23.2 (CH_3 NHAc), 17.0 (C-6''), 9.2 (CH_3 Et_3NHOAc). ^{13}C-HMBC NMR (151 MHz, D_2O, T= 306 K) δ 99.9 ($J_{C1\text{-}H1}$ = 170.9 Hz, C-1), 98.8 ($J_{C1''\text{-}H1''}$ = 172.5 Hz, C-1''), 97.1 ($J_{C1'\text{-}H1'}$ = 172.0 Hz, C-1'); HRMS $[M+H]^+$ calcd for $C_{24}H_{37}N_2O_{19}$ 657.19850, found 657.19866.

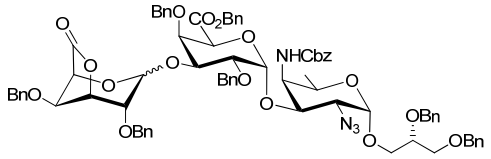


2,4-Di-*O*-benzyl-α-D-galactopyranosiduronyl-3,6-lactone-(1→3)-4-(*N*-benzyloxycarbonyl)-amino-2-azido-2,4,6-trideoxy-α-D-galactopyranosyl-(1→3)-1,2-di-*O*-benzyl-sn-glycerol (36). 257 mg of lactone 20 was coupled to 220 mg alcohol 20 (382 µmol, 0.66 equiv.) according to the general procedure for glycosidations using Ph_2SO/Tf_2O, yielding 244 mg of the title compound **36** (267 µmol, 70%) after size exclusion chromatography (DCM/MeOH 1/1 v/v) and flash column chromatography (eluent: EtOAc/PE 1/3 → 3/7). Rf 0.68 (EtOAc/Toluene, 1/4, v/v); $[\alpha]_D^{22}$ +106 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2872, 2110, 1798, 1717, 1454, 1026, 696; ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC); δ 7.55 – 7.11 (m, 25H, H_{arom}), 5.14 (d, J = 2.3 Hz, 1H, H-1'), 5.13 – 4.99 (m, 3H, NH, CH_2 Cbz), 4.82 (d, J = 3.8 Hz, 1H, H-1), 4.79 (d, J = 11.7 Hz, 1H, CH_2 Bn), 4.73 – 4.61 (m, 3H, CH_2 Bn, H-3'), 4.58 – 4.47 (m, 5H, CH_2 Bn, H-4'), 4.29 – 4.17 (m, 3H, CH_2 Bn, H-5', H-3), 4.10 (dd, J = 5.0, 2.3 Hz, 1H, H-2'), 4.01 (dd, J = 9.6, 2.9 Hz, 1H, H-4), 3.94 (q, J = 6.1 Hz, 1H, H-5), 3.82 – 3.73 (m, 2H, CH Gro, CH_2 Gro), 3.62 (d, J = 4.5 Hz, 2H, CH_2 Gro), 3.60 – 3.53 (m, 1H, CH_2 Gro), 3.15 (dd, J = 10.8, 3.8 Hz, 1H, H-2), 1.05 (d, J = 6.4 Hz, 3H, H-6). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 171.9 (C=O), 156.6 (C=O Cbz), 138.3, 138.0, 136.8, 135.8 (C_q Ph), 128.7, 128.5, 128.5, 128.3, 128.0, 127.7, 127.6, 127.4 (CH_{arom}), 98.2 (C-1), 95.6 (C-1'), 80.4 (C-3'), 76.7 (CH Gro), 75.8 (C-4'), 75.1 (C-2'), 74.3 (CH_2 Bn), 73.5 (C-3), 73.4 (CH_2 Bn), 72.0 (CH_2 Bn, C-5'), 71.4 (CH_2 Bn), 69.3 (CH_2 Bn), 67.9 (CH_2 Bn), 67.0 (CH_2 Cbz), 64.2 (C-5), 58.3 (C-2), 51.8 (C-4), 16.4 (C-6); HRMS $[M+Na]^+$ calcd for $C_{51}H_{54}N_4O_{12}Na$ 937.36304, found 937.36340.

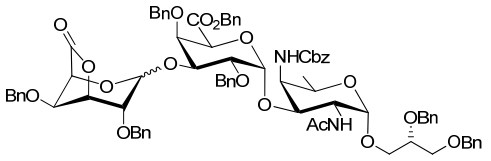


Benzyl 2,4-di-*O*-benzyl-α-D-galactopyranosyluronate-(1→3)-4-(*N*-benzyloxycarbonyl)-amino-2-azido-2,4,6-trideoxy-α-D-galactopyranosyl-(1→3)-1,2-di-*O*-benzyl-sn-glycerol (37). To a solution of 88 mg of lactone **36** (96 µmmol, 1 equiv.) in 2 mL DCM was added 13 mg TMSONa (115 µmol, 1.2 equiv.). After 50 minutes TLC indicated complete consumption of the starting material and the reaction was quenched with 28 µL AcOH (481 µmol, 5.0 equiv), after which the mixture was coevaporated with toluene and subsequently dissolved in 2 mL DMF. Next, 17 µL BnBr (144 µmol, 1.5 equiv) and 39 mg Cs_2CO_3 (120 µmol, 1.25 equiv.) were added and the reaction was stirred until TLC analysis showed complete consumption of the starting material. The mixture was diluted with EtOAc and washed with H_2O and brine. Drying over $MgSO_4$, filtration and concentration

under reduced pressure gave the crude product. Purification by flash column chromatography using EtOAc/toluene (1/4) gave the title compound **37** in pure form (86 mg, 84 µmol, 88% over 2 steps). Rf 0.46 (EtOAc/Toluene, 1/3, v/v); $[\alpha]_D^{22}$ +122 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2880, 2104, 1761, 1719, 1094, 1026, 696; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.37 – 7.07 (m, 30H, H_{arom}), 5.59 (d, J = 3.0 Hz, 1H, H-1'), 5.11 – 4.96 (m, 4H, NH, CH_2 Bn), 4.88 (d, J = 3.8 Hz, 1H, H1), 4.75 (d, J = 12.2 Hz, 1H, CH_2 Bn), 4.70 – 4.58 (m, 5H, H-5', CH_2 Bn), 4.55 – 4.45 (m, 2H, CH_2 Bn), 4.40 (m, 2H, CH_2 Bn), 4.28 – 4.20 (m, 4H, H-4', H-4, H-3, H-3'), 3.97 – 3.90 (m, 2H, H-2', H-5), 3.81 – 3.70 (m, 2H, CH_2 Gro, CH Gro), 3.61 – 3.53 (m, 3H, CH_2 Gro), 3.30 (dd, J = 10.5, 3.9 Hz, 1H, H-2), 2.18 (d, J = 4.0 Hz, 1H, OH), 1.03 (d, J = 6.4 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 168.1 (C=O COOBn), 156.8 (C=O Cbz), 138.3, 138.1, 138.0, 137.8, 135.9, 134.9 (C_q Ph), 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 127.4 (CH_{arom}), 97.7 (C-1), 92.3 (C-1'), 77.6 (C-4'), 76.8 (CH Gro), 74.8 (CH_2 Bn), 74.8 (C-2'), 73.3 (CH_2 Bn), 72.1, 72.0 (CH_2 Bn), 70.6 (C-5'), 69.5 (C-3), 69.3 (CH_2 Gro), 69.1 (C-3'), 67.9 (CH_2 Gro), 66.9, 66.9 (CH_2 Cbz, CH_2 COOBn), 65.0 (C-5), 59.2 (C-2), 50.8 (C-4), 16.2 (C-6); HRMS $[M+Na]^+$ calcd for $C_{58}H_{62}N_4O_{13}Na$ 1045.42056, found 1045.42095.

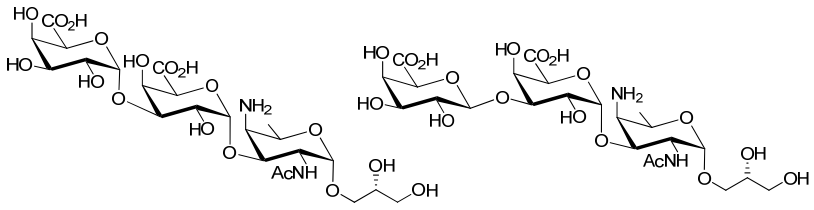


2,4-Di-*O*-benzyl-α/β-D-galactopyranosiduronyl-3,6-lactone-(1→3)-benzyl 2,4-di-*O*-benzyl-α-D-galactopyranosyluronate-(1→3)-4-(*N*-benzyloxycarbonyl)-amino-2-azido-2,4,6-trideoxy-α-D-galactopyranosyl-(1→3)-1,2-di-*O*-benzyl-sn-glycerol (38). 62 mg of lactone **4** (139 µmol) was coupled to 95 mg alcohol **37** (93 µmol, 0.67 equiv.) according to the general procedure for glycosidations using Ph_2SO/Tf_2O, yielding 99 mg of the title epimers (73 µmol, 78%, α/β 5:4) after size exclusion chromatography (DCM/MeOH 1/1 v/v) and flash column chromatography (eluent: EtOAc/PE 1/4 → 3/7). Rf 0.42 (EtOAc/PE, 2/3, v/v); IR (neat, cm^{-1}) 2870, 2106, 1801, 1761, 1717, 1497, 1454, 1028, 696; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.42 – 6.81 (m, 72H, H_{arom}), 5.67 (d, J = 2.9 Hz, 0.8H, H-1'β), 5.49 (d, J = 2.5 Hz, 1H, H-1'α), 5.45 (s, 0.8H, H-1''β), 5.14 – 4.58 (m, 22H), 4.57 – 4.35 (m, 14.4H), 4.35 – 4.00 (m, 12.4H), 4.00 – 3.84 (m, 3.4H), 3.85 – 3.69 (m, 4.6H), 3.58 – 3.56 (m, 5.4H), 3.37 (dd, J = 10.6, 3.9 Hz, 0.8H, H-2β), 3.31 (dd, J = 10.6, 3.9 Hz, 1H, H-2α), 1.03 – 0.98 (m, 5.4H, H-6α, H-6β). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 173.5, 171.6, 168.0, 167.9, 156.7, 139.3, 138.5, 138.3, 138.1, 137.8, 137.3, 136.9, 136.8, 136.7, 136.2, 136.0, 135.1, 134.8, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 127.1, 126.9, 99.9 (C-1''β), 97.7 (C-1α, C-1β), 95.2 (C-1''α), 93.4 (C-1'α), 91.9 (C-1'β), 80.1, 79.0, 78.5, 77.2, 76.9, 76.4, 75.9, 75.8, 75.7, 75.4, 75.1, 74.7, 74.3, 74.0, 73.4, 73.0, 72.7, 72.4, 72.2, 72.1, 71.7, 71.4, 71.3, 71.2, 70.6, 70.3, 69.8 (C-3β), 69.6 (C-3α), 69.5, 68.1, 68.0, 67.1, 66.8, 66.7, 66.6, 65.1 (C-5β, C-5α), 59.5 (C-2β), 59.1 (C-2α), 50.8 (C-4α), 50.7 (C-4β), 16.3 (C-6α), 16.2 (C-6β). HRMS $[M+Na]^+$ calcd for $C_{78}H_{80}N_4O_{18}Na$ 1383.53598, found 1383.53760.



2,4-di-*O*-benzyl-α/β-D-galactopyranosiduronyl-3,6-lactone-(1→3)-benzyl 2,4-di-*O*-benzyl-α-D-galactopyranosyluronate-(1→3)-2-acetamido-4-(*N*-benzyloxycarbonyl)-amino-2,4,6-trideoxy-α-D-galactopyranosyl-(1→3)-1,2-di-*O*-benzyl-sn-glycerol (39). To an ice cooled solution of 61 mg epimeric azides **38** (45 µmol) in 1.5 mL pyridine was added 1.5 mL of freshly distilled thiolacetic acid. The mixture was stirred at room temperature for 3 hours, concentrated under reduced pressure and coevaporated with toluene. Flash column chromatography using EtOAc/PE (2/3) afforded title epimers **39** (25 mg, 18 µmol, α/β 1:1, 40%). Rf 0.67 (EtOAc/PE, 3/2, v/v); IR (neat, cm^{-1}) 2930, 1802, 1718, 1668, 1497, 1454, 1027, 731, 695; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.48 – 6.84 (m, 80H, H_{arom}), 5.73 (dd, *J* = 15.8, 9.2 Hz, 2H, NH), 5.45 (s, 1H, H-1''β), 5.29 (d, J = 2.9 Hz, 1H, H-1'α or H-1'β), 5.22 – 4.99 (m, 8H), 4.95 (d, J = 12.4 Hz, 1H), 4.87 (m, 2H), 4.79 (d, J = 12.6 Hz, 1H), 4.75 – 4.26 (m, 34H), 4.26 – 4.07 (m, 7H), 4.05 – 3.65 (m, 13H), 3.62 – 3.39 (m, 6H), 1.72 (s, 3H, CH_3 NHAc), 1.71 (s, 3H, CH_3 NHAc),

1.06 (m, 6H, H-6α, H-6β); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 173.7, 171.7, 170.2, 170.1, 168.4, 168.2, 156.8, 139.3, 138.7, 138.2, 138.1, 138.0, 137.9, 137.8, 137.4, 136.9, 136.8, 136.4, 135.7, 135.0, 134.8, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.0, 126.9, 99.8 (C-1''β), 98.1 (C-1α or C1-β), 97.9 (C-1α or C1-β), 97.6 (C-1'α or C1'-β), 95.5 (C-1''α), 95.4 (C-1'α or C1'-β), 80.0, 79.2, 77.3, 77.1, 76.8, 76.6, 76.0, 75.7, 75.5, 75.4, 75.0, 74.5, 74.2, 73.8, 73.7, 73.6, 73.5, 73.1, 72.4, 72.0, 71.9, 71.7, 71.6, 71.4, 71.2, 71.0, 70.6, 69.4, 69.3, 68.2, 67.1, 66.8, 66.5, 66.4, 65.7 (C-5α or C-5β), 65.5 (C-5α or C-5β), 52.5 (C-4α or C-4β), 52.1 (C-4α or C-4β), 48.8 (C-2α or C-2β), 48.5 (C-2α or C-2β), 22.9 (2x CH_3 NHAc), 16.5 (C-6α, C-6β); HRMS $[M+Na]^+$ calcd for $C_{80}H_{84}N_2O_{19}Na$ 1399.55605 $C_{29}H_{35}N_3O_7S$, found 1399.55602.



α-D-Galactopyranosyl uronate-(1→3)-α-D-galactopyranosyl uronate-(1→3)-2-acetamido-4-amino-2,4,6-trideoxy-α-D-galactopyranosyl-(1→3)-sn-glycerol (3a) and β-D-galactopyranosyluronate-(1→3)-α-D-galactopyranosyluronate-(1→3)-2-acetamido-4-amino-2,4,6-trideoxy-α-D-galactopyranosyl-(1→3)-sn-glycerol (3b). To a solution of 35 mg (25μmol, 1 equiv.) of epimeric mixture **39** in 1.5 mL DCM was added 11.4 mg TMSONa (102 μmol, 4 equiv.). The mixture was stirred for 1 hour, followed by evaporation and elution over a plug of silica (eluent: EtOAc, then EtOAc/MeOH/H_2O/AcOH 88/10/1/1). After removal of the eluent, the crude product was dissolved in ^{t}BuOH/H_2O (4/1 v/v) and stirred under Argon atmosphere. A catalytic amount of palladium on activated charcoal and 170 μL of 1M aq. HCl were added and the mixture was allowed to stir for 2 days under hydrogen atmosphere. Filtration over Celite, gel filtration (HW-40, 0.15M Et_3NHOAc in H_2O) and ion exchange column chromatography (30 mM NaOAc (aq) / 100 mM NaOH (aq) → 80 mM NaOAc (aq) / 100 mM NaOH (aq)) yielded 2 fractions that were both subjected to another gel filtration step (HW-40, 0.15M Et_3NHOAc in H_2O) to give the 2 title epimers in pure form after lyophilisation. (α-epimer 3a: 4.4 mg, 7.0 μmol 28% over 2 steps, β-epimer 3b: 2.7 mg, 4.3 μmol, 17% over 2 steps). α-epimer 3a: ^{1}H NMR (600 MHz, D_2O, HH-COSY, HSQC, HMBC, TOCSY, T= 298 K) δ 5.17 (d, J = 3.1 Hz, 1H, H-1''), 5.07 (d, J = 2.6 Hz, 1H, H-1'), 4.89 (d, J = 3.8 Hz, 1H, H-1), 4.66 (s, 1H, H-5'), 4.46 (s, 1H, H-4'), 4.35 (q, J = 6.4 Hz, 1H, H-5), 4.31 – 4.25 (m, 2H, H-4'', H-3), 4.19 – 4.13 (m, 2H, H-2, H-5''), 3.99 – 3.93 (m, 3H, H-3', H-3'', H-2'), 3.93 – 3.89 (m, 1H, CH Gro), 3.87 (dd, J = 10.5, 3.2 Hz, 1H, H-2''), 3.82 (d, J = 4.0 Hz, 1H, H-4), 3.77 (dd, J = 10.6, 3.5 Hz, 1H, CH_2 Gro), 3.65 (dd, J = 11.7, 4.7 Hz, 1H, CH_2 Gro), 3.58 (dd, J = 11.7, 6.2 Hz, 1H, CH_2 Gro), 3.46 (dd, J = 10.5, 6.6 Hz, 1H, CH_2 Gro), 3.18 (q, *J* = 7.3 Hz, 1.2H, CH_2 Et_3NHOAc), 1.97 (s, 3H, CH_3 NHAc), 1.29 (d, J = 6.7 Hz, 3H, H-6), 1.26 (t, *J* = 7.3 Hz, 1.9H, CH_3 Et_3NHOAc); ^{13}C NMR (151 MHz, D_2O, HH-COSY, HSQC, HMBC, TOCSY, T= 298 K) δ 176.3, 175.5, 175.4 (C=O), 99.7 (C-1'), 98.3 (C-1), 97.4 (C-1''), 76.3 (C-3'), 73.8(C-3), 73.0 (C-5''), 72.6 (C-5), 71.6 (C-4''), 71.4 (CH Gro), 70.4 (C-3''), 70.0 (CH_2 Gro), 68.8 (C-2''), 68.5 (C-4'), 66.7 (C-2'), 63.4 (C-5), 63.2 (CH_2 Gro), 53.7 (C-4), 48.7 (C-2), 47.6 (CH_2 Et_3NHOAc), 22.7 (CH_3 NHAc), 16.5 (C-6), 9.2 (CH_3 Et_3NHOAc); ^{13}C-HMBC NMR (151 MHz, D_2O, T= 298 K) δ 99.7 ($J_{C1'-H1'}$ = 170.3 Hz, C-1'), 98.3 (J_{C1-H1} = 173.6 Hz, C-1), 97.4 ($J_{C1''-H1''}$ = 170.3 Hz,C-1''); HRMS $[M+H]^+$ calcd for $C_{23}H_{39}N_2O_{18}$ 631.21924, found 631.21927. β-epimer 3b: ^{1}H NMR (600 MHz, D_2O, HH-COSY, HSQC, HMBC, TOCSY, T= 298 K) δ 5.09 (d, J = 3.6 Hz, 1H, H-1'), 4.90 (d, J = 3.8 Hz, 1H, H-1), 4.61 (d, J = 7.8 Hz, 1H, H-1''), 4.58 (s, 1H, H-4'), 4.36 (q, J = 6.5 Hz, 1H, H-5), 4.29 (dd, J = 11.3, 4.4 Hz, 1H, H-3), 4.20 – 4.15 (m, 2H, H-4'', H-2), 4.14 (s, 1H, H-5'), 4.06 (s, 1H, H-5''), 4.05 – 3.98 (m, 2H, H-2', H-3'), 3.91 (dd, J = 9.6, 5.3 Hz, 1H, CH Gro), 3.84 (d, J = 3.7 Hz, 1H, H-4), 3.77 (dd, J = 10.6, 3.6 Hz, 1H, CH_2 Gro), 3.70 (dd, J = 10.0, 3.5 Hz, 1H, H-3''), 3.65 (dd, J = 11.7, 4.7 Hz, 1H, CH_2 Gro), 3.63 – 3.56 (m, 2H, CH_2 Gro, H-2''), 3.46 (dd, J = 10.6, 6.6 Hz, 1H, CH_2 Gro), 1.97 (s, 3H, CH_3 NHAc), 1.89 (s, 1H, CH_3 AcOH), 1.31 (t, J = 6.7 Hz, 3H, H-6); ^{13}C NMR (151 MHz, D_2O, HH-COSY, HSQC, HMBC, TOCSY, T= 298 K) δ 176.1, 176.0, 175.5 (C=O), 104.7 (C-1''), 99.0 (C-1'), 98.3 (C-1), 80.3 (C-3'), 76.5 (C-5''), 73.6 (C-3''), 73.3 (C-3), 73.2 (C-5'), 71.5 (C-2''), 71.4 (CH Gro), 71.2 (C-4''), 70.7

(C-4'), 70.0 (CH Gro), 67.5 (C-2'), 63.2 (C-5), 53.7 (C-4), 48.7 (C-2), 22.7 (CH_3 NHAc), 16.5 (C-6); ^{13}C-HMBC NMR (151 MHz, D_2O, T= 298 K) δ 104.7 ($J_{C1''\text{-}H1''}$ = 161.5 Hz, C-1''), 99.0 ($J_{C1'\text{-}H1'}$ = 170.0 Hz, C-1'), 98.3 ($J_{C1\text{-}H1}$ = 173.5 Hz, C-1); HRMS $[M+H]^+$ calcd for $C_{23}H_{39}N_2O_{18}$ 631.21924, found 631.21923.

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Chapter 4

On the Reactivity and Selectivity of Galacturonic Acid Lactones[1]

Introduction

Galacturonic acid and derivatives thereof are found in various naturally occurring polysaccharides. Due to the synthetic challenge they present and their interesting biological profile, several of these polysaccharides have been subject of synthetic studies, such as pectin[2] and the zwitterionic polysaccharide Sp1 (addressed in the previous chapter).[3,4] The selection of the best suitable glycosylation partners depends heavily on the desired stereochemical outcome of the glycosylation reaction combined with the intrinsic reactivity of both reacting species. Conformational restriction of glycosyl donors has been used to influence both the stereoselectivity and reactivity of the donors at hand.[5] Crich and co-workers have shown that the installment of a 4,6-*O*-benzylidene type protecting group on a mannosyl donor can give rise to a mannosylating agent which reacts with excellent stereoselectivity to provide β-mannosides.[6] The use of conformationally armed glycosides has been reported by various groups.[7] For instance, Bols and co-workers have shown that placing multiple bulky silyl ethers on the hydroxyl groups of a glycosyl donor can lead to a conformational flip of the pyranosyl ring to avoid gauche interactions of the bulky protecting group.[8] This provides "axially rich" donor glycosides, which are significantly more reactive

than their non-flipped counterparts. These "super-armed" donors have extended the relative reactivity spectrum beyond the realm of classical armed donors. Galacturonic acid-3,6-lactones have already been introduced as versatile building blocks that can be used effectively in oligosaccharide synthesis.[4,9] The 3,6-lactone bridge forces these galacturonic acids in a $^1C_4$-chair conformation, which has a major impact on their reactivity, both as a donor and as an acceptor. Because of the $^1C_4$ conformation, the galactopyranosyl C4-OH, generally regarded to be a poor nucleophile,[10] is positioned in an accessible equatorial position and it therefore is an apt nucleophile. It was also found that S-phenyl galacturonic acid-3,6-lactones, equipped with a non-participating C2-benzyl ether, are readily activated at low temperature with the diphenylsulfoxide (Ph_2SO)-trifluoromethanesulfonic anhydride (Tf_2O) couple,[11] to provide a powerful glycosylating species that reacts with excellent stereoselectivity to give the α-galacturonic linkage. To put the glycosylation behavior of galacturonic acid-3,6-lactone thioglycoside donors in perspective this chapter present a study of their reactivity and stereoselectivity in comparison with the reactivity of related galactose and galacturonic acid building blocks.

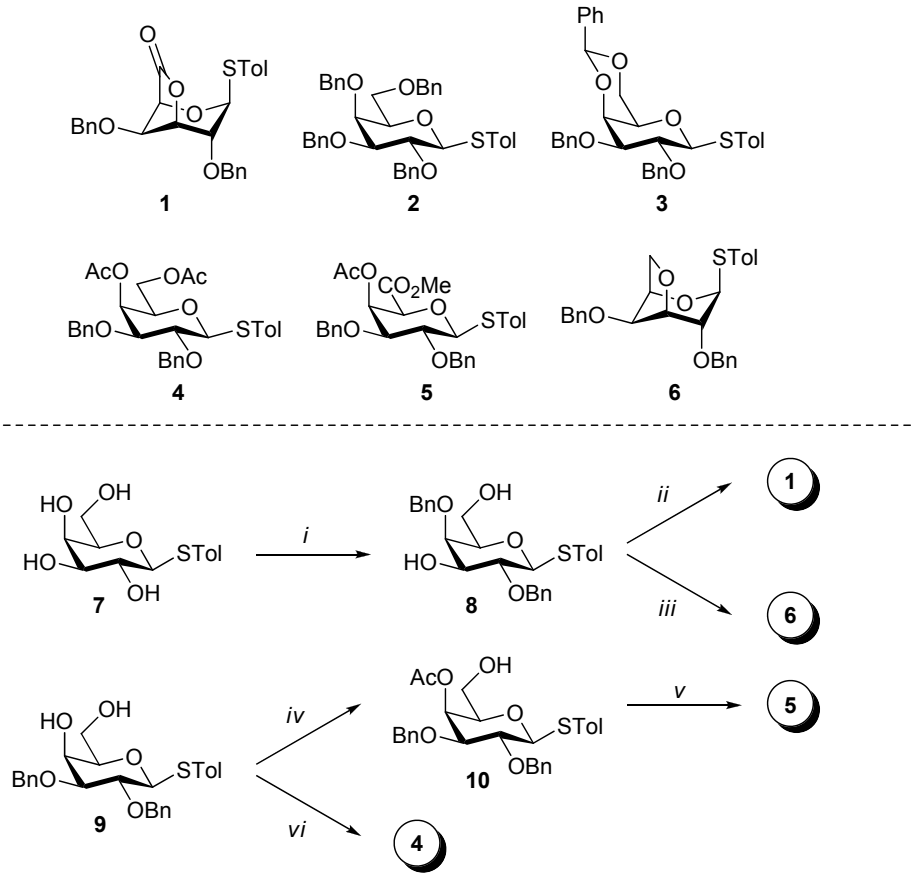
Results and discussion

The set of building blocks used in this study is depicted in Scheme 1, and includes galacturonic acid-3,6-lactone thioglycoside **1**, per-benzylated thiogalactoside **2**,[12] 4,6-benzylidene thiogalactoside **3**,[12] 4,6-di-*O*-acetyl thiogalactoside **4**, galacturonic acid thioglycoside **5** and 3,6-anhydro thiogalactoside **6**. The latter compound has been taken along in the study to investigate the influence of the 3,6-bridge, and the resulting conformational flip, on the reactivity of these donors.

The synthesis of the donors **1**, **4**, **5** and **6** is depicted in Scheme 1. Galacturonic acid lactone **1** was constructed from tolyl 1-thio-β-D-galactopyranoside **7** by regioselective silylation of the C6-OH and C3-OH and subsequent benzylation of the remaining hydroxyls and desilylation to afford diol **8**. 2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO)/[bis(acetoxy)iodo]benzene (BAIB)-mediated[13] oxidation and *in situ* lactone formation yielded thioglycoside **1**. Tosylation of the C6-OH in diol **8** and treatment of the resulting tosylate with sodium hydride led to 3,6-anhydro thiogalactoside **6**. From 2,3-di-*O*-benzylthiogalactoside **9** donors **4** and **5** were accessed through acetylation of both hydroxyl functions (→ **4**) or a silylation, acetylation, desilylation, oxidation sequence (→ **5**).

First, the relative reactivity of the set of donors was mapped. To gain more insight into the relative reactivity of glycosyl donors, Ley,[14] Wong,[12] and Bols[15] have determined the reactivity of a wide variety of thioglycosides in a series of competition experiments leading to an extensive relative reactivity value (RRV) scale. Recently, the determination of the relative reactivity of mannuronic[16] and glucuronic acid thioglycosyl donors was reported.[17] In contrast to the common perception that the C-5 carboxylic acid ester is a strongly electron withdrawing ("disarming") substituent, it was found that in the β-*manno*-series the C-5 carboxylate (in combination with a 4-*O*-acetyl group) was in fact less disarming than the

Scheme 1



Syntheses of the studied thiogalactosyl donors. *Reagents and conditions:* (*i*) (1) TBDMSCl, imidazole, DMF; (2) BnBr, NaH, DMF, 0°C; (3) TBAF, THF, (66% over 3 steps); (*ii*) TEMPO, BAIB, DCM, H_2O, 51%; (*iii*) (1) TsCl, pyridine; (2) NaH, DMF (40% over 2 steps); *(iv)* (1) TBDMSCl, pyridine, then Ac_2O; (2) $Et_3N{\cdot}3HF$, THF (86% over 3 steps); *(v)* (1) TEMPO, BAIB, DCM, H_2O; (2) MeI, K_2CO_3, DMF (45% over 2 steps); *(vi)* Ac_2O, pyridine (81%).

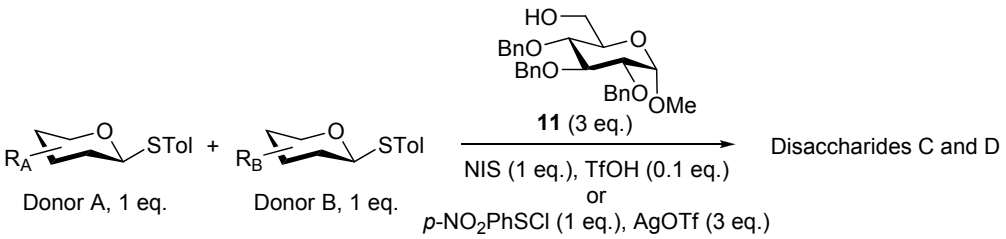
4,6-*O*-benzylidene functionality. In the β-*gluco* series the effect of the carboxylate was more in line with expectations, although the disarming nature proved to be less severe than often presumed. In the vast majority of competition experiments to date thioglycoside donors have been combined with the *N*-iodosuccinimide (NIS)-triflic acid (TfOH) activator system. Therefore the initial focus was set on probing the relative reactivity of the set of thiogalactosyl donors **1**-**6** under the aegis of this activator system. However, during the course of the investigation it became apparent that galacturonic acid lactone **1** was inert to this activator. Therefore, the donors were also studied in a set of competition experiments using *para*-nitrophenylsulfenyl triflate (*p*-NO_2PhSOTf),[18] generated from *para*-nitrophenylsulfenyl chloride (*p*-NO_2PhSCl) and silver triflate (AgOTf), as a thiophilic promoter system. The reason for the reluctance of donor **1** to react with NIS/TfOH remains unclear.

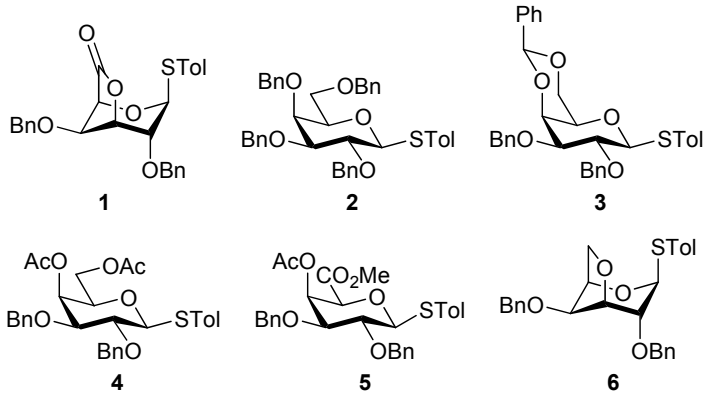
This lack of reactivity is in contrast with a recent study reported by Furukawa *et al.*,[19] who investigated glucuronic acid-3,6-lactone donors in combination with this activator. They reported that thiophenyl 2,4-di-*O*-acetyl glucuronic acid-3,6-lactone donors are reactive glucuronylating species when activated with NIS/TfOH, and that its 2,4-di-*O*-benzyl counterpart was too reactive to be used as a donor.

Table 1 compiles the results of the competition experiments. In both the NIS/TfOH and *p*-NO_2PhSOTf mediated glycosylation the two donors compete for a limited amount of activator in the presence of excess of nucleophile (methyl tri-*O*-benzyl-α-D-glucopyranoside **11**). From the series of NIS/TfOH mediated experiments the following relative reactivities appear. Perbenzylated donor **2** is twice as reactive as benzylidene donor **3** (Entry 1). This result corresponds to the relative reactivities determined by Wong and co-workers (**2**: 17000, **3**: 7180).12 The disarming effect of the 4,6-benzylidene group in **3** is less than the disarming effect of the two acetyl groups in **4** as revealed in Entry 2. Notably, in the *gluco* and *manno* series the 4,6-benzylidene group proved to be more deactivating than two acetyl groups at the C4- and C6-hydroxyls. These results can be explained by taking into account that the benzylidene group in galactosyl donor **3** poses less strain on the pyranosyl ring when adopting a flattened structure to accommodate the developing positive charge at the anomeric center in an oxocarbenium ion or oxocarbenium ion like intermediate. Furthermore, in the *cis*-decalin system in **3**, the C-6 substituent is positioned in a *gg* position, which is less disarming than the *tg* orientation of the C-6 substituent in the *gluco* and *manno*-4,6-benzylidene donors.[20] Entries 3 and 4 show that the C-5 carboxylic acid ester has a significant disarming effect on the reactivity of the donors studied,[21] and galacturonic acid **5** is the least reactive donor in the NIS/TfOH series. 3,6-Anhydro thiogalactosyl donor **6** is slightly more reactive than perbenzylated thiogalactoside **2**, and presents the most reactive donor of the series. This is in line with previous studies on the glycosylation behavior of 3,6-anhydrogalactosyl orthoester donors, which were found to be more reactive than comparable orthoesters of glycosides in a normal conformation.[22] It is also of interest to note that Bols and co-workers have reported that forcing a galactosyl donor in an “axial rich” conformation, by positioning three bulky *tert*-butyldimethylsilyl ethers at C2, C3 and C4, leads to a more reactive donor.8 A possible explanation for the fact that the reactivity of anhydro thiogalactosyl donor **6** is only marginally higher than the reactivity of perbenzylated thiogalactoside **2** can be that the conformational restriction in **6** prohibits the through space stabilization of the developing oxocarbenium ion character by the substituents.[23]

The series of competition reactions using the *p*-NO_2PhSCl/AgOTf reveals the same trends as seen with the NIS/TfOH-promoter,[24] albeit with significantly less pronounced reactivity differences. Thus, the reactivity order is 3,6-anhydro donor **6** > perbenzyl donor **2** > benzylidene donor **3** > diacetyl donor **4** > galacturonic acid donor **5**. The competition experiments with the galacturonic acid-3,6-lactone **1** indicate that this donor is less reactive than galacturonic acid **5**, which contrasts the perception of the high reactivity of these donors. This finding is also surprising in light of the “axial rich” nature of this compound as compared to galacturonic acid **5**. The explanation forwarded to account for the small

Table 1



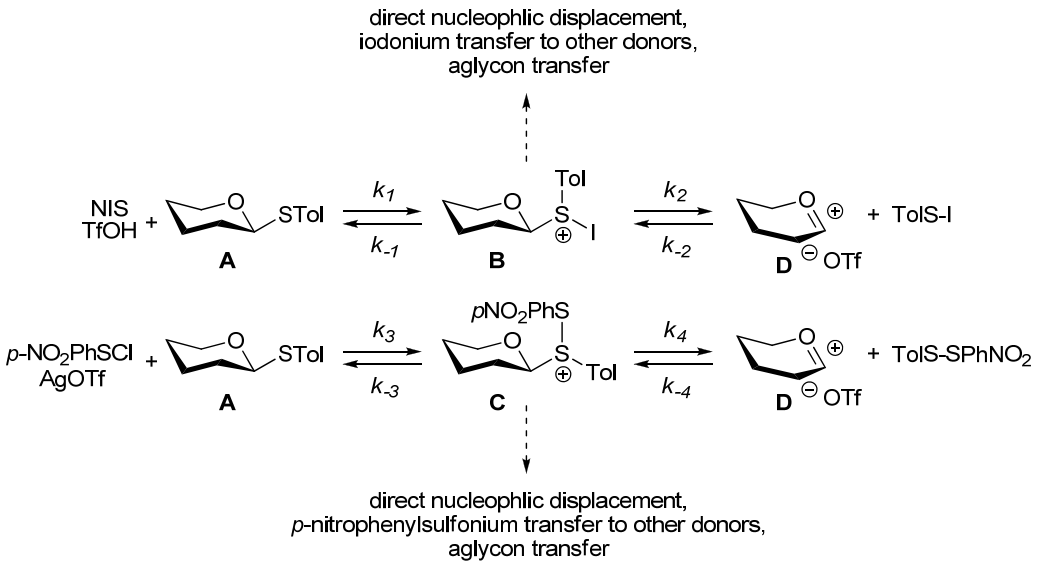


Entry	Donor		Product ratio[a] (Disaccharide C/ Disaccharide D) and yield (%)		Disaccharide[c]	
	A	B	NIS/TfOH[b]	*p*-NO_2PhSCl/AgOTf[b]	C	D
1	2	3	2.2 : 1 (70%)	1.8 : 1 (87%)	13	14
2	4	3	1 : 5.2 (95%)	1 : 1.1 (85%)	15	14
3	3	5	16 : 1 (86%)	4.8 : 1 (80%)	14	16
4	4	5	11 : 1 (86%)	1.3 : 1 (81%)	15	16
5	2	6	1 : 1.3 (quant.)	1 : 1.2 (quant.)	13	17
6	3	6	1 : 2.5 (99%)	1 : 2.2 (quant.)	14	17
7	1	6	*lactone **1** inert*	1 : 2.4 (quant.)	12	17
8	1	5	*lactone **1** inert*	1: 2.4 (78%)	12	16

(a) Product ratio was determined by integration of diagnostic ^{1}H NMR signals of the four possible disaccharides after size exclusion chromatography; (b) In CH_2Cl_2, -40 ^oC to rT; (c) Disaccharide structures can be found in the experimental section.

increase in reactivity of 3,6-anhydro thiogalactoside **6**, with respect to thiogalactoside **2** (*vide supra*), can also be valid here. An explanation that accounts for the down-tuned reactivity differences found with the *p*-NO_2PhSCl/AgOTf system and the relatively low reactivity of the lactone donor can also be found in the differences in the rate constants involved in the activation of thioglycosides with the two different activator systems (Scheme 2). In case reversion of the charged thioglycosyl donor (**C** in Scheme 2) into the parent thioglycoside (**A**) and the activator (indicated with rate constant k_{-3}) for the *p*-NO_2PhSOTf system is slower than the corresponding reversion with the NIS/TfOH system (species B and rate constant k_{-1}), the overall competition for the activator will be determined less by the relative ease of oxocarbenium ion (**D**) formation (k_2 and k_4).[25] In other words the first step of the activation, the attack of the anomeric thiogroup on the electrophile, plays a relatively larger role in the *p*-NO_2PhSOTf activated system and leads to the attenuated reactivity differences of the donors studied.

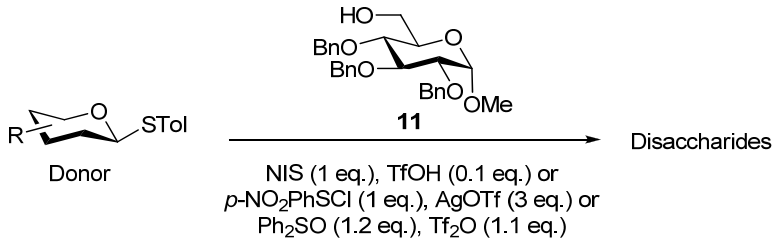
Scheme 2



Possible reaction pathways upon activation of thioglycosides using *p*-NO_2PhSOTf and NIS/TfOH.

Next, the stereoselectivity of the set of donors was evaluated under the two different activation conditions and with glucoside **11** as a nucleophile. Table 2 records the outcomes of these experiments. It is readily apparent from this table that most condensations proceed with very little to no selectivity, the most important exception being

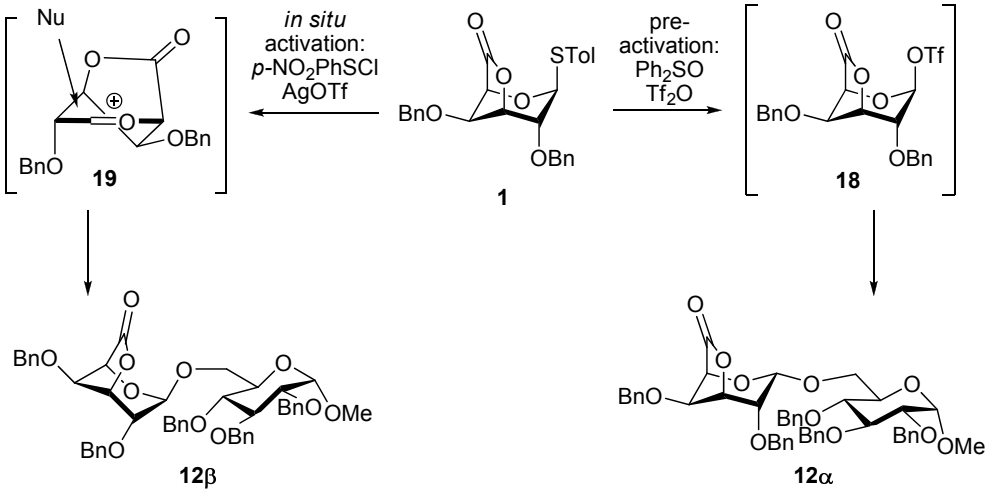
Table 2



Entry	Donor	Product ratio[a] (α/β) and yield (%)			Disaccharide
		NIS/TfOH[b]	*p*-NO_2PhSCl/AgOTf[b]	Ph_2SO/Tf_2O[c]	
1	1	*lactone **1** inert*	0 : 1 (73%)	10 : 1 (69%)	12
2	2	1 : 1.1 (99%)	1 : 1.6 (quant.)	n.d.	13
3	3	1 : 1.2 (70%)	1 : 1.8 (82%)	n.d.	14
4	4	1 : 1.2 (76%)	1 : 1.8 (94%)	n.d.	15
5	5	1 : 1.3 (77%)	1 : 3.4 (84%)	n.d.	16
6	6	1.2 : 1 (65%)	1 : 5.3 (quant.)	5.2 : 1 (70%)	17

(a) Anomeric ratios were determined by integration of ^{1}H NMR signals of the disaccharides. (b) In CH_2Cl_2, -40 °C to RT. (c) In the presence of 2,4,6-tri-*tert*-butyl pyrimidine (TTBP) (2.5 equiv) in CH_2Cl_2, -50 °C, then acceptor **11**, warming to rT.

the *p*-NO_2PhSOTf mediated condensations of the bridged galacturonic acid lactone **1** and its non-oxidized counterpart 3,6-anhydro thiogalactoside **6**. The condensations of these donors and alcohol **11** proceed with very high (in the case of lactone **1**) or high (for the anhydrogalactoside **6**) stereoselectivity to provide the β-linked disaccharides. The former result stands in sharp contrast to previous findings that galacturonic acid lactones such as **1** are highly α-selective glycosyl donors using the Ph_2SO/Tf_2O pre-activation protocol. It is now well appreciated that (pre-)activation of thioglycosides with electrophiles featuring a triflate counterion can produce intermediate anomeric triflates. These species can be displaced in an S_N2-like process leading to the coupled product with inversion of configuration at the anomeric center (with regard to the intermediate anomeric triflate). The pre-activation of donor **1** was therefore studied with the Ph_2SO/Tf_2O couple in a low-temperature NMR experiment. This experiment revealed that, with this activator system, donor **1** was rapidly transformed at -80 °C into β-triflate **12** (see Scheme 3 and Figure 1), which proved to be stable up to -10 °C. Having identified triflate **12** as a possible intermediate in the



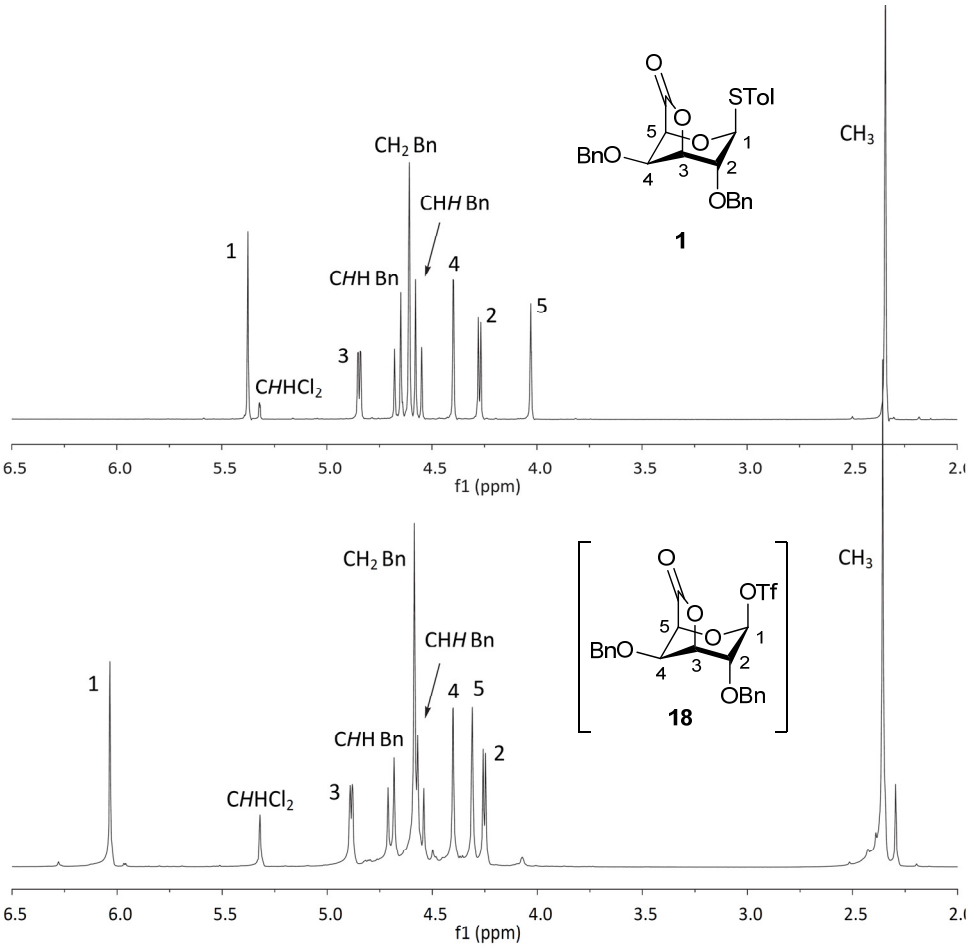
A rationale for the formation of the dimers **12α** and **12β** using a pre-activation and an *in situ* activation protocol.

condensations of the galacturonic acid lactone donors, the contrasting stereochemical outcome of the condensations under Ph_2SO/Tf_2O pre-activation and *in situ* activation with *p*-NO_2PhSCl and AgOTf can be rationalized (Scheme 3). Pre-activation of donor **1** leads to an intermediate triflate, which is substituted in a concerted fashion to provide the α-linked product. When donor **1** is activated in the presence of a reactive glycosyl acceptor such as **11**, the nucleophile can intercept the intermediate oxocarbenium ion **13**, which will adopt a structure that is close to a $^3H_4$-half chair, because of the geometrical constraints imposed by the bridging lactone ring. Nucleophilic attack on this reactive species will occur preferentially from the diastereotopic face leading to the product *via* a chair-like transition state, *i.e.* the β-face. Notably, a similar stereochemical result has been reported for the condensation of acceptor **11** with pentenyl 2,4-di-*O*-benzyl-3,6-anhydroglucopyranose.[26] To examine whether pre-activation of 3,6-anhydro galactopyranoside **6** can also lead to the α-linked disaccharide upon condensation with acceptor **11**, donor **6** was treated with Ph_2SO/Tf_2O at -80 ^oC after which glucoside **11** was added. As revealed in Table 2, entry 6, this condensation protocol indeed led to the predominant formation of the α-linked product, showing that 3,6-anhydro galactopyranoside **6** and lactone **1** behave in a stereochemical analogous manner.

Conclusion

In summary, the reactivity and stereoselectivity of a galacturonic acid-3,6-lactone donor has been investigated in relation to a set of galactosyl donors using two different activator systems, NIS/TfOH and *p*-NO_2PhSCl/AgOTf respectively. The mode of action not only affects the stereoselectivity of the glycosylation reactions reported here, but also has a significant effect on the relative reactivities of the studied galactosyl donors. The use of a *p*-NO_2PhSCl/AgOTf *in situ* activation protocol leads to attenuated reactivity differences with

Figure 1



Part of the ^{1}H-NMR spectrum of donor **1** obtained before and after treatment with Ph_2SO/Tf_2O in DCM-d_2 at -80 ^{o}C. The anomeric configuration of **18** has been deduced from the $^{1}J_{C1\text{-}H1}$ coupling constant (189 Hz).[27]

respect to the NIS/TfOH system. In the establishment of the relative reactivity of galacturonic acid-3,6-lactone donor **1**, only the *p*-NO_2PhSCl/AgOTf could be used because lactone **1** proved completely inert to activation with NIS/TfOH. Using the former activator, lactonedonor **1** proved to be less reactive than the galacturonic acid donor **5**, revealing that in this case the relatively axial rich conformation is not beneficial for reactivity. The use of the different thiophilic activator systems also led to greatly varying stereochemical outcomes. With the bridged lactone and anhydro donors **1** and **6** both the α- and β-linked products can be selectively accessed depending on the activator system and the timing of the activation. Pre-activation of these donors with Ph_2SO/Tf_2O provides α-selective glycosylations, presumably through the intermediacy of an axial β-triflate, where an *in situ* activation

protocol with *p*-NO_2PhSCl/AgOTf leads to the corresponding β-products, through a direct substitution of an oxocarbenium ion like intermediate.

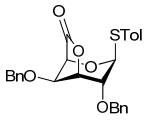
Experimental section

General Procedures: All chemicals were used as received. Trifluoromethanesulfonic anhydride (Tf_2O) was distilled from P_2O_5 and stored in a Schlenk flask. TLC analysis was conducted on silica gel-coated aluminum TLC sheets (Merck, silica gel 60, F_{245}). Compounds were visualized by UV absorption (245 nm), by spraying with 20% H_2SO_4 in ethanol or with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ 25 g/L, $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ 10 g/L, 10% H_2SO_4 in H_2O followed by charring at ~140 °C. Flash chromatography was performed on silica gel (Screening Devices, 40-63 µm 60Å, www.screeningdevices.com) using technical grade, distilled solvents. NMR spectra were recorded on a Bruker AV400. For solutions in $CDCl_3$ chemical shifts (δ) are reported relative to tetramethylsilane (^1H) or $CDCl_3$ (^{13}C). Peak assignments were made based on HH-COSY and HSQC measurements. Optical rotation was measured using a Propol automatic polarimeter. The IR absorbance was recorded using a Shimadzu FTIR-83000 spectrometer. Mass analysis was performed using a PE/SCIEX API 165 with an Electrospray Interface (Perkin-Elmer).

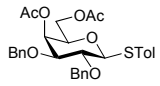
General procedure for competitive and non-competitive NIS/TfOH-promoted glycosylation: The donor(s) (~0.1 mmol, 1 equiv each) and the acceptor (3 equiv) were mixed in a round bottom flask and co-evaporated twice with toluene. Freshly distilled DCM (donor concentration 0.05 M) and 3 Å activated molecular sieves were added and the mixture was stirred under argon for 30 minutes at room temperature. NIS (1 equiv) was added and the mixture was cooled to -40 °C. TfOH (0.1 equiv, 0.1 M stock solution in distilled DCM) was added and the mixture was allowed to warm to 0 °C in about 3 hours. Triethylamine (0.1 mL) was added and the mixture was diluted with EtOAc, washed with sat. aq. $Na_2S_2O_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Size exclusion chromatography on Sephadex LH-20 (DCM/MeOH, 1/1, v/v) enabled isolation of the disaccharide products and recovery of the monosaccharide rest fraction.

General procedure for competitive and non-competitive AgOTf/*p*-NO_2PhSCl-promoted glycosylation: A suspension of the donor(s) (~0.11 mmol, 1 equiv each), acceptor **11** (1.5-3 equiv), 72 mg silver triflate (0.33 mmol, ~3 equiv) and 3Å molecular sieves in anhydrous DCM (1 mL) was stirred, with the exclusion of light, for 10 min at room temperature under Ar before it was cooled to -40 °C. A solution of *p*-nitrobenzenesulfenyl chloride (95% purity, ~0.11 mmol, 1 equiv) in anhydrous DCM (0.5 mL) was dropped into the above suspension at -40 °C and the mixture was allowed to warm to 0 °C in about 3 hours. Triethylamine (0.2 mL) was added and the suspension was diluted with DCM and filtered through celite. Size exclusion chromatography on Sephadex LH-20 (eluent DCM/MeOH, 1/1, v/v) enabled isolation of the disaccharide products and recovery of a monosaccharide rest fraction.

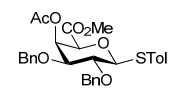
General procedure for Ph_2SO/Tf_2O-promoted glycosylation: A solution of the donor (~0.11 mmol, 1 equiv), diphenyl sulfoxide (1.2 equiv.) and tri-*tert*-butylpyrimidine (2.5 equiv.) in DCM (0.05M) was stirred over activated 3Å molecular sieves for 30 min. The mixture was cooled to -60°C before triflic acid anhydride (1.1 equiv.) was added. The mixture was allowed to warm up to -50°C in 15 minutes followed by addition of acceptor **11** (2 equiv.) in DCM (0.15M). The mixture was allowed to warm up to 0 °C in about 3 hours. Triethylamine (0.5 mL) was added and the mixture was diluted with DCM, washed once with sat. aq. $NaHCO_3$ and the aqueous layer was extracted with DCM. The combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Size exclusion chromatography on Sephadex LH-20 (eluent DCM/MeOH, 1/1, v/v) enabled isolation of the disaccharide products and recovery of a monosaccharide rest fraction.



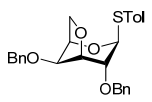
***p*-Tolyl 2,4-*O*-di-benzyl-1-thio-β-D-galactopyranosidurono-6,3-lactone (1):** To a vigorously stirred mixture of 5.39 g compound **8** (11.5 mmol, 1 equiv) in 54 mL DCM/H_20 (2/1 v/v) was added 358 mg TEMPO (2.3 mmol, 0.2 equiv.) and 9.28 g iodobenzene diacetate (28.8 mmol, 2.5 equiv.). After complete conversion the reaction was quenched by the addition of 10% aq. $Na_2S_2O_3$ and sat aq. $NaHCO_3$. The mixture was extracted twice with EtOAc and the combined layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by column chromatography yielded 2.72 g of the title compound **1** as an oil (5.88 mmol, 51%). R_f 0.46 (toluene); IR (neat, cm^{-1}) 2952, 1802, 1495, 1455, 1154, 1101, 813, 741, 699, 510; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.40 – 7.24 (m, 12H, H_{arom}), 7.11 (d, *J* = 8.0 Hz, 2H, H_{arom}), 5.34 (s, 1H, H-1), 4.80 (dd, *J* = 4.7, 1.3 Hz, 1H, H-3), 4.63 (d, *J* = 11.8 Hz, 1H, CH_2 Bn), 4.58 (2s, 2H, CH_2 Bn), 4.53 (d, *J* = 11.8 Hz, 1H, CH_2 Bn), 4.39 (d, J = 1.2 Hz, 1H, H-4), 4.25 (d, *J* = 4.7 Hz, 1H, H-2), 4.03 (br s, 1H, H-5), 2.32 (s, 3H, CH_3 Tol); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): δ 172.7 (C=O), 138.5, 136.6, 136.5, (C_q), 133.3, 129.9, 129.7, 128.7, 128.6, 128.4, 128.2, 127.9, 127.8 (CH_{arom}), 86.0 (C-1), 78.9 (C-3), 78.4 (C-2), 76.0 (C-4), 72.9, 71.4 (CH_2 Bn), 70.8 (C-5), 21.1 (CH_3 Tol); $[\alpha]_D^{22}$ = -192° (c = 1, DCM); HRMS $[M+Na]^+$ calc for $C_{27}H_{26}O_5SNa$ 485.13932, found 485.13905.



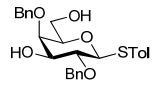
***p*-Tolyl 4,6-di-*O*-acetyl-2,3-di-*O*-benzyl-1-thio-β-D-galactopyranoside (4):** A solution of 4.00 g compound **9** (8.57 mmol) in 60 mL pyridine/Ac_2O (3/1 v/v) was stirred overnight at room temperature. After complete conversion the reaction was quenched with MeOH at 0°C. The mixture was concentrated *in vacuo* and the residue was taken up in EtOAc. The organic mixture was washed with 1M aq. HCl, sat. aq. $NaHCO_3$, and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound **4** (3,82 g, 6.94 mmol, 81%). R_f 0.31 (EtOAc/PE 1/4); IR (neat, cm^{-1}) 2870, 1745, 1494, 1454, 1370, 1229, 1104, 810, 737, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.24 (m, 12H, CH_{arom}), 7.09 (d, *J* = 7.9 Hz, 2H, CH_{arom}), 5.53 (d, *J* = 1.6 Hz, 1H, H-4), 4.81 – 4.69 (m, 3H, CH_2 Bn), 4.63 – 4.57 (m, 1H, H-1), 4.49 (d, *J* = 11.0 Hz, 1H, CH_2 Bn), 4.16 (d, *J* = 6.5 Hz, 2H, H-6), 3.81 – 3.74 (m, 1H, H-5), 3.68 – 3.60 (m, 2H, H-2, H-3), 2.32 (s, 3H, CH_3 Tol), 2.14 (s, 3H, CH_3 Ac), 2.06 (s, 3H, CH_3 Ac); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 170.3 (C=O), 138.1, 137.8, 137.4 (C_q), 132.7, 129.5 (CH_{arom}), 129.4 (C_q), 128.4, 128.3, 128.1, 127.8, 127.8 (CH_{arom}), 87.9 (C-1), 81.0, 76.5 (C-2, C-3), 75.7 (CH_2 Bn), 74.3 (C-5), 72.0 (CH_2 Bn), 66.5 (C-4), 62.3 (C-6), 21.0 (CH_3 Tol), 20.8, 20.7 (CH_3 Ac); $[\alpha]_D^{22}$ = + 25° (c = 1, DCM); HRMS $[M+Na]^+$ calc for $C_{31}H_{34}O_7SNa$ 573.19175, found 573.19140.



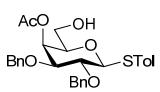
Methyl (*p*-tolyl 4-*O*-acetyl-2,3-di-*O*-benzyl-1-thio-β-D-galactopyranoside)uronate (5): To a solution of 1.70 g compound **9** (3.35 mmol, 1 equiv) in 24 mL DCM/H_2O (2/1 v/v), 105 mg TEMPO (0.67 mmol, 0.2 equiv.) and 2.70 g BAIB (8.38 mmol, 2.5 equiv.) were added. The reaction was quenched with 10% $Na_2S_2O_3$. The mixture was extracted twice with DCM and once with EtOAc. The combined extracts were dried over $MgSO_4$, filtrated and concentrated. To a solution of the crude acid in 32 mL DMF was added 2.31 g K_2CO_3 (16.75 mmol, 5 equiv.) and 271 µL MeI (4.36 mmol, 1.3 equiv.). After complete conversion the mixture was quenched with 1.9 mL AcOH and the mixture was partitioned between EtOAc and H_2O. The organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$, filtered and concentrated. Purification by column chromatography using EtOAc/PE (3/17→1/4) gave the title compound **5** (45% over 2 steps). R_f 0.56 (EtOAc/PE 3/7); IR (neat, cm^{-1}) 1746, 1371, 1265, 1227, 1101, 1061, 1028, 810, 731, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d d, *J* = 8.1 Hz, 2H, H_{arom}), 7.39 (d, *J* = 7.0 Hz, 2H, H_{arom}), 7.36 – 7.22 (m, 8H, H_{arom}), 7.08 (d, *J* = 8.0 Hz, 2H, H_{arom}), 5.80 (s, 1H, H-4), 4.73 (m, 3H. CH_2 Bn), 4.58 (d, *J* = 8.9 Hz, 1H, H-1), 4.47 (d, *J* = 11.1 Hz, 1H, CH_2 Bn), 4.11 (s, 1H, H-5), 3.72 (s, 3H, CH_3 OMe), 3.66 (s, 1H, H-3), 3.64 (s, 1H, H-2), 2.29 (s, 3H, CH_3 Tol), 2.07 (s, 3H, CH_3 OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 166.9 (C=O), 137.9, 137.7, 137.1 (C_q), 133.0, 129.3 (CH_{arom}), 128.9 (C_q), 128.2, 128.1, 127.9, 127.6, 127.5 (CH_{arom}), 87.5 (C-1), 80.3 (C-3), 75.8 (C-2), 75.4 (CH_2 Bn), 75.2 (C-5), 71.7 (CH_2 Bn), 67.4 (C-4), 52.3 (CH_3 OMe), 20.8 (CH_3 Tol), 20.5 (CH_3 OAc); $[\alpha]_D^{22}$ = + 25° (c = 5, DCM); $[M+Na]^+$ calc for $C_{30}H_{32}O_7SNa$, 559.17610 found 559.17566.



***p*-Tolyl 3,6-anhydro-2,4-di-*O*-benzyl-β-D-galactopyranoside (6):** To a solution of 3.9 g *p*-tolyl 2,4-di-*O*-benzyl-1-thio-β-D-galactopyranoside (8.25 mmol, 1 equiv) in 41 ml pyridine was added 1.75 g tosyl chloride (9.08 mmol, 1.1 equiv) at 0°C. The mixture was stirred for 3 days under argon atmosphere at room temperature. The reaction was quenched with 3.3 ml MeOH and the mixture was partitioned between EtOAc and aq. 1M HCl solution. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with sat aq. $NaHCO_3$ solution, H_2O, and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was dissolved in 100 ml DMF and 300 mg NaH (60% in mineral oil, 12.4 mmol, 1.5 equiv) was added at 0 °C. The mixture was stirred overnight at room temperature. The mixture was partitioned between H_2O and diethyl ether and the aqueous layer was extracted. The combined organic layers were washed with sat aq. $NaHCO_3$ solution, H_2O, and brine, dried over $MgSO_4$, filtered and concentrated. Flash column chromatography using EtOAc/PE (1/19→1/4) afforded 1.6 g of the title compound **6** (3.5 mmol, 40% over 2 steps). R_f 0.6 (EtOAc/PE, 3/7, v/v); IR (neat,cm^{-1}) 2938, 1494, 1455, 1069, 805, 738, 698, 632, 536; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 10H, CH_{arom}), 7.27 – 7.22 (m, 2H, CH_{arom}), 7.09 (d, *J* = 8.0 Hz, 2H, CH_{arom}), 5.28 (s, 1H, H-1), 4.84 (d, *J* = 9.6 Hz, 1H, H-6), 4.62 – 4.52 (m, 3H, CH_2 Bn), 4.46 – 4.43 (m, 2H, H-3, CH_2 Bn), 4.37 (br s, 1H, H-5), 4.28 (d, *J* = 1.7 Hz, 1H, H-4), 4.10 (d, *J* = 5.9 Hz, 1H, H-2), 3.96 (dd, *J* = 9.6, 2.7 Hz, 1H, H-6), 2.31 (s, 3H, CH_3 Tol); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6, 137.3, 137.1, 132.3 (C_q), 131.1, 129.7, 129.7, 128.4, 128.4, 127.9, 127.8, 127.7, 127.6, 125.2 (CH_{arom}), 84.9 (C-1), 82.1 (C-2), 77.9 (C-4), 77.6 (C-3), 76.9 (C-5) , 72.4, 71.1 (CH_2 Bn), 69.9 (C-6), 21.0 (CH_3 STol); $[\alpha]_D^{22}$ = -21° (c = 1, DCM); HRMS $[M+Na]^+$ calcd for $C_{27}H_{28}O_4SNa$ 471.16005, found 471.15984.

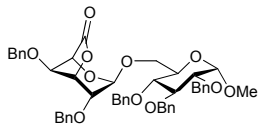


***p*-Tolyl 2,4-di-*O*-benzyl-1-thio-β-D-galactopyranoside (8)**: To a mixture of 7.3 g *p*-tolyl 1-thio-β-D-galactopyranoside (25.4 mmol, 1 equiv) in 130 mL DMF was added 6.1 g of imidazole (88.9 mmol, 3.5 equiv) and 11.5 g of TBSCl (76.2 mmol, 3 equiv). After 2 hours of stirring, TLC analysis showed complete consumption of the starting material. The reaction was quenched by the addition of 3 mL MeOH. The mixture was partitioned between H_2O and EtOAc, and the aqueous layer was extracted. The combined organic phases were washed with aq 1M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was dissolved in 130 mL DMF. To this solution were added 9.1 mL benzyl bromide (76.2 mmol, 3 equiv) and 3.11 g NaH (60% in mineral oil, 76.2 mmol, 3 equiv) at 0 °C. After stirring at ambient temperature overnight, the reaction was quenched with MeOH at 0 °C and the mixture was taken up in Et_2O, washed with 5% aq. LiCl and brine. After drying over $MgSO_4$, filtration, and concentration under reduced pressure, the residue was dissolved in 34 mL THF and treated with 102 mL 1M TBAF in THF (101.6 mmol, 4 equiv). The mixture was stirred for 3 hours and subsequently partitioned between EtOAc and H_2O. The water layer was extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography using EtOAc/PE (3/7→1/1) afforded 7.9 g *p*-tolyl 2,4-di-*O*-benzyl-1-thio-*β*-D-galactopyranoside (16.9 mmol, 66% over 3 steps). R_f 0.2 (EtOAc/PE 3/7); IR (neat,cm^{-1}) 3420, 2868, 1494, 1454, 1358, 1055, 866, 809, 734, 697, 530; ^{1}H NMR (400 MHz, $CDCl_3$) 7.44 (d, *J* = 8.1 Hz, 2H, CH_{arom}), 7.40 – 7.26 (m, 10H, CH_{arom}), 7.05 (d, *J* = 8.0 Hz, 2H, CH_{arom}), 4.92 (d, *J* = 10.9 Hz, 1H, CH_2 Bn), 4.76 (d, *J* = 11.6 Hz, 1H, CH_2 Bn), 4.66 – 4.60 (m, 2H, CH_2 Bn), 4.58 – 4.51 (m, 1H, H-1), 3.84 (dd, *J* = 11.3, 7.3 Hz, 1H, H-6), 3.75 (s, 1H, H-4), 3.69 – 3.65 (m, 2H, H-2, H-3), 3.59 – 3.50 (m, 1H, H-6), 3.44 (dd, *J* = 6.8, 5.4 Hz, 1H, H-5), 2.43 (s, 1H, OH), 2.31 (s, 3H, CH_3 STol), 2.05 (s, 1H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1 (C_q), 138.0 (C_q), 137.4 (C_q), 132.7, 131.9 (CH_{arom}), 129.9 (C_q), 129.7, 128.5, 128.4, 128.2, 128.2, 128.0, 128.0, 127.9, 127.6 (CH_{arom}), 87.5 (C-1), 78.9 (C-5), 78.2 (C-2), 75.8, 75.7 (C-3, C-4), 75.2, 74.7 (CH_2 Bn), 62.1 (C-6), 21.0 (CH_3 Tol); $[\alpha]_D^{22}$ = +2° (c = 1, DCM); HRMS $[M+Na]^+$ calcd for $C_{27}H_{30}O_5SNa$ 489.17062, found 489.17017.

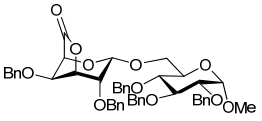


***p*-Tolyl 4-*O*-acetyl-2,3-di-*O*-benzyl-1-thio-β-D-galactopyranoside (10):** To a solution of 1.74 g *p*-tolyl 2,3-di-*O*-benzyl-1-thio-β-D-galactopyranoside (3.72 mmol, 1 equiv.) in 20 ml pyridine was added 673 mg TBDMSCl (4.46 mmol, 1.2 equiv.) and the reaction mixture was stirred at room temperature overnight. 5 mL Ac_2O was added

and the reaction mixture was stirred overnight again. The reaction was quenched with 10 mL MeOH and the solvent was removed under reduced pressure. The crude material was coevaporated with toluene and dissolved in 20 mL THF. Next, 4.85 mL TEA·3HF (29.8 mmol, 8 equiv.) was added and the reaction mixture was stirred at 70°C for 1 hour. The reaction mixture was allowed to cool to room temperature and was partitioned between EtOAc and sat. aq. $NaHCO_3$. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with sat. aq. $NaHCO_3$ and brine. After drying over $MgSO_4$, filtration and concentration, the crude mixture was purified by column chromatography using EtOAc/PE (1/4→2/3) to yield 1.64 g of the title compound **10** (3.21 mmol, 86% over 3 steps). R_f 0.21 (EtOAc/PE 3/7); IR (neat, cm^{-1}) 3462, 2870, 1741, 1494, 1454, 1369, 1232, 1090, 734, 699; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.50 – 7.22 (m, 12H, CH_{arom}), 7.08 (d, *J* = 8.0 Hz, 2H, CH_{arom}), 5.46 (d, *J* = 2.6 Hz, 1H, H-4), 4.81 – 4.70 (m, 2H, CH_2 Bn), 4.67 (d, *J* = 11.2 Hz, 1H, CH_2 Bn), 4.61 (d, *J* = 9.0 Hz, 1H, H-1), 4.50 (d, *J* = 11.2 Hz, 1H, CH_2 Bn), 3.74 – 3.61 (m, 3H, H-6, H-2, H-3), 3.57 (t, *J* = 6.4 Hz, 1H, H-5), 3.50 (dd, *J* = 11.2, 6.2 Hz, 1H, H-6), 2.67 (s, 1H, OH), 2.30 (s, 3H, CH_3 Tol), 2.13 (s, 3H, CH_3 Ac); ^{13}C NMR (101 MHz, $CDCl_3$, HH-COSY, HSQC) δ 171.2 (C=O), 138.0, 137.7, 137.3 (C_q), 132.4, 129.5 (CH_{arom}), 129.3 (C_q), 128.3, 128.2, 128.0, 127.9, 127.8, 127.7 (CH_{arom}), 87.7 (C-1), 80.8 (C-3), 77.1 (C-5), 76.7 (C-2), 75.6, 71.8 (CH_2 Bn), 67.0 (C-4), 60.8 (C-6), 21.0 (CH_3 Ac), 20.7 (CH_3 STol); $[\alpha]_D^{22}$ = +17 ° (c = 1, DCM); HRMS $[M+Na]^+$ calc for $C_{29}H_{32}O_6SNa$ 531.18118, found 531.18093.

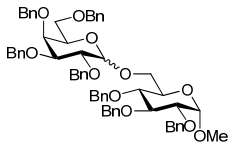


Methyl *O*-(2,4-di-*O*-benzyl-β-D-galactopyranosylurono-6,3-lactone)-(1→6)-2,3,4-tri-*O*-benzyl-α-glucopyranoside (12β): Compound **12β** was prepared according to the procedure described for AgOTf/*p*-NO_2PhSCl-promoted glycosylation using 49 mg donor **1** (109 µmol) and 77 mg acceptor **11** (165 µmol, 1.5 equiv). The β-coupled product was obtained in 73% yield (64 mg, 79 µmol), whereas its α-configured epimer was observed in trace amounts only. R_f 0.7 (EtOAc/PE, 3/7, v/v); IR (neat,cm^{-1}) 2919, 1800, 1498, 1454, 1362, 1058, 1028, 927, 736, 696, 531, 458, 354; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.16 (m, 25H, H_{arom}), 4.96 (d, *J* = 10.8 Hz, 1H, CH_2 Bn), 4.89 – 4.83 (m, 2H, H-1', CH_2 Bn), 4.80 – 4.74 (m, 2H, CH_2 Bn), 4.73 (dd, *J* = 4.6, 1.3 Hz, 1H, H-3'), 4.65 (d, *J* = 12.1 Hz, 1H, CH_2 Bn), 4.58 – 4.49 (m, 5H, H-1, CH_2 Bn), 4.42 (d, *J* = 11.8 Hz, 1H, CH_2 Bn), 4.33 (d, *J* = 0.9 Hz, 1H, H-4'), 4.03 – 3.95 (m, 3H, H-3, H-2', H-5'), 3.91 (dd, *J* = 11.1, 1.9 Hz, 1H, H-6), 3.83 – 3.77 (m, 1H, H-5), 3.53 – 3.43 (m, 2H, H-2, H-6), 3.35 (s, 3H, CH_3 OMe), 3.27 (dd, *J* = 10.0, 9.0 Hz, 1H, H-4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8 (C=O), 138.6, 138.1, 136.8, 136.7 (C_q), 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5 (CH_{arom}), 100.3 (C-1'), 97.7 (C-1), 81.8 (C-3), 79.9 (C-2), 78.6 (C-3'), 78.3 (C-4), 77.2 (C-2'), 75.9 (C-4'), 75.7, 74.5, 73.3, 72.8, 71.2 (CH_2 Bn), 70.6 (C-5'), 69.7 (C-5), 67.6 (C-6), 55.0 (CH_3 OMe); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 100.3 ($J_{C1'β-H-1'β}$ = 172.8 Hz, C-1'), 97.7 ($J_{C1β-H-1β}$ = 167.8 Hz, C-1); HRMS $[M+Na]^+$ calcd for $C_{48}H_{50}O_{11}Na$ 825.32453, found 825.32458.

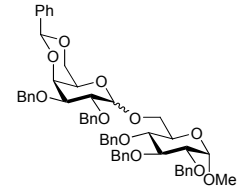


Methyl *O*-(2,4-di-*O*-benzyl-α-D-galactopyranosylurono-6,3-lactone)-(1→6)- 2,3,4-tri-*O*-benzyl-α-glucopyranoside (12α): Compound **12α** was prepared according to the procedure described for Ph_2SO/Tf_2O-promoted glycosylation using 46 mg donor **1** (100 µmol, 1 equiv) and 93 mg acceptor **11** (0.2 mmol, 2 equiv). This gave a 10/1 α/β mixture (55 mg, 69 µmol, 69%). IR (neat, cm-1): 694, 734, 979, 1026, 1141, 1203, 1355, 1436, 1759; ^{1}H NMR (α-coupled product, 400 MHz, $CDCl_3$) δ = 3.22 (s, 3H, CH_3 OMe), 3.42 (dd, 1H, *J* = 10.0 Hz, *J* = 3.5 Hz, H-2), 3.54 (t, 1H, *J* = 9.5 Hz, H-4), 3.68 (d, 1H, *J* = 11.0 Hz, H-6), 3.73 (d, 1H, *J* = 9.5 Hz, H-5), 3.97 (t, 1H, *J* = 9.5 Hz, H-3), 4.00 (bs, 1H, H-2'), 4.11 (s, 1H, H-5'), 4.19 (dd, 1H, *J* = 11.0 Hz, *J* = 3.5 Hz, H-6), 4.44 (s, 1H, H-4'), 4.54 (s, 1H, H-1), 4.55 (s, 2H, CH2Ph), 4.57 (d, 1H, *J* = 12.5 Hz, CH*H*Ph), 4.62 (d, 1H, *J* = 12.0 Hz, CH*H*Ph), 4.65 (d, 1H, *J* = 10.0 Hz, CH*H*Ph), 4.69 (d, 1H, *J* = 5.0 Hz, H-3'), 4.76 (d, 1H, *J* = 10.5 Hz, C*H*HPh), 4.79 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.83 (d, 1H, *J* = 11.0 Hz, CH*H*Ph), 4.89 (s, 1H, H-1'), 4.90 (d, 1H, *J* = 12.5 Hz, C*H*HPh), 4.96 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 7.24 – 7.65 (m, 25H, H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 55.1 (CH_3 OMe), 68.5 (C-6), 69.8 (C-5), 71.9 (C-5') 71.6 (CH_2 Bn), 73.3 (CH_2 Bn), 74.2 (CH_2 Bn), 74.4 (C-2'), 75.1 (CH_2 Bn), 76.0 (C-4'), 77.7 (C-4), 79.9 (C-2), 80.2 (C-3'), 81.7 (C-3), 98.0 (C-1), 98.8 (C-1'), 124.7 – 130.9 (CH_{arom}), 136.7 (C_q Bn), 137.5 (C_q Bn), 138.0 (C_q

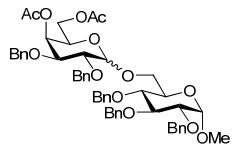
Bn), 138.1 (C_q Bn), 138.7 (C_q Bn), 171.6 (C=O lactone); ^{13}C-GATED (125 MHz, $CDCl_3$): 98.0 ($J_{C1,H1}$ = 161 Hz, C-1), 102.4 ($J_{C1',H1'}$ = 163 Hz, C-1'); ESI-MS: 825.3 $[M+Na]^+$.



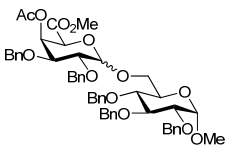
Methyl *O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-glucopyranoside (13): Compound **13** was prepared according to the procedure described for NIS/TfOH-promoted glycosylation using 70 mg donor **2** (107 µmol) and 140 mg acceptor **11**. The product was obtained as a 1/1.1 α/β mixture (75 mg, 76 µmol, 71% yield). R_f 0.74 (EtOAc/PE, 3/7, v/v); IR (neat cm^{-1}) 1454, 1265, 1057, 731, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.11 (m, 73.5H, H_{arom}), 5.00 (d, *J* = 3.5 Hz, 1H, H-1'α), 4.98 – 4.90 (m, 5.3H, CH_2 Bn), 4.88 – 4.47 (m, 22.1H, CH_2 Bn, H-1α, H-1β), 4.46 – 4.33 (m, 4.1H, CH_2 Bn), 4.31 (d, *J* = 7.7 Hz, 1.1H, H-1'β), 4.14 (dd, *J* = 10.7, 1.7 Hz, 1.1H, H-6β), 4.06 – 3.70 (m, 12.5H, H-2'α, H-3α, H-3β, H-4'/H-5', H3'α, H-4'/H-5', H-2'β, H-4'/H-5', H-5β, H-6α, H-5α), 3.65 – 3.43 (m, 10.6H, H-6β, H-4α, H-4'α/H-5α', H-6', H-3'β, H-4β, H-2β), 3.41 (dd, *J* = 9.6, 3.6 Hz, 1H, H-2α), 3.31 – 3.27 (m, 6.3H, CH_3 OMe); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8, 138.7, 138.6, 138.4, 138.3, 138.1, 138.0, 137.8 (C_q), 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3 (CH_{arom}), 104.1 (C-1'β), 97.9 (C-1'α), 97.8 (C-1β, C-1α), 82.2 (C-3'β), 82.0 (C-3α), 81.9 (C-3β), 80.1 (C-2α), 79.8 (C-2β), 79.2 (C-2'β), 78.2 (C-3'α), 78.0 (C-4β), 77.9 (C-4α), 76.4 (C-2'α), 75.6, 75.1 (CH_2 benzyl), 75.0 (C-4'/C-5'), 74.9, 74.8, 74.7, 74.5 (CH_2 benzyl), 73.4 (CH_2 benzyl, C-4'/C-5'), 73.3 (CH_2 benzyl, C-4'/C-5'), 72.8, 72.7, 72.5 (CH_2 benzyl), 70.2 (C-5α), 69.8 (C-5β), 69.3 (C-4'/C-5'), 68.8 (C-6'), 68.5 (C-6β, C-6'), 66.3 (C-6α), 55.1 (CH_3 OMe-α), 55.0 (CH_3 OMe-β); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 104.1 ($J_{C1'β-H-1'β}$ = 158.7 Hz, C-1'β), 97.9 ($J_{C1'α-H-1'α}$ = 169.6 Hz, C-1'α), 97.8 ($J_{C1β-H-1β}$ = 168.1 Hz, C-1β, $J_{C1α-H-1α}$ = 167.3 Hz, C-1α); HRMS $[M+Na]^+$ calcd for $C_{62}H_{66}O_{11}Na$ 1009.44973, found 1009.45089. Preparation of the same title compound according to the procedure described for AgOTf/*p*-NO_2PhSCl-promoted glycosylation using 71 mg donor **2** (110 µmol, 1 equiv) and 77 mg acceptor **11** (165 µmol, 1.5 equiv), furnished a 1/1.6 α/β mixture (100 mg, 101 µmol, 92% yield).



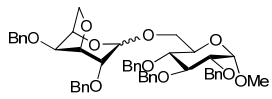
Methyl *O*-(4,6-*O*-benzylidene-2,3-di-*O*-benzyl-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-glucopyranoside (14): Compound **14** was prepared according to the procedure described for NIS/TfOH-promoted glycosylation using 56 mg donor **3** (101 µmol) and 140 mg acceptor **11**. The product was obtained as a 1/1.2 α/β mixture (77 mg, 86 µmol, 85% yield). R_f 0.23, 0,50 (EtOAc/PE, 3/7, v/v); IR (neat,cm^{-1}) 2912, 1498, 1454, 1368, 1058, 1027, 912, 823, 732, 696, 637, 458, 418; δ ^{1}H NMR (400 MHz, $CDCl_3$) 7.58 – 7.12 (m, 66H, H_{arom}), 5.46 (s, 1.2H, PhCH-β), 5.43 (s, 1.0H, PhCH-α), 5.05 (d, *J* = 3.4 Hz, 1H, H-1α'), 5.01 – 4.85 (m, 4.4H, CH_2 benzyl), 4.84 – 4.49 (m, 19.8H, CH_2 benzyl, H-1β, H-1α), 4.30 (d, *J* = 7.8 Hz, 1.2H, H-1'β), 4.25 (d, *J* = 11.5 Hz, 1.2H, H-6'β), 4.18 (dd, *J* = 11.0, 1.7 Hz, 1.2H, H-6β), 4.13 – 4.02 (m, 4.2H, H-6'α, H-4'α/H-3'α, H-2'α, H-4'β), 4.02 – 3.81 (m, 8.8H, H-6'β, H-3α, H-3β, H-4'α/H-3'α, H-2'β, H-5β, H-6'a), 3.81 – 3.72 (m, 2.0H, H-5α, H-6α), 3.72 – 3.65 (m, 2H, H-6α, H-6β), 3.61 – 3.40 (m, 7.6H, H-4α, H-4β, H-2β, H-3'β, H-5'α, H-2α), 3.33 (s, 3.6H, CH_3 OMe-β), 3.28 (s, 3H, CH_3 OMe-α), 3.19 (s, 1.2H, H-5'β); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8, 138.7, 138.6, 138.5, 138.4, 138.3, 138.1, 137.8 (C_q), 128.8, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 126.4, 126.3 (CH_{arom}), 104.1 (C-1'β), 101.2 (PhCH-β), 101.0 (PhCH-α), 98.3 (C-1'α), 97.9 (C-1β), 97.8 (C-1α), 82.0 (C-3α), 82.0 (C-3β), 80.1 (C-2α), 79.8 (C-2β), 79.3 (C-3'β), 78.1, 78.0 (C-2'β, C-4β), 77.9 (C-4α), 75.6 (CH_2 Bn), 75.6 (CH_2 Bn, C-2'α), 75.5 (CH_2 Bn), 75.2, 74.9, 74.8 (C-4'α, C-3'α, CH_2 Bn), 73.7 (C-4'β), 73.3, 73.2, 72.8, 71.8 (CH_2 Bn), 70.1 (C-5α), 69.9 (C-5β), 69.3 (C-6'α), 69.0 (C-6'β), 68.6 (C-6β), 66.4 (C-6α), 66.3 (C-5'β), 62.5 (C-5'α), 55.2 (CH_3 OMe-β), 55.0 (CH_3 OMe-α); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 104.1 ($J_{C1'β-H-1'β}$ = 157.7 Hz, C-1'β), 98.3 ($J_{C1'α-H-1'α}$ = 170.3 Hz, C-1'α), 97.9 ($J_{C1β-H-1β}$ = 168.2 Hz, C-1β), 97.8 ($J_{C1α-H-1α}$ = 167.5 Hz, C-1α); HRMS $[M+Na]^+$ calcd for $C_{55}H_{58}O_{11}Na$ 917.38713, found 917.38704. Preparation of the same title compound according to the procedure described for AgOTf/*p*-NO_2PhSCl-promoted glycosylation using 61 mg donor **3** (110 µmol, 1 equiv) and 77 mg acceptor **11** (165 µmol, 1.5 equiv), furnished a 1/1.8 α/β mixture (81 mg, 90 µmol, 82% yield).



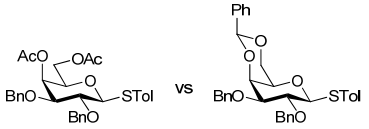
Methyl *O*-(4,6-di-*O*-acetyl-2,3-di-*O*-benzyl-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-glucopyranoside (15): Compound **15** was prepared according to the procedure described for NIS/TfOH-promoted glycosylation using 60 mg donor **4** (109 µmol) and 140 mg acceptor **11**. The product was obtained as a 1/1.2 α/β mixture (74 mg, 81 µmol, 76% yield). R_f 0.33, 0.42 (EtOAc/PE 3/7); IR (neat cm^{-1}) 1742, 1454, 1368, 1225, 1047, 1026, 733, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 55H, H_{arom}), 5.48 (d, *J* = 3.0, 2.2H, H-4'α, H-4'-β), 4.96 (m, 3.2H, H-1'α+ CH_2 Bn), 4.87 (d, *J* = 11.0, 2.2H, CH_2 Bn), 4.82 – 4.48 (m, 19.8H, H-1β, H-1α, CH_2 Bn), 4.31 (d, *J* = 7.7, 1.2H, H-1'β), 4.18 – 4.04 (m, 5.6H, H-6β, H-6'β, H-6'α, H-5'α), 4.02 – 3.93 (m, 3.2H, H-3α, H-3β, H-6'α), 3.89 (dd, *J* = 10.0, 3.3 Hz, 1H, H-3'α), 3.86 – 3.61 (m, 8.8H, H-5β, H-2'α, H-5α, H-6α, H-5'β, H-6β, H-2'β), 3.58 – 3.47 (m, 4.8H, H-3'β, H-4α, H-2β, H-4β), 3.41 (dd, *J* = 9.6, 3.5 Hz, 1H, H-2α), 3.33 (s, 3.6H, CH_3 OMe-β), 3.28 (s, 3H, CH_3 OMe-α), 2.10 (s, 6.6H, CH_3 Ac-α, CH_3 Ac-β), 2.04 (s, 3.6H, CH_3 Ac-β), 1.97 (s, 3H, CH_3 Ac-α); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 170.4, 170.3 (C=O), 138.7, 138.7, 138.6, 138.4, 138.3, 138.1, 137.9, 137.6 (C_q), 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.2, 128.1, 128.0, 127.9, 127.9, 127.9, 127.9, 127.8, 127.7, 127.6, 127.6, 127.6, 127.5, 127.5, 127.4, 127.4 (CH_{arom}), 103.9 (C-1'β), 98.0 (C-1β), 97.8 (C-1'α), 97.7 (C-1α), 82.0 (C-3α), 81.9 (C-3β), 78.0 (C-2α), 79.7 (C-2β), 79.2 (C-3'β), 78.4 (C-2'β), 77.9 (C-4α), 77.8 (C-4β), 75.7, 75.6 (CH_2 Bn), 75.4 (C-2'α), 75.3 (CH_2 Bn), 75.0 (C-3'α), 74.9, 74.7, 73.3, 73.3, 72.8, 72.1, 71.8 (CH_2 Bn), 70.6 (C-5'β), 70.1 (C-5α), 69.7 (C-5β), 68.7 (C-6β), 67.8 (C-4'α), 66.7 (C-5'α), 66.4 (C-6α), 66.3 (C-4'β), 62.4 (C-6'α), 61.9 (C-6'β), 55.2 (CH_3 OMe-β), 55.0 (CH_3 OMe-α), 20.8, 20.7 (CH_3 OAc); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 103.9 ($J_{C1'β-H-1'β}$ = 158.6 Hz, C-1'β), 98.0 ($J_{C1β-H-1β}$ = 167.8 Hz, C-1β), 97.8 ($J_{C1'α-H-1'α}$ = 169.2 Hz C-1'α), 97.7 ($J_{C1α-H-1α}$ = 169.2 Hz, C-1α); HRMS $[M+Na]^+$ calcd for $C_{52}H_{58}O_{13}Na$ 913.37696, found 913.37813. Preparation of the same title compound according to the procedure described for AgOTf/*p*-NO_2PhSCl-promoted glycosylation using 61 mg donor **4** (110 µmol, 1 equiv) and 77 mg acceptor **11** (165 µmol, 1.5 equiv), furnished a 1/1.8 α/β mixture (92 mg, 103 µmol, 94% yield).



Methyl *O*-(Methyl (4-*O*-acetyl-2,3-di-*O*-benzyl-D-galactopyranosyl)uronate)-(1→6)-2,3,4-tri-*O*-benzyl-α-glucopyranoside (16): Compound **16** was prepared according to the procedure described for NIS/TfOH-promoted glycosylation using 54 mg donor **5** (101 µmol) and 140 mg acceptor **11**. The product was obtained as a 1/1.3 α/β mixture (68 mg, 78 µmol, 77% yield). R_f 0.17, 0,24 (EtOAc/PE, 3/7, v/v); IR (neat, cm^{-1}) 1748, 1454, 1361, 1231, 1157, 1088, 1061, 1026, 914, 735, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.11 (m, 57.5H, H_{arom}), 5.75 (d, *J* = 2.6 Hz, 2.3H, H-4'α, H-4'β), 5.05 (d, *J* = 3.2 Hz, 1H, H-1'α), 4.96 (dd, *J* = 10.8, 5.3 Hz, 2.3H, CH_2 Bn), 4.93 – 4.83 (m, 2.3H, CH_2 Bn), 4.82 – 4.60 (m, 12.8H, CH_2 Bn), 4.60 – 4.47 (m, 8.9H, CH_2 Bn, H-1β, H-5'α, H-1α), 4.30 (d, *J* = 7.7 Hz, 1.3H, H-1'β), 4.23 (d, *J* = 10.8 Hz, 1.3H, H-6β), 4.03 – 3.89 (m, 4.6H, H-5'β, H-3β, H-3α, H-3'α), 3.89 – 3.61 (m, H-5β, H-2'α, H-5α, H-6α, H-2'β, H-6β, CH_3 CO_2Me, 13.8H), 3.60 – 3.43 (m, 4.9H, H-3'β, H-4α, H-4β, H-2β), 3.39 (dd, *J* = 9.5, 3.4 Hz, 1H, H-2α), 3.30 (s, 3.9H, CH_3 OMe-β), 3.26 (s, 3H, CH_3 OMe-α), 2.08 (s, 3.9H, CH_3 Ac-β), 2.06 (s, 3H, CH_3 Ac-α); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.9, 168.3, 167.2 (C=O), 138.8, 138.7, 138.4, 138.3, 138.1, 137.7, 137.5 (C_q), 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5 (CH_{arom}), 103.7 (C-1'β), 98.2 (C-1'α), 97.9 (C-1β, C-1α), 82.0 (C-3α), 82.0 (C-3β), 80.0 (C-2α), 79.8 (C-2β), 78.6 (C-3'β), 78.0 (C-2'β), 77.9 (C-4β), 77.7 (C-4α), 75.7, 75.6, 75.3 (CH_2 Bn), 74.8 (CH_2 Bn, C-2'α), 74.7 (CH_2 Bn), 74.5 (C-3'α), 73.3, 72.9 (CH_2 Bn), 72.4 (C-5'β), 72.0, 71.9 (CH_2 Bn), 70.1 (C-5α), 69.9 (C-5β), 68.9, 68.8 (C-4'α, C-5'α, C-6β), 67.5 (C-4'β), 67.0 (C-6α), 55.1 (CH_3 OMe-β), 55.0 (CH_3 OMe-α), 52.5 (CH_3 CO_2Me-β), 52.4 (CH_3 CO_2Me-α), 20.8 (CH_3 Ac); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 103.7 ($J_{C1'β-H-1'β}$ = 159.7 Hz, C-1'β), 98.2 ($J_{C1'α-H-1'α}$ = 172.1 Hz, C-1'α), 97.9 ($J_{C1β-H-1β}$ = 167.9 Hz, C-1β, $J_{C1α-H-1α}$ = 167.2 Hz, C-1α); HRMS $[M+Na]^+$ calcd for $C_{51}H_{56}O_{13}Na$ 899.36131, found 899.36231. Preparation of the same title compound according to the procedure described for AgOTf/*p*-NO_2PhSCl-promoted glycosylation using 59 mg donor **5** (110 µmol, 1 equiv) and 77 mg acceptor **11** (165 µmol, 1.5 equiv), furnished a 1/3.4 α/β mixture (82 mg, 93 µmol, 84% yield).

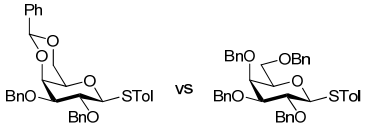


Methyl *O*-(3,6-anhydro-2,4-di-*O*-benzyl-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-glucopyranoside (17): Compound **17** was prepared according to the procedure described for NIS/TfOH-promoted glycosylation using 45 mg donor **6** (100 µmol) and 140 mg acceptor **11**. The product was obtained as a 1.2/1 α/β mixture (51 mg, 65 µmol, 65% yield). R_f 0.34, 0,59 (EtOAc/PE, 3/7, v/v); IR (neat,cm^{-1}) 2924, 1497, 1454, 1364, 1072, 939, 905, 737, 697, 631, 532; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.13 (m, 55H, H_{arom}), 5.00 – 4.94 (m, 2.2H, CH_2 Bn), 4.93 (d, *J* = 2.3 Hz, 1.2H, H-1'α), 4.90 – 4.74 (m, 7.8H, CH_2 Bn), 4.71 – 4.45 (m, 14.4H, H-1'β, H-1α, H-1β, CH_2 Bn), 4.44 – 4.37 (m, 2.2H, H-4'α, CH_2 Bn), 4.36 (d, *J* = 4.7 Hz, 1H, H-3'β), 4.34 – 4.29 (m, 2.4H, H-3'α, H-5'α), 4.27 (s, 1H, H-5'β), 4.26 – 4.19 (m, 2H, H-6'β, H-4'β), 4.14 (dd, *J* = 11.1, 3.8 Hz, 1.2H, H-6α), 4.05 – 3.90 (m, 5.6H, H-3β, H-6'α, H-3α, H-6β), 3.87 (dd, *J* = 9.4, 3.1 Hz, 1H, H-6'β), 3.79 – 3.67 (m, 5.6H, H-2'α, H-2'β, H-5α, H-5β, H-6α), 3.59 – 3.46 (m, 4.2H, H-6β, H-4α, H-2β, H-4β), 3.43 (dd, *J* = 9.6, 3.5 Hz, 1.2H, H-2α), 3.35 (s, 3H, CH_3 OMe-β), 3.33 (s, 3.6H, CH_3 OMe-α); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8, 138.8, 138.4, 138.4, 138.3, 138.1, 138.1, 137.8, 137.8, 137.5 (C_q), 128.4, 128.4, 128.3, 128.3, 128.3, 128.1, 128.1, 128.0, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7, 127.6, 127.5, 127.4, 127.4 (CH_{arom}), 100.0 (C-1'β), 98.0, 97.9 (C-1'α, C-1β, C-1α), 82.0 (C-3β), 81.8 (C-3α), 80.1 (C-2'β), 80.0 (C-2β), 79.9 (C-2α), 78.2 (C-3'α), 78.1 (C-4'β), 78.0 (C-4β), 77.9 (C-4α), 77.8 (C-4'α), 77.0 (C-3'β), 76.6 (C-2'α), 76.0 (C-5'β), 75.7 (CH_2 Bn), 75.5 (C-5'α), 75.1, 75.0, 73.7, 73.4, 72.3, 71.3, 71.1 (CH_2 Bn), 70.5 (C-6'β), 70.1 (C-5α), 70.0 (C-5β), 69.5 (C-6'α), 67.8 (C-6α), 66.8 (C-6β), 55.1 (CH_3 OMe); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 100.0 ($J_{C1'\beta\text{-}H\text{-}1'\beta}$ = 169.1 Hz, C-1'β), 98.0, 97.9 ($J_{C1'\alpha\text{-}H\text{-}1'\alpha}$ = 162.5 Hz, C-1'α, $J_{C1\beta\text{-}H\text{-}1\beta}$ = 167.8 Hz, C-1β, $J_{C1\alpha\text{-}H\text{-}1\alpha}$ = 169.0 Hz, C-1α); $[\alpha]_D^{22}$ = - 24° (c = 1, $CHCl_3$); HRMS $[M+Na]^+$ calcd for $C_{48}H_{52}O_{10}Na$ 811.3427, found 811.34532. Preparation of the same title compound according to the procedure described for AgOTf/*p*-NO_2PhSCl-promoted glycosylation using 49 mg donor **6** (110 µmol, 1 equiv) and 77 mg acceptor **11** (165 µmol, 1.5 equiv), furnished a 1/5.3 α/β mixture (87 mg, 110 µmol, quant.). Preparation of the same title compound according to the procedure described for Ph_2SO/Tf_2O -promoted glycosylation using 45 mg donor **6** (100 µmol, 1 equiv) and 93 mg acceptor **11** (0.2 mmol, 2 equiv), furnished a 5.2/1 α/β mixture (55 mg, 69 µmol, 70%).



AgOTf/*p*-NO_2PhSCl-promoted experiment: Diacetyl protected donor **4** (61 mg, 110 µmol) and donor **3** (61 mg, 110 µmol) were used in a competitive glycosylation reaction using acceptor **11** (3 equiv) and following the general procedure described for AgOTf/*p*-NO_2PhSCl-promoted glycosylations. The experiment yielded a 1/1.1 mixture of dimeric products **15**/**14** (84 mg, 94 µmol, 85%). Diagnostic peaks used for the determination of the product ratio: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (d, *J* = 3.4 Hz, 0.32H, H-1α' product **14**), 3.19 (s, 0.48H, H-5'β product **14**), 2.10 (s, 2.27H, CH_3 Ac-α, CH_3 Ac-β product **15**), 2.04 (s, 1.27H, CH_3 Ac-β product **15**), 1.97 (s, 1.00H, CH_3 Ac-α product **15**).

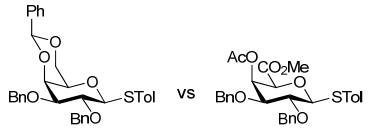
NIS/TfOH-promoted experiment: Diacetyl protected donor **4** (55 mg, 100 µmol) and donor **3** (56 mg, 100 µmol) were used in a competitive glycosylation reaction using acceptor **11** (3 equiv) and following the general procedure described for NIS/TfOH-promoted glycosylations. The experiment yielded a 1/5.2 mixture of dimeric products **15**/**14** (85 mg, 95 µmol, 95%). Diagnostic peaks used for the determination of the product ratio: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (d, *J* = 3.4 Hz, 1.00H, H-1α' product **14**), 3.19 (s, 1.20H, H-5'β product **14**), 2.10 (s, 1.14H, CH_3 Ac-α, CH_3 Ac-β product **15**), 2.04 (s, 0.53H, CH_3 Ac-β product **15**), 1.97 (s, 0.65H, CH_3 Ac-α product **15**).



AgOTf/*p*-NO_2PhSCl-promoted experiment: Benzylidene protected donor **3** (61 mg, 110 µmol) and donor **2** (71 mg, 110 µmol) were used in a competitive glycosylation reaction using acceptor **11** (3 equiv) and following the general procedure described for AgOTf/*p*-NO_2PhSCl-promoted glycosylations. The experiment yielded a 1/1.8 mixture of dimeric products **14**/**13** (92 mg, 96 µmol, 87%). Diagnostic peaks used for the determination of the product ratio: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (s, 0.64H, PhCH-β

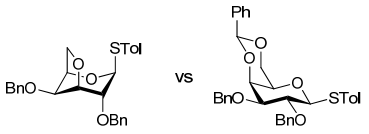
product **14**), 5.43 (s, 0.37H, PhCH-α, product **14**), 3.33 (s, 2.08H, CH_3 OMe-β product **14**), 3.29-3.28 (m, 6.36H, CH_3 OMe-α product **14**, CH_3 OMe-α product **13**, CH_3 OMe-β product **13**).

NIS/TfOH-promoted experiment: Benzylidene protected donor **3** (56 mg, 100 µmol) and donor **2** (65 mg, 100 µmol) were used in a competitive glycosylation reaction using acceptor **11** (3 equiv) and following the general procedure described for NIS/TfOH-promoted glycosylations. The experiment yielded a 1/2.2 mixture of dimeric products **14**/**13** (67 mg, 70 µmol, 70%). Diagnostic peaks used for the determination of the product ratio: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (s, 0.53H, PhCH-β product **14**), 5.43 (s, 0.48H, PhCH-α, product **14**), 3.33 (s, 1.68H, CH_3 OMe-β product **14**), 3.29-3.28 (m, 8.12H, CH_3 OMe-α product **14**, CH_3 OMe-α product **13**, CH_3 OMe-β product **13**).



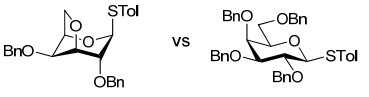
AgOTf/*p*-NO_2PhSCl-promoted experiment: Benzylidene protected donor **3** (61 mg, 110 µmol) and donor **5** (59 mg, 110 µmol) were used in a competitive glycosylation reaction using acceptor **11** (3 equiv) and following the general procedure described for AgOTf/*p*-NO_2PhSCl-promoted glycosylations. The experiment yielded a 4.76/1 mixture of dimeric products **14**/**16** (79 mg, 88 µmol, 80%). Diagnostic peaks used for the determination of the product ratio: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (s, 0.58H, PhCH-β product **14**), 5.43 (s, 0.42H, PhCH-α, product **14**), 2.08 (s, 0.40H, CH_3 Ac-β product **16**), 2.06 (s, 0.23H, CH_3 Ac-α product **16**).

NIS/TfOH-promoted experiment: Benzylidene protected donor **3** (56 mg, 100 µmol) and donor **5** (54 mg, 100 µmol) were used in a competitive glycosylation reaction using acceptor **11** (3 equiv) and following the general procedure described for NIS/TfOH-promoted glycosylations. The experiment yielded a 15.8/1 mixture of dimeric products **14**/**16** (77 mg, 86 µmol, 86%). Diagnostic peaks used for the determination of the product ratio: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (s, 0.53H, PhCH-β product **14**), 5.43 (s, 0.47H, PhCH-α, product **14**), 2.08 (s, 0.11H, CH_3 Ac-β product **16**), 2.06 (s, 0.08H, CH_3 Ac-α product **16**).



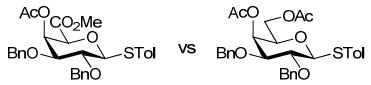
AgOTf/*p*-NO_2PhSCl-promoted experiment: Anhydro donor **6** (49 mg, 110 µmol) and donor **3** (61 mg, 110 µmol) were used in a competitive glycosylation reaction using acceptor **11** (3 equiv) and following the general procedure described for AgOTf/*p*-NO_2PhSCl-promoted glycosylations. The experiment yielded a 2.2/1 mixture of dimeric products **17**/**14** (90 mg, 110 µmol, quant.). Diagnostic peaks used for the determination of the product ratio: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (d, *J* = 3.4 Hz, 0.64H, H-1α' product **14**), 4.44 – 4.37 (m, 3.65H, H-4'α product **17**, CH_2 Bn-β product **17**), 3.19 (s, 1.00H, H-5'β product **14**).

NIS/TfOH-promoted experiment: Anhydro donor **6** (49 mg, 110 µmol) and donor **3** (61 mg, 110 µmol) were used in a competitive glycosylation reaction using acceptor **11** (3 equiv) and following the general procedure described for NIS/TfOH-promoted glycosylations. The experiment yielded a 2.5/1 mixture of dimeric products **17**/**14** (89 mg, 109 µmol, 99%). Diagnostic peaks used for the determination of the product ratio: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (d, *J* = 3.4 Hz, 0.49H, H-1α' product **14**), 4.44 – 4.37 (m, 3.05H, H-4'α product **17**, CH_2 Bn-β product **17**), 3.19 (s, 0.71H, H-5'β product **14**).



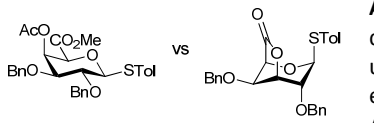
AgOTf/*p*-NO_2PhSCl-promoted experiment: Anhydro donor **6** (49 mg, 110 µmol) and donor **2** (71 mg, 110 µmol) were used in a competitive glycosylation reaction using acceptor **11** (3 equiv) and following the general procedure described for AgOTf/*p*-NO_2PhSCl-promoted glycosylations. The experiment yielded a 1.2/1 mixture of dimeric products **17**/**13** (97 mg, 110 µmol, quant.). Diagnostic peaks used for the determination of the product ratio: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 (s, 1.61H, CH_3 OMe-β product **17**), 3.33 (s, 1.45H, CH_3 OMe-α product **17**), 3.31 – 3.27 (m, 2.63H, CH_3 OMe product **13**).

NIS/TfOH-promoted experiment: Anhydro donor **6** (37 mg, 82 µmol) and donor **2** (45 mg, 82 µmol) were used in a competitive glycosylation reaction using acceptor **11** (3 equiv) and following the general procedure described for NIS/TfOH-promoted glycosylations. The experiment yielded a 1.3/1 mixture of dimeric products **17**/**13** (68 mg, 82 µmol, quant.). Diagnostic peaks used for the determination of the product ratio: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 (s, 1.98H, CH_3 OMe-β product **17**), 3.33 (s, 3.13H, CH_3 OMe-α product **17**), 3.31 – 3.27 (m, 4.00H, CH_3 OMe product **13**).

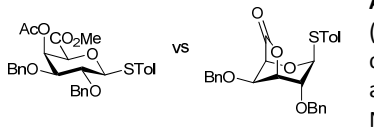


AgOTf/*p*-NO_2PhSCl-promoted experiment: Uronic acid donor **5** (59 mg, 110 µmol) and donor **4** (61 mg, 110 µmol) were used in a competitive glycosylation reaction using acceptor **11** (3 equiv) and following the general procedure described for AgOTf/*p*-NO_2PhSCl-promoted glycosylations. The experiment yielded a 1/1.3 mixture of dimeric products **16**/**15** (79 mg, 90 µmol, 81%). Diagnostic peaks used for the determination of the product ratio: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (d, *J* = 2.6 Hz, 0.77H, H-4'α product **16**, H-4'β product **16**), 5.48 (d, *J* = 3.0, 1.00H, H-4'α product **15**, H-4'-β, product **15**).

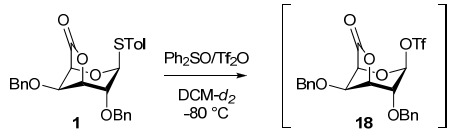
NIS/TfOH-promoted experiment: Uronic acid donor **5** (54 mg, 100 µmol) and donor **4** (55 mg, 100 µmol) were used in a competitive glycosylation reaction using acceptor **11** (3 equiv) and following the general procedure described for NIS/TfOH-promoted glycosylations. The experiment yielded a 1/11 mixture of dimeric products **16**/**15** (76 mg, 86 µmol, 86%). Diagnostic peaks used for the determination of the product ratio: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (d, *J* = 2.6 Hz, 0.09H, H-4'α product **16**, H-4'β product **16**), 5.48 (d, *J* = 3.0, 1.00H, H-4'α product **15**, H-4'-β, product **15**).



AgOTf/*p*-NO_2PhSCl-promoted experiment: Uronic acid lactone donor **1** (49 mg, 110 µmol) and donor **6** (49 mg, 110 µmol) were used in a competitive glycosylation reaction using acceptor **11** (3 equiv) and following the general procedure described for AgOTf/*p*-NO_2PhSCl-promoted glycosylations. The experiment yielded a 1/2.4 mixture of dimeric products **12**/**17** (79 mg, 110 µmol, quant.). Diagnostic peaks used for the determination of the product ratio: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (dd, *J* = 4.6, 1.3 Hz, 0.33H, H-3'β product **12β**[28]), 4.14 (dd, *J* = 11.1, 3.8 Hz, 1.26H, H-6α product **17**), 4.11 (s, 0.63H, H-4'α product **12α**[28]), 3.87 (dd, *J* = 9.4, 3.1 Hz, 1.00H, H-6'β product **17**).



AgOTf/*p*-NO_2PhSCl-promoted experiment: Uronic acid donor **5** (59 mg, 110 µmol) and donor **1** (49 mg, 110 µmol) were used in a competitive glycosylation reaction using acceptor **11** (3 equiv) and following the general procedure described for AgOTf/*p*-NO_2PhSCl-promoted glycosylations. The experiment yielded a 2.4/1 mixture of dimeric products **16**/**12** (74 mg, 86 µmol, 78%). Diagnostic peaks used for the determination of the product ratio: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (d, *J* = 2.6 Hz, 1.20H, H-4'α product **16**, H-4'β product **16**), 4.33 (s, 0.17H, H-4'β product **12β**[28]), 4.11 (s, 0.33H, H-4'α product **12α**[28]).



[2,4-*O*-di-benzyl-β-D-galactopyranosyluronosyl-6,3-lactone] triflate (18): Uronic acid lactone donor **1** (13 mg, 30 µmol, 1 equiv) and Ph_2SO (8 mg, 39 µmol, 1.3 equiv) were coevaporated together with toluene (2x). The residue was dissolved in DCM-d_2 (0.6 mL) and transferred to an NMR tube under an argon atmosphere. The tube was capped with a septum. The NMR probe was cooled to -80 °C and the sample was locked and shimmed. In an acetone bath (-80 °C) the sample was treated with Tf_2O (39 µmol, 1.3 equiv), shaken thrice and placed back in the NMR magnet. The first ^{1}H spectrum was immediately recorded. The stability of the observed anomeric triflate **18** was checked by repeatedly allowing the temperature to rise 10 °C and recording ^{1}H spectra. The triflate was stable up to -10 °C. ^{1}H NMR (400

MHz, CD_2Cl_2, T = 193 K) δ 6.06 (s, 1H, H-1), 4.91 (d, *J* = 4.5 Hz, 1H, H-3), 4.69 (d, *J* = 11.4 Hz, 1H, CH_2 Bn), 4.61 – 4.50 (m, 3H, CH_2 Bn), 4.40 (s, 1H, H-4), 4.35 (s, 1H, H-5), 4.27 (d, *J* = 4.6 Hz, 1H, H-2). ^{13}C NMR (100 MHz, CD_2Cl_2, HH-COSY, HSQC, T = 193 K): δ 170.4 (C=O), 104.2 (C-1), 77.5 (C-3), 75.1 (C-2), 73.4 (C-4), 73.1, 71.1 (CH_2 Bn), 71.0 (C-5); ^{13}C-GATED (125 MHz, $CDCl_3$): 104.2 ($J_{C1,H1}$ = 189 Hz).

References and notes

1. Original publication: Christina, A. E.; Muns, J. A.; Olivier, J. Q. A.; Visser, L.; Hagen, B.; van den Bos, L. J.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *Eur. J. Org. Chem.* doi: 10.1002/ejoc.201200717
2. See for examples of syntheses of pectin fragments and for the use of uronic acids in synthesis in general: Codée, J. D. C.; Christina, A. E.; Walvoort, M. T. C.; Overkleeft, H. S.; van der Marel, G. A. *Top. Curr. Chem.* **2011**, *301*, 253–289.
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23. When 3,6-anhydro thiogalactoside **6** is regarded as a deoxy sugar, the anhydro bridge does not seem to contribute favorably to the reactivity of the donor. For comparison: Wong and co-workers have established that per-benzylated fucose (RRV 72000) is 4 times as reactive as the corresponding perbenzylated galactosyl donor.
24. The RRV's in the *p*-NO_2PhSCl/AgOTf glycosylations do not show a quantitative correlation throughout the series and the analysis is therefore limited to the trends observed in this series.
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27. The $^1J_{C1\text{-}H1}$ coupling constant for an equatorial anomeric proton is generally higher (by approximately 10 Hz) than that of the corresponding axial anomeric proton. In analogy to the coupling constant obtained for 4,6-*O*-benzylidene-2,3-*O*-methyl-α-D-mannosyl triflate ($^1J_{C1\text{-}H1}$ = 185 Hz), having an equatorially oriented anomeric proton [Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217 – 11223], and the $^1J_{C1\text{-}H1}$ coupling constant in [methyl (4-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy mannopyranosyl uronosyl)] triflate, having an axially oriented proton when adopting a $^1C_4$ conformation ($^1J_{C1\text{-}H1}$ = 177 Hz) [Walvoort, M. T. C.; Lodder, G.; Mazurek, J.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Am. Chem. Soc.* **2009**, *131*, 12080-12081], the large value for the $^1J_{C1\text{-}H1}$ coupling constant in **12** is indicative of an axial triflate .
28. In the non-competitive glycosylation only the β-coupled product was observed, in this case however, the α-product was also found. At the moment it is unclear what lies at the basis of this observed phenomenon.

Chapter 5a

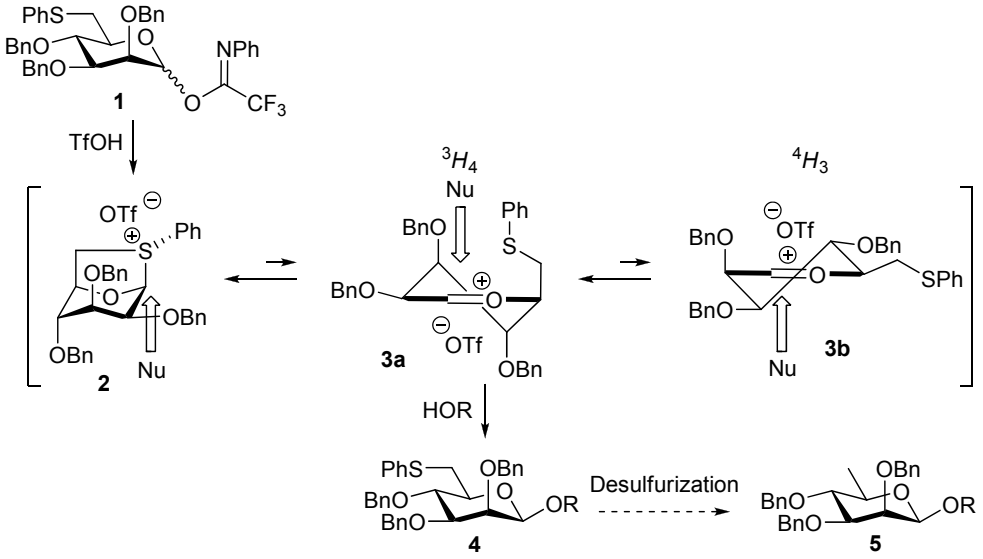
6-Thio Mannosides as 1,2-*Cis* Selective Glycosyl Donors[1]

Introduction

Neighboring group participation is a powerful means to steer the stereochemical course of a synthetic transformation. Especially in the area of carbohydrate chemistry it takes up a prominent position and the placement of a participating N- or O-acyl function at the C-2 position of a carbohydrate donor is commonly used to secure the stereoselective formation of 1,2-*trans* glycosidic bonds.[2] C-2-thio- and C-2-seleno-ethers have also been exploited to direct the stereochemical outcome of glycosylation reactions and various groups have reported on their use for the construction of 1,2-*trans* linkages.[3,4,5] Alternatively, Boons and co-workers recently developed a chiral auxiliary for the stereoselective formation of 1,2-*cis* glucosyl and galactosyl linkages based on a participating chiral thioether grafted on the C-2-hydroxyl of the donor.[6] Turnbull and co-workers have reported on glycosylations of bicyclic methyl sulfonium xylofuranosides, which, upon reaction with an acceptor nucleophile, provided the α-linked disaccharides with moderate selectivity.[7] The rate of success of participating thio functions appears to depend on the relative stability of the sulfonium species on the one hand and the corresponding oxocarbenium ions on the other, in combination with the ease of substitution of both species.[3,8] As Woerpel and co-workers

have convincingly demonstrated, the intermediate sulfonium ions can serve as a reservoir for the corresponding oxocarbenium ions, which often are more reactive and react in a distinct stereochemical manner.[9] Based on these precedents it was reasoned that activation of a mannosyl donor (such as **1**, Scheme 1), equipped with a thio ether at C-6, can lead to the formation of a bicyclic sulfonium ion **2**.

Scheme 1



Mechanistic strategy for the synthesis of β-rhamnosides.

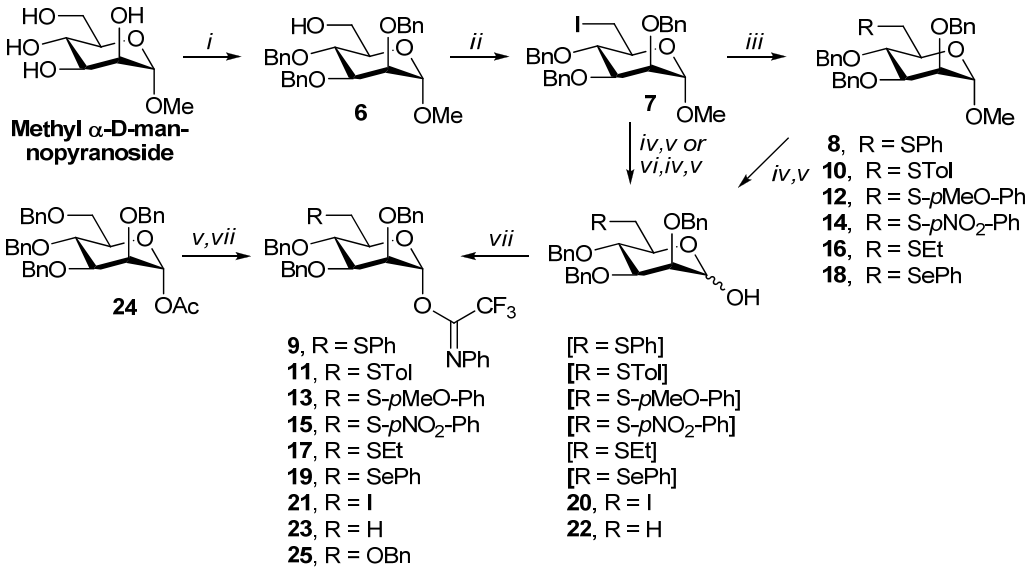
This sulfonium ion can serve as a reservoir for the structurally closely related but more reactive oxocarbenium ion-triflate anion pairs **3a** and **3b**. The $^3H_4$ oxocarbenium ion **3a** should be favored over its $^4H_3$ counterpart **3b**, because the former places all ring substituents in a favorable spatial orientation.[10] As indicated by Woerpel and co-workers, the C-2 alkoxy group preferentially takes up a *pseudo* equatorial position in a pyranosyl oxocarbenium ion half chair, thereby allowing for hyperconjugative stabilization of the cation by donation of electron density of the perpendicular $\sigma_{C\text{-}H}$ bond. Beside, alkoxy substituents at C-3 and C-4 prefer to occupy a *pseudo* axial orientation to minimize their electron-withdrawing effect,[11] and to allow for the donation of electron density from the heteroatom lone pairs into the electron-deficient oxocarbenium ion.[10] It was hypothesized that the C-5 methylene thioether in a *pseudo* axial orientation contributes to the relative stability of **3a** with respect to **3b** by stabilizing the anomeric positive charge by the sulfur lone pair electrons. An incoming nucleophile preferentially attacks oxocarbeniums **3a** or **3b** on the diastereotopic faces leading to a chair-like transition state to ultimately give the β- or α-product, respectively. Like **3b**, nucleophilic attack on bicyclic sulfonium ion **2** will result in the formation of the α-

product. Thus, although the product forming intermediates **2**, **3a** and **3b** occur in a dynamic equilibrium, the involvement of the C-5 methylene thioether in the stereochemical outcome can be deduced from the formation of β-product **4**. Desulfurization of this β-6-thio mannoside can then provide the corresponding β-D-rhamnoside **5** in a straightforward manner.[12,13]

Results and Discussion

To investigate the stereodirecting effect in glycosylation reactions a variety of C-6 thioethers, a C-6-selenoether, and a C-6-iodide[3,14] compounds **9**, **11**, **13**, **15**, **17**, **19** and **21** were synthesized. All these functionalities have previously been used as participating groups. The perbenzylated mannosyl donor **25** and the C-6 deoxy donor **23** were produced to be included in the study as reference donors (Scheme 2).

Scheme 2



Reagents and conditions: (*i*) (1) TrCl, pyridine, 50 °C, (2) BnBr, NaH, DMF, (3) *p*-TsOH, MeOH (75% over 3 steps); (*ii*) ref. 15; (*iii*) DiPEA (NaH for **16**), RH, DMF (89% (**8**), 94% (**10**), 92% (**12**), 72% (**14**), 79% (**16**), quant. (**18**)) (*iv*) cat. H_2SO_4, Ac_2O; (*v*) piperidine, THF (81% over 2 steps (**20**), 81% over 3 steps (**22**)); (*vi*) $NaBH_4$, DMSO, 100 °C; (*vii*) $CF_3C(=NPh)Cl$, Cs_2CO_3, acetone, H_2O (86% (**21**), 73% (**23**) 53% over 2 steps (**25**), yield over 3 steps: 94% (**9**), 98% (**11**), 95% (**13**), 81% (**15**), 90% (**17**), 77% (**19**)).

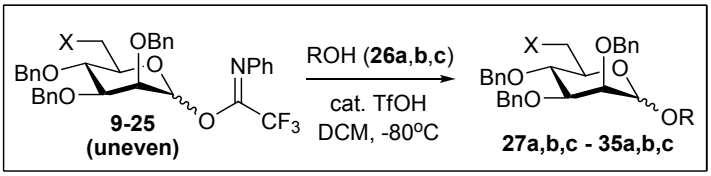
Thus, methyl D-mannopyranoside was converted to alcohol **6** in 75% over 3 steps: tritylation of the primary alcohol, benzylation of the remaining alcohols and acid-mediated detritylation. Iodination of the primary alcohol was accomplished in toluene using triphenylphosphine, iodine and imidazole.[15] Nucleophilic displacement of the primary iodide

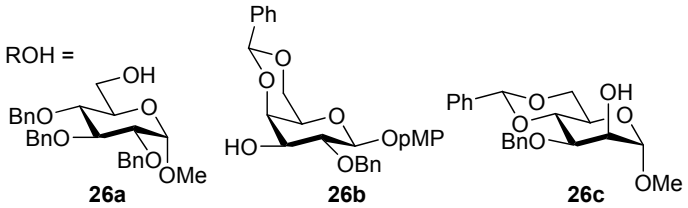
in **7** using suitable thiols and phenylselenol afforded thioethers **8**, **10**, **12**, **14** and **16** and selenoether **18**. These compounds were all converted to the corresponding hemiacetals by sulfuric acid-catalyzed acetolysis and subsequent nucleophilic acetyl cleavage. Installation of the *N*-phenyltrifluoroacetimidate[16] moiety gave mannosyl donors **9**, **11**, **13**, **15**, **17** and **19**. 6-Deoxy-6-iodo donor **21** was accessed by subjecting methyl mannoside **7** to the last mentioned three reaction steps. Reduction of the iodide in **7** with $NaBH_4$ at elevated temperatures followed by two step conversion of the anomeric methoxide to a lactol function gave rhamnose **22**. Treatment with 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride and base furnished donor **23**. Finally, known acetyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside[17] **24** was converted to donor **25** by deacetylation and installment of an anomeric *N*-phenyltrifluoroacetimidate functionality.

Next, donors **9**, **11**, **13**, **15**, **17**, **19**, **21**, **23** and **25** were combined with three acceptors (**26a**, **26b**, **26c**) in a series of condensation reactions. Table 1 records the outcome of the glycosylations. The perbenzylated imidate **25** provided little to moderate β-selectivity, depending on which acceptor was used, in line with known results obtained with a perbenzylated mannosyl thiophenyl donor.[18] Condensations of rhamnose donor **23** proceeded with low selectivity with all three acceptors, also in line with known results.[18] The C-6-thio, seleno and iodo functionalized mannosyl donors on the other hand, all preferentially provided the 1,2-*cis* linked disaccharides, with the C-6-*S*-phenyl donor **9** performing best and the C-6-*S*-ethyl mannoside **17** showing least selectivity.

Although these results indicate that for the donors **9**, **11**, **13**, **15**, **17**, **19** and **21** the $^3H_4$-oxocarbenium ion **3b** can be the main product forming intermediate, no simple correlation between the nature of the C-6-thio-, C-6-seleno, or C-6-iodo functionality and stereochemical outcome of the reactions can be distilled from Table 1. Small changes in the dynamic equilibrium of the reactive intermediates **2**, **3a** and **3b** as a result of the different C-6 functionalities in combination with the different nucleophilicity of the three acceptors, contribute to the observed variation in stereoselectivity. Although direct S_N2 displacement of the activated imidate donors (having predominantly the α-configuration) by the acceptors is conceivable, this reaction mode is excluded as a major pathway because the variation in the amount of β-product in the different glycosylations, including the role of the C-thio/iodo/seleno function, cannot be accounted for by this pathway. Illustrative for this is the finding that most condensations with secondary acceptor **26b** proceed with better β-selectivity than the corresponding couplings with primary alcohol **26a**. The same reasoning holds for the intermediacy of α-triflates, that have been shown to be product forming intermediates in glycosylations using 4,6-*O*-benzylidene mannosyl donors[19] and mannosides equipped with electron withdrawing substituents.[20] Given the reactive ("armed") and conformationally unconstrained nature of the mannosyl donors used here, triflate intermediates are probably not the major product forming species.[20b,c] Because the C-6-*S*-phenyl donor **9** performed best in the model glycosylations the study was continued with donor **9**. The formation of the bridged sulfonium ion **36** from this donor and its reactivity was assessed in a variable temperature NMR experiment (Scheme 3).

Table 1 Condensations of donors **9**, **11**, **13**, **15**, **17**, **19**, **21**, **23** and **25**.



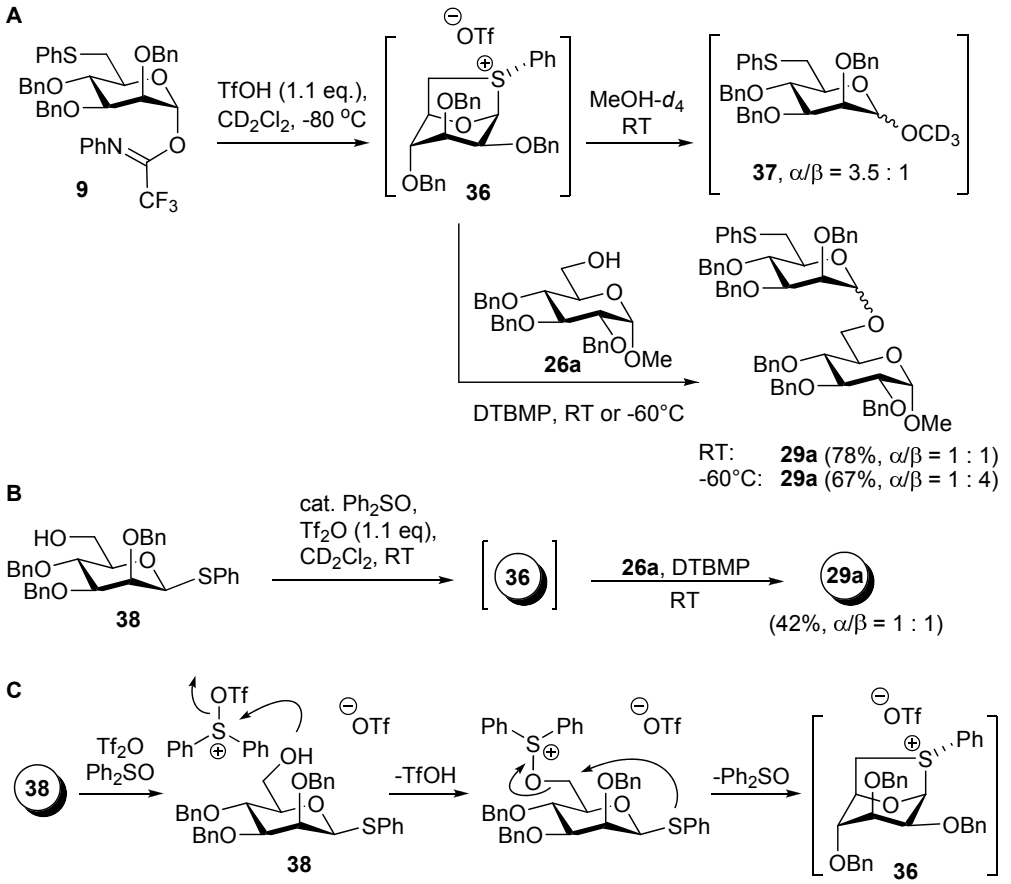


Entry	Donor	**26a**	**26b**	**26c**
		Product (yield,α/β)[a,b]		
1	**25**, X = OBn	**27a** (94%, 1:3.5)	**27b** (88%, 1:1)	**27c** (99%, 1:4)
2	**23**, X = H	**28a** (91%, 1:2.5)	**28b** (87%, 1:1.5)	**28c** (90%, 1:1)
3	**9**, X = SPh	**29a** (90%, 1:7)	**29b** (89%, 1:11)	**29c** (87%, 1:5)
4	**11**, X = STol	**30a** (86%, 1:5)	**30b** (56%, 1:8)	**30c** (89%, 1:3.5)
5	**13**, X = S-*p*MeOPh	**31a** (85%, 1:5)	**31b** (58%, 1:7)	**31c** (88%, 1:4.5)
6	**15**, X = S-*p*NO_2Ph	**32a** (79%, 1:7)	**32b** (91%, 1:4)	**32c** (90%, 1:4)
7	**17**, X = SEt	**33a** (80%, 1:4)	**33b** (86%, 1:3.5)	**33c** (78%, 1:1.5)
8	**19**, X = SePh	**34a** (99%, 1:7)	**34b** (96%, 1:10)	**34c** (92%, 1:3)
9	**21**, X = I	**35a** (84%, 1:7)	**35b** (95%, 1:6)	**35c** (87%, 1:3)

(a) Isolated yield after size exclusion chromatography. Anomeric ratio based on ^{1}H NMR of the epimeric mixture. The anomeric configuration of the mannosidc linkages has been established using C1'-H1' coupling constants; (b) Disaccharide structures can be found in the experimental section.

Treatment of **9** with an equimolar amount of triflic acid (TfOH) at -80 ^{o}C in CD_2Cl_2 led to the near instantaneous formation of **36**, tentatively assigned as the exo-sulfonium isomer. This species proved to be stable up to room temperature (decomposition set in after several hours at room temperature) and treatment of the mixture with excess MeOH-*d*4 led, after 16

Scheme 3



Formation of and reactions with bicyclic sulfonium ion **36**.

hours, to the formation of methyl mannoside **37** as an anomeric mixture (α/β= 3.5 : 1, Scheme 3A).Interestingly, sulfonium ion **36** could also be generated from the C-6-OH β-*S*-phenyl mannoside **38** by treating this thiomannoside with a catalytic amount of diphenylsulfoxide (Ph_2SO) and equimolar triflic anhydride (Tf_2O).[21,22] The outcome of this latter experiment substantiated the result of the former pre-activation experiment. It also shows that the primary alcohol in **38** is more nucleophilic towards diphenylsulfonium bistriflate than the anomeric thiophenyl functionality[22] and that a catalytic amount of Ph_2SO can be used for complete activation of donor **38**. Scheme 3C provides a mechanistic picture of this activation pathway. Addition of acceptor **26a** to sulfonium ion **36**, generated from **38** at room temperature, provided disaccharide **29a** in 42% yield as a 1:1 α/β mixture (Scheme 3B). A similar stereochemical result was obtained when **9** was pre-activated with an equimolar amount of TfOH at -80 °C followed by reaction with **26a** in the presence of di-*tert*-butylmethylpyridine (DTBMP) at room temperature (Scheme 3A).[23] Importantly, β-selectivity

was restored when the coupling reaction was executed at low temperature: generation of **36** from **9** using an equimolar amount of TfOH at -80 °C, and ensuing reaction with acceptor **26a** at -60 °C delivered **29a** in a 1 : 4 α/β-ratio (67% yield). These results can be rationalized by the mechanistic proposal in Scheme 1. The equilibrium of bridged sulfonium ion **2** (with R = Ph) and oxocarbenium ions **3a** and **3b** lies to the side of the sulfonium ion. At low temperatures this species is not reactive enough to react with an incoming nucleophile, in line with the recent results obtained by Woerpel[9] and Turnbull.[7] Reaction takes place from the more reactive oxocarbenium ion **3a**, the formation of which is favored over the alternative half chair oxocarbenium ion **3b**, to produce the β-linked product in a Curtin-Hammett type kinetic scenario. At higher temperatures sulfonium ion **2** and/or oxocarbenium ions **3a,b** can be attacked leading to the loss of stereoselectivity.

Conclusions

The selectivity of a panel of C-6 thioether donors, a C-6-selenoether donor, and a C-6-iodide *N*-phenyltrifluoroacetimidate mannosyl donor was probed in a series of condensation reactions. While all of these donors preferentially provided 1,2-*cis* linked disaccharides, C-6-*S*-phenyl donor **9** showed the best potential as a 1,2-*cis*-mannosylating agent. Variable temperature NMR experiments showed the formation of a bridged sulfonium ion upon activation of S-phenyl donor **9**. The stereoselectivity in the *cis*-mannosylation reaction can be rationalized with a Curtin-Hammett kinetic scenario in which the quasi-stable bicyclic $^{1}C_{4}$-sulfonium ion intermediate is in equilibrium with the more reactive and β-selective mannosyl $^{3}H_{4}$-oxocarbenium, which places all ring-substituents in an electronically favorable position. The applicability of the 1,2-*cis*-mannosylating agent **9** in the synthesis of rhamnosides shall be addressed in the following chapter.

Experimental section

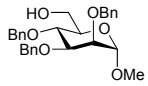
General Procedures: All chemicals were used as received. Trifluoromethanesulfonic anhydride (Tf_2O) was distilled from P_2O_5 and stored in a Schlenk flask. TLC analysis was conducted on silica gel-coated aluminum TLC sheets (Merck, silica gel 60, F_{245}). Compounds were visualized by UV absorption (245 nm), by spraying with 20% H_2SO_4 in ethanol or with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ 25 g/L, $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ 10 g/L, 10% H_2SO_4 in H_2O followed by charring at ~140 °C. Flash chromatography was performed on silica gel (Screening Devices, 40-63 µm 60Å, www.screeningdevices.com) using technical grade, distilled solvents. NMR spectra were recorded on a Bruker AV400. For solutions in $CDCl_3$ chemical shifts (δ) are reported relative to tetramethylsilane (^{1}H) or $CDCl_3$ (^{13}C). Peak assignments were made based on HH-COSY and HSQC measurements. Optical rotation was measured using a Propol automatic polarimeter. The IR absorbance was recorded using a Shimadzu FTIR-83000 spectrometer. Mass analysis was performed using a PE/SCIEX API 165 with an Electrospray Interface (Perkin-Elmer).

General experimental procedure for the preparation of 6-deoxy-6-thio/selenomannosides (8, 10, 12, 14, 16, 18): To a 0.1 M solution of the starting 6-deoxy-6-iodo-mannoside in DMF were added DiPEA

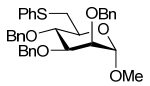
(1.2 equiv) and thiol/selenol (1.2 equiv). After stirring overnight the reaction mixture was diluted with Et_2O, washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. Flash column chromatography afforded the pure products.

General experimental procedure for the preparation of (*N*-phenyl)trifluoroacetimidates (9, 11, 13, 15, 17, 19): To the subject methyl glycoside was added 3 mL of a H_2SO_4/Ac_2O (1/999, v/v) solution and the reaction was stirred for 90 minutes. The solution was neutralized with triethylamine, concentrated and coevaporated with toluene. To the crude acetate was added 3 mL of a piperidine/THF (1/19, v/v) solution and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc, washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude hemiacetal was dissolved in 2.85 mL acetone and 0.15 mL H_2O, 224 mg Cs_2CO_3 and 114 µL $ClC(C{=}NPh)CF_3$ were added. After stirring for 3 days, the mixture was filtered over celite and the filtrate was evaporated. Purification of the crude product by flash column chromatography (silica was pretreated with triethylamine/PE (1/19 → 0/1)) using toluene/PE (1/1 → 1/0) as eluent yielded the desired imidates.

General glycosylation procedure: The donor (0.22 mmol, 1 equiv) and acceptor (0.33 mmol, 1.5 equiv) were dissolved in 4.4 mL DCM and stirred over 3Å molecular sieves for 30 minutes. The mixture was then cooled to -80 °C after which TfOH (0.044 mmol) in DCM (0.1 mL) was added and the reaction was stirred overnight at -80 °C. The reaction was quenched by the addition of 1mL Et_3N at -80 °C. After filtration over celite, the mixture was washed with sat. aq. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by size exclusion chromatography (DCM/MeOH, 1/1, v/v) yielded the coupled products.

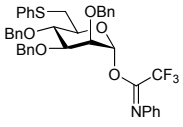


Methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (6): A solution of methyl α-D-mannopyranoside (9.71 g, 50.0 mmol) and TrCl (15.33 g, 55.0 mmol) in pyridine (250 mL) was heated to 50 °C and stirred overnight. The mixture was quenched by the addition of MeOH (10 mL) and concentrated *in vacuo*. The product was dissolved in EtOAc and washed with H_2O three times. The organic layer was dried over $MgSO_4$ and concentrated. The now obtained yellow oil was dissolved in DMF (250 mL) and BnBr (20 mL, 165 mmol) was added. The mixture was cooled to 0 °C, NaH (60 % in mineral oil, 6.6 g, 165 mmol) was added portion wise and the reaction was left to stir for 24 hours. The mixture was then quenched by addition of MeOH (20 mL). DMF was removed by diluting the mixture with Et_2O and washing it three times with H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The remaining brown oil was dissolved in a mixture of DCM (50 mL) and MeOH (200 mL). To this solution a catalytic amount of *p*-toluenesulfonic acid monohydrate was added until the pH was approximately 1 and the reaction was left to stir at room temperature over the weekend. After neutralization with Et_3N the solvents were removed. The remaining oil was purified by column chromatography using EtOAc/PE (1/4 → 2/3) as the eluent to give 17.33 g of the title compound **6** (37.3 mmol, 75 % over 3 steps). Spectroscopic data were in accordance with known literature data.[24]

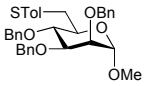


Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-*S*-phenyl-6-thio-α-D-mannopyranoside (8): Iodine **7** (287 mg, 500 µmol) was treated with thiophenol according to the general procedure delivering 6-phenylmannoside **8** (248 mg, 445 µmol, 89%). Flash column chromatography eluent: EtOAc/PE (0/1 → 1/4). R_f 0.49 (EtOAc/PE, 1/9, v/v); $[\alpha]_D^{22}$ +17 (c 2.0, CH_2Cl_2); IR (neat, cm^{-1}) 3030, 2912, 1584, 1497, 1482, 1454, 1439, 1065, 732, 695; ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.50 – 6.95 (m, 20H, H_{arom}), 4.97 (d, *J* = 11.1 Hz, 1H, CH_2 benzyl), 4.76 – 4.64 (m, 3H, CH_2 benzyl, H-1), 4.64 – 4.53 (m, 3H, CH_2 benzyl), 3.91 – 3.71 (m, 4H, H-3, H-4, H-2, H-5), 3.42 (dd, *J* = 13.4, 1.7 Hz, 1H, H-6), 3.27 (s, 3H, CH_3 OMe), 3.02 (dd, *J* = 13.4, 8.6 Hz, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 138.3, 138.2, 138.1 (C_q), 137.0, 128.7, 128.4, 128.3, 128.2, 127.8, 127.7, 127.5, 125.4 (CH_{arom}), 98.7 (C-1), 80.1 (C-3), 77.7 (C-4), 75.0 (CH_2 benzyl), 74.4 (C-2), 72.6,

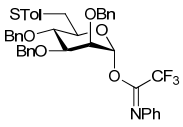
71.9 (CH_2 benzyl), 70.9 (C-5), 54.6 (CH_3 OMe), 35.6 (C-6); HRMS $[M+Na]^+$ calcd for $C_{34}H_{36}O_5SNa$ 579.21757, found 579.21688.



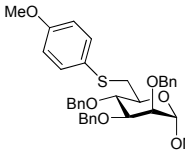
2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-phenyl-6-thio-D-mannopyranosyl (*N*-phenyl)trifluoroacetimidate (9): 6-*S*-phenyl-6-thio-α-D-mannopyranoside **8** (248 mg, 445 µmol) was converted according to the general procedure to the title imidate (299 mg, 419 µmol, 94% over 3 steps) with trace amounts of its β configured epimer. R_f 0.46 (toluene); IR (neat, cm^{-1}) 3033, 2872, 1718, 1598, 1490, 1454, 1116, 736, 693; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, T = 333 K) δ 7.39 – 6.99 (m, 23H, H_{arom}), 6.77 (d, *J* = 7.7 Hz, 2H, H_{arom}), 6.15 (br s, 1H, H-1), 4.92 (d, *J* = 11.2 Hz, 1H, CH_2 benzyl), 4.70 – 4.54 (m, 5H, CH_2 benzyl), 4.00 – 3.90 (m, 2H, H-4, H-5), 388 – 3.80 (m, 2H, H-3, H-2), 3.37 (d, *J* = 13.1 Hz, 1H, H-6), 3.11 – 2.99 (m, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC, T = 333 K) δ 143.6, 138.3, 138.1, 137.8, 136.8 (C_q), 129.8, 129.5, 128.8, 128.7, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 126.1, 124.3, 119.5 (CH_{arom}), 95.4 (C-1), 79.3 (C-3), 77.1 (C-4), 75.2 (CH_2 benzyl), 74.1 (C-5), 73.9 (C-2), 72.9, 72.7 (CH_2 benzyl), 36.5 (C-6); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$, T = 333 K) δ 95.4 ($J_{C1\text{-}H1}$ = 176.1 Hz, C-1); HRMS $[M+Na]^+$ calcd for $C_{42}H_{38}F_3NO_5SNa$ 736.23150, found 736.23161.



Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-*S*-*p*-tolyl-6-thio-α-D-mannopyranoside (10): Iodine **7** (287 mg, 500 µmol) was treated with thiocresol according to the general procedure delivering 6-tolylmannoside **10** (267 mg, 468 µmol, 94%). Flash column chromatography eluent: EtOAc/PE (0/1 → 1/4). R_f 0.52 (EtOAc/PE, 1/9, v/v); $[\alpha]_D^{22}$ +17 (c 2.0, CH_2Cl_2); IR (neat, cm^{-1}) 2913, 1495, 1454, 1067, 735, 697; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.39 – 7.18 (m, 17H, H_{arom}), 7.01 (d, *J* = 8.0 Hz, 2H, H_{arom}), 4.96 (d, *J* = 11.2 Hz, 1H, CH_2 benzyl), 4.75 – 4.66 (m, 3H, CH_2 benzyl, H-1), 4.62 – 4.53 (m, 3H, CH_2 benzyl), 3.88 – 3.71 (m, 4H, H-3, H-4, H-2, H-5), 3.39 (dd, *J* = 13.4, 1.9 Hz, 1H, H-6), 3.29 (s, 3H, CH_3 OMe), 3.01 (dd, *J* = 13.4, 8.7 Hz, 1H, H-6), 2.26 (s, 3H, CH_3 Tol); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 138.6, 138.5, 138.4, 135.8, 133.5 (C_q), 129.7, 129.5, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8, 127.7 (CH_{arom}), 99.0 (C-1), 80.4 (C-3), 78.0 (C-4), 75.3 (CH_2 benzyl), 74.7 (C-2), 72.9, 72.2 (CH_2 benzyl), 71.2 (C-5), 54.8 (CH_3 OMe), 36.7 (C-6), 21.1 (CH_3 Tol); HRMS $[M+Na]^+$ calcd for $C_{35}H_{38}O_5SNa$ 593.23322, found 593.23261.

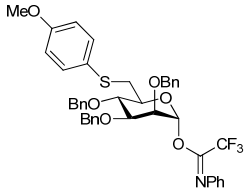


2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-*p*-tolyl-6-thio-D-mannopyranosyl (*N*-phenyl)trifluoroacetimidate (11): 6-*S*-*p*-tolyl-6-thio-α-D-mannopyranoside **10** (267 mg, 468 µmol) was converted according to the general procedure to the title imidate **11** (333 mg, 458 µmol, 98% over 3 steps) with trace amounts of its β configured epimer. R_f 0.51 (toluene); IR (neat, cm^{-1}) 3031, 2920, 1714, 1598, 1490, 1454, 1118, 735, 694; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, T = 333 K) δ 7.36 – 7.16 (m, 19H, H_{arom}), 7.07 (t, *J* = 7.4 Hz, 1H, H_{arom}), 7.02 (d, *J* = 8.0 Hz, 2H, H_{arom}), 6.77 (d, *J* = 7.7 Hz, 2H, H_{arom}), 6.16 (br s, 1H, H-1), 4.91 (d, *J* = 11.1 Hz, 1H, CH_2 benzyl), 4.68 – 4.53 (m, 5H, CH_2 benzyl), 3.96 – 3.88 (m, 2H, H-4, H-5), 3.88 – 3.80 (m, 2H, H-3, H-2), 3.33 (d, *J* = 13.1 Hz, 1H, H-6), 3.02 (dd, *J* = 13.6, 7.0 Hz, 1H, H-6), 2.27 (s, 3H, CH_3 Tol); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC, T = 333 K) δ 143.7, 138.3, 138.2, 137.8, 136.3, 133.0 (C_q), 130.7, 130.4, 129.6, 129.5, 129.1, 128.7, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 124.3, 119.5 (CH_{arom}), 95.4 (C-1), 79.3 (C-3), 77.1 (C-4), 75.2 (CH_2 benzyl), 74.1 (C-5), 74.0 (C-2), 72.9, 72.7 (CH_2 benzyl), 37.2 (C-6), 20.9 (CH_3 Tol); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$, T = 333 K) δ 95.4 ($J_{C1\text{-}H1}$ = 178.1 Hz, C-1); HRMS $[M+Na]^+$ calcd for $C_{42}H_{40}F_3NO_5SNa$ 750.24715, found 750.24723.

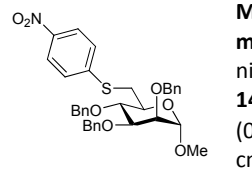


Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-*S*-*p*-methoxyphenyl-6-thio-α-D-mannopyranoside (12): Iodine **7** (287 mg, 500 µmol) was treated with *p*-methoxythiophenol according to the general procedure delivering 6-*p*-methoxymannoside **12** (271 mg, 462 µmol, 92%). Flash column chromatography eluent: EtOAc/PE (0/1 → 1/4). R_f 0.31 (EtOAc/PE, 1/9, v/v); $[\alpha]_D^{22}$ +17 (c 2.0, CH_2Cl_2); IR (neat, cm^{-1}) 3030, 2910, 1593, 1494, 1454, 1243, 1066, 735, 697; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.39 – 7.20 (m, 17H, H_{arom}), 6.80 – 6.73 (m,

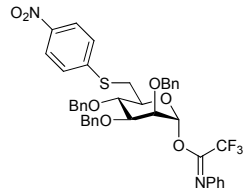
2H, H_{arom}), 4.94 (d, *J* = 11.1 Hz, 1H, CH_2 benzyl), 4.75 – 4.66 (m, 3H, CH_2 benzyl, H-1), 4.59 – 4.54 (m, 3H, CH_2 benzyl), 3.87 – 3.72 (m, 4H, H-3, H-4, H-2, H-5), 3.71 (s, 3H, CH_3 PhOMe), 3.35 – 3.25 (m, 4H, H-6, CH_3 OMe), 3.00 (dd, *J* = 13.4, 8.6 Hz, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 158.7, 138.6, 138.5, 138.4 (C_q), 132.5, 128.5, 128.0, 127.8, 127.7 (CH_{arom}), 127.4 (C_q), 114.7 (CH_{arom}), 98.9 (C-1), 80.4 (C-3), 78.0 (C-4), 75.2 (CH_2 benzyl), 74.7 (C-2), 72.8, 72.2 (CH_2 benzyl), 71.3 (C-5), 55.4 (CH_3 PhOMe), 54.9 (CH_3 OMe), 38.1 (C-6); HRMS $[M+Na]^+$ calcd for $C_{35}H_{38}ClO_6SNa$ 609.22813, found 609.22768.



2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-*p*-methoxyphenyl-6-thio-D-mannopyranosyl (*N*-phenyl)trifluoroacetimidate (13): 6-*S*-*p*-methoxyphenyl-6-thio-α-D-mannopyranoside **12** (271 mg, 462 µmol) was converted according to the general procedure to the title imidate **13** (325 mg, 437 µmol, 95% over 3 steps) with trace amounts of its β configured epimer. Rf 0.37 (toluene); IR (neat, cm^{-1}) 3034, 2930, 1714, 1596, 1494, 1454, 1118, 736, 695; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, T = 333 K) δ 7.38 – 7.18 (m, 19H, H_{arom}), 7.08 (t, *J* = 7.5 Hz, 1H, H_{arom}), 6.81 – 6.73 (m, 4H, H_{arom}), 6.16 (br s, 1H, H-1), 4.90 (d, *J* = 11.2 Hz, 1H, CH_2 benzyl), 4.68 – 4.54 (m, 5H, CH_2 benzyl), 3.94 – 3.88 (m, 2H, H-4, H-5), 3.87 – 3.80 (m, 2H, H-3, H-4), 3.73 (s, 3H, CH_3 OMe), 3.26 (dd, *J* = 13.8, 1.9 Hz, 1H, H-6), 2.98 (dd, *J* = 13.7, 7.2 Hz, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC, T = 333 K) δ 159.2, 143.7, 138.3, 138.1, 137.8 (C_q), 133.6, 133.4, 128.7, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7 (CH_{arom}), 127.0 (C_q), 124.3, 119.5, 114.7 (CH_{arom}), 95.5 (C-1), 79.2 (C-3), 77.1 (C-4), 75.1 (CH_2 benzyl), 74.1 (C-5), 73.9 (C-2), 72.9, 72.7 (CH_2 benzyl), 55.3 (CH_3 OMe), 38.4 (C-6); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$, T = 333 K) δ 95.5 ($J_{C1\text{-}H1}$ = 176.1 Hz, C-1); HRMS $[M+Na]^+$ calcd for $C_{42}H_{40}F_3NO_6SNa$ 766.24206, found 766.24223.

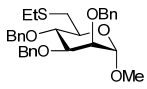


Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-*S*-*p*-nitrophenyl-6-thio-α-D-mannopyranoside (14): Iodine **7** (5.00 g, 8.70 mmol) was treated with *p*-nitrothiophenol according to the general procedure delivering 6-thiomannoside **14** (3.75 g, 6.23 mmol, 72%). Flash column chromatography eluent: EtOAc/PE (0/1 → 3/7). Rf 0.30 (EtOAc/PE, 1/9, v/v); $[\alpha]_D^{22}$ +12 (c 2.0, CH_2Cl_2); IR (neat, cm^{-1}) 3031, 2911, 1579, 1508, 1480, 1454, 1335, 1065, 737, 697; ^{1}H NMR (300 MHz, $CDCl_3$, HH-COSY, HSQC) δ 8.01 – 7.97 (m, 2H, H_{arom}), 7.49 – 7.12 (m, 17H, H_{arom}), 5.05 (d, *J* = 11.2 Hz, 1H, CH_2 benzyl), 4.78 – 4.63 (m, 5H, CH_2 benzyl, H-1), 4.61 (s, 2H, CH_2 benzyl), 3.91 – 3.81 (m, 2H, H-3, H-4), 3.81 – 3.78 (m, 1H, H-2), 3.78 – 3.70 (m, 1H, H-5), 3.42 (dd, *J* = 13.5, 1.7 Hz, 1H, H-6), 3.25 (s, 3H, CH_3 OMe), 3.02 (dd, *J* = 13.6, 8.8 Hz, 1H, H-6); ^{13}C NMR (75 MHz, $CDCl_3$, HH-COSY, HSQC) δ 147.7, 144.7, 138.1, 138.0 (C_q), 128.5, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 126.0, 124.3, 123.7 (CH_{arom}), 98.9 (C-1), 80.1 (C-3), 77.5 (C-4), 75.2 (CH_2 benzyl), 74.3 (C-2), 72.8, 71.9 (CH_2 benzyl), 70.9 (C-5), 54.7 (CH_3 OMe), 34.0 (C-6); HRMS $[M+Na]^+$ calcd for $C_{34}H_{35}NO_7SNa$ 624.20264, found 624.20243.

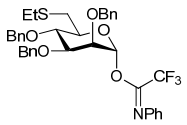


2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-*p*-nitrophenyl-6-thio-D-mannopyranosyl (*N*-phenyl)trifluoroacetimidate (15): 6-*S*-*p*-nitrophenyl-6-thio-α-D-mannopyranoside **14** (188 mg, 312 µmol) was converted according to the general procedure to the title imidate **15** (192 mg, 253 µmol, 81% over 3 steps) with trace amounts of its β configured epimer. Rf 0.43 (toluene); IR (neat, cm^{-1}) 3031, 2926, 1714, 1596, 1581, 1512, 1455, 1336, 1116, 741, 694; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, T = 333 K) δ 7.99 (d, *J* = 8.8 Hz, 2H, H_{arom}), 7.40 – 7.19 (m, 19H, H_{arom}), 7.09 (t, *J* = 7.3 Hz, 1H, H_{arom}), 6.72 (d, *J* = 7.7 Hz, 2H, H_{arom}), 6.09 (br s, 1H, H-1), 5.00 (d, *J* = 11.3 Hz, 1H, CH_2 benzyl), 4.72 – 4.54 (m, 5H, CH_2 benzyl), 4.00 – 3.85 (m, 3H, H-4, H-5, H-3), 3.83 (br s, 1H, H-2), 3.49 – 3.34 (m, 1H, H-6), 3.06 (dd, *J* = 13.8, 7.1 Hz, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC, T = 333 K) δ 147.2, 143.4, 138.1, 137.9, 137.7 (C_q), 128.8, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 128.0, 127.9, 127.0, 124.5, 123.8, 119.4 (CH_{arom}), 95.2 (C-1), 79.3 (C-3), 76.9 (C-4), 75.4 (CH_2 benzyl), 74.0 (C-5), 73.9 (C-2), 73.1, 72.7 (CH_2 benzyl), 34.6. (C-6); ^{13}C-HMBC

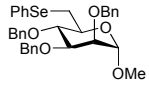
NMR (100 MHz, $CDCl_3$, T = 333 K) δ 95.2 ($J_{C1\text{-}H1}$ = 177.3 Hz, C-1); HRMS $[M+Na]^+$ calcd for $C_{42}H_{40}F_3NO_6SNa$ 766.24206, found 766.24209.



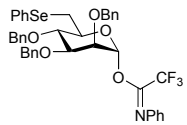
Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-*S*-ethyl-6-thio-α-D-mannopyranoside (16): To a solution of 3.22 g iodine **7** (5.61 mmol, 1 equiv) in 63 mL DMF was added 0.49 mL ethanethiol (6.55 mmol, 1.2 equiv) and 270 mg NaH (60% in mineral oil, 6.75 mmol, 1.2 equiv). The reaction was stirred for 1 hour at room temperature and quenched by the addition of acetic acid. The mixture was partitioned between Et_2O and water and the organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated. Flash column chromatography using EtOAc/PE (1/44 → 1/4) gave the title compound **16** (2.66 g, 4.42 mmol, 79%). R_f 0.56 (EtOAc/PE, 1/9, v/v); $[\alpha]_D^{22}$ +27 (c 2.0, CH_2Cl_2); IR (neat, cm^{-1}) 2916, 1497, 1454, 1055, 732, 696; ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.39 – 7.22 (m, 15H, H_{arom}), 4.96 (d, *J* = 11.1 Hz, 1H, CH_2 benzyl), 4.76 – 4.66 (m, 3H, H-1, CH_2 benzyl), 4.64 (d, *J* = 11.1 Hz, 1H, CH_2 benzyl), 4.59 (s, 2H, CH_2 benzyl), 3.87 (dd, *J* = 9.1, 2.9 Hz, 1H, H-3), 3.82 (t, *J* = 9.1 Hz, 1H, H-4), 3.77 (dd, *J* = 2.8, 1.9 Hz, 1H, H-2), 3.72 (td, *J* = 8.8, 2.0 Hz, 1H, H-5), 3.33 (s, 3H, CH_3 OMe), 2.95 (dd, *J* = 13.5, 2.1 Hz, 1H, H-6), 2.70 (dd, *J* = 13.5, 8.6 Hz, 1H, H-6), 2.60 (q, *J* = 7.4 Hz, 2H, CH_2 ethyl), 1.23 (t, *J* = 7.4 Hz, 3H, CH_2 ethyl); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 138.4, 138.3, 138.1 (C_q), 128.2, 127.8, 127.7, 127.5, 127.4 (CH_{arom}), 98.6 (C-1), 80.1 (C-3), 77.7 (C-4), 75.1 (C-2), 74.5 (C-2), 72.5 (CH_2 benzyl), 72.2 (C-5), 71.9 (CH_2 benzyl), 54.5 (CH_3 OMe), 33.4 (C-6), 26.7 (CH_2 ethyl), 14.7 (CH_3 ethyl); HRMS $[M+Na]^+$ calcd for $C_{30}H_{36}O_5SNa$ 531.21757, found 531.21699.



2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-ethyl-6-thio-D-mannopyranosyl (*N*-phenyl)trifluoroacetimidate (17): 6-*S*-ethyl-6-thio-α-D-mannopyranoside **16** (244 mg, 480 µmol) was converted according to the general procedure to the title imidate **17** (288 mg, 432 µmol, 90% over 3 steps) with trace amounts of its β configured epimer. R_f 0.47 (toluene); IR (neat, cm^{-1}) 2926, 1714, 1598, 1490, 1454, 1117, 735, 694; ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, T = 333 K) δ 7.37 – 7.18 (m, 17H, H_{arom}), 7.08 (t, *J* = 7.5 Hz, 1H, H_{arom}), 6.77 (d, *J* = 7.6 Hz, 2H, H_{arom}), 6.14 (br s, 1H, H-1), 4.93 (d, *J* = 11.1 Hz, 1H, CH_2 benzyl), 4.73 – 4.56 (m, 5H, CH_2 benzyl), 4.00 – 3.85 (m, 3H, H-4, H-5, H-3), 3.82 (t, *J* = 2.5 Hz, 1H, H-2), 2.94 (dd, *J* = 14.1, 2.2 Hz, 1H, H-6), 2.71 (dd, *J* = 14.1, 7.1 Hz, 1H, H-6), 2.59 (q, *J* = 7.4 Hz, 2H, CH_2 ethyl), 1.21 (t, *J* = 7.4 Hz, 3H, , CH_3 ethyl); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC, T = 333 K) δ 143.7, 138.4, 138.2, 137.9 (C_q), 128.7, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 124.3, 119.5 (CHa_{rom}), 95.5 (C-1), 79.2 (C-3), 77.1 (C-4), 75.5 (C-5), 75.2 (CH_2 benzyl), 74.1 (C-2), 72.9, 72.7 (CH_2 È◀摧ÃÈ摧, 26.9 (CH_2 ethyl), 14.7 (CH_3 ethyl); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$, T = 333 K) δ ($J_{C1\text{-}H1}$ = 179.1 Hz, C-1); HRMS $[M+Na]^+$ calcd for $C_{37}H_{38}F_3NO_5SNa$ 688.23150, found 688.23146.

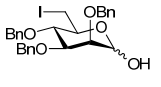


Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-*Se*-phenyl-6-seleno-α-D-mannopyranoside (18): Iodine **7** (287mg, 500 µmol) was treated with phenylselenol according to the general procedure delivering 6-selenomannoside **18** (301 mg, 499 µmol, quant). Flash column chromatography eluent: EtOAc/PE (0/1 → 3/17). R_f 0.56 (EtOAc/PE, 1/9, v/v); $[\alpha]_D^{22}$ +21 (c 2.0, CH_2Cl_2); IR (neat, cm^{-1}) 3030, 2908, 1579, 1497, 1479, 1438, 1454, 1062, 732, 696; ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.50 – 7.11 (m, 20H, H_{arom}), 4.95 (d, *J* = 11.1 Hz, 1H, CH_2 benzyl), 4.76 – 4.66 (m, 3H, H-1, CH_2 benzyl), 4.61 – 4.56 (m, 3H, CH_2 benzyl), 3.88 – 3.79 (m, 3H, H-3, H-4, H-5), 3.78 (dd, *J* = 2.8, 1.9 Hz, 1H, H-2), 3.36 (dd, *J* = 12.3, 1.6 Hz, 1H, H-6), 3.31 (s, 3H, CH_3 OMe), 3.11 – 3.01 (m, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 138.6, 138.5, 138.6 (C_q), 132.0 (CH_{arom}), 131.4 (C_q), 129.1, 128.5, 128.1, 128.0, 127.8, 127.7, 126.6 (CH_{arom}), 99.0 (C-1), 80.4 (C-3), 78.8 (C-4), 75.32 (CH_2 benzyl), 74.8 (C-2), 72.9 (CH_2 benzyl), 72.2 (CH_2 benzyl), 71.9 (C-5), 54.9 (CH_3 OMe), 30.2 (C-6); HRMS $[M+Na]^+$ calcd for $C_{34}H_{36}O_5SeNa$ 627.16202, found 627.16156.

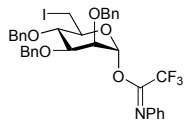


2,3,4-Tri-*O*-benzyl-6-deoxy-6-*Se*-phenyl-6-seleno-D-mannopyranosyl (*N*-phenyl)trifluoroacetimidate (19): 6-Se-phenyl-6-seleno-α-D-mannopyranoside **18** (302 mg, 500 µmol) was converted according to the general procedure to the title imidate **19** (292 mg, 384 µmol, 77% over 3 steps) with trace amounts of its β

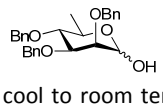
configured epimer. R_f 0.57 (toluene); IR (neat, cm^{-1}) 3030, 2870, 1714, 1598, 1490, 1454, 1117, 732, 692; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, T = 333 K) δ 7.56 – 7.42 (m, 2H, H_{arom}), 7.39 – 7.11 (m, 20H, H_{arom}), 7.08 (t, *J* = 7.4 Hz, 1H, H_{arom}), 6.79 (d, *J* = 7.4 Hz, 2H, H_{arom}), 6.15 (br s, 1H, H-1), 4.90 (d, *J* = 11.2 Hz, 1H, CH_2 benzyl), 4.72 – 4.53 (m, 5H, CH_2 benzyl), 4.02 – 3.95 (m, 1H, H-5), 3.92 (t, *J* = 8.8 Hz, 1H, H-4), 3.86 (dd, *J* = 8.5, 3.0 Hz, 1H, H-3), 3.84 – 3.78 (m, 1H, H-2), 3.33 (dd, *J* = 12.6, 2.6 Hz, 1H, H-6), 3.06 (dd, *J* = 12.6, 7.6 Hz, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC, T = 333 K) δ 143.7, 138.3, 138.2, 137.9 (C_q), 132.8 (CH_{arom}), 130.9 (C_q), 129.0, 128.7, 128.4, 128.0, 127.9, 127.8, 127.7, 126.8, 124.3, 119.5 (CH_{arom}), 95.4 (C-1), 79.2 (C-3), 77.9 (C-4), 75.2 (CH_2 benzyl), 74.6 (C-5), 74.1 (C-2), 72.9, 72.7 (CH_2 benzyl), 30.1 (C-6); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$, T = 333 K) δ 95.4 ($J_{C1\text{-}H1}$ = 177.1 Hz, C-1); HRMS $[M+Na]^+$ calcd for $C_{41}H_{38}F_3NO_5SeNa$ 784.17595, found 784.17586.



2,3,4-Tri-*O*-benzyl-6-deoxy-6-iodo-D-mannopyranose (20): The pH of a solution of 3.00 g iodine **7** (5.23 mmol, 1 equiv) in 25 mL Ac_2O was adjusted to approximately 1 by the addition of H_2SO_4 at 0°C. After stirring at ambient temperature for 7 hours, the mixture was neutralized by the addition of triethylamine, concentrated *in vacuo* and coevaporated with toluene. The crude acetate was dissolved in 30 mL THF and 1.55 mL piperidine (15.69 mmol, 3 equiv) was added. After stirring overnight at room temperature, the mixture was partitioned between EtOAc and water and the organic layer was washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. Flash column chromatography using EtOAc/PE (1/9 → 1/2) gave the title compound **20** (2.37 g, 4.24 mmol, 81% over 2 steps). R_f 0.29 (EtOAc/PE, 1/4, v/v); IR (neat, cm^{-1}) 3404, 3031, 2862, 1497, 1454, 1100, 736, 697; NMR data of the major anomer: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.42 – 7.22 (m, 15H, H_{arom}), 5.24 (br s, 1H, H-1), 4.98 (d, *J* = 10.9 Hz, 1H, CH_2 benzyl), 4.79 – 4.66 (m, 3H, CH_2 benzyl), 4.62 (s, 2H, CH_2 benzyl), 3.97 (dd, *J* = 9.2, 3.0 Hz, 1H, H-3), 3.85 – 3.79 (m, 2H, H-4, H-2), 3.72 – 3.67 (m, 1H, H-5), 3.52 (dd, *J* = 10.6, 2.5 Hz, 1H, H-6), 3.36 (dd, *J* = 10.6, 6.8 Hz, 1H, H-6), 2.85 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 138.2 (C_q), 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8 , 127.6 (CH_{arom}), 92.7 (C-1), 79.2 (C-3), 78.5 (C-4), 75.4 (CH_2 benzyl), 74.8 (C-2), 72.7, 72.1 (CH_2 benzyl), 71.3 (C-5), 7.8 (C-6); HRMS $[M+Na]^+$ calcd for $C_{27}H_{29}IO_5Na$ 583.09519, found 583.09522.

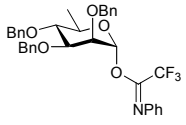


2,3,4-Tri-*O*-benzyl-6-deoxy-6-iodo-D-mannopyranosyl (*N*-phenyl)trifluoroacetimidate (21): To a solution of 1.04 g hemiacetal **20** (1.85 mmol, 1 equiv.) in 8.55 mL acetone and 0.45 mL H_2O were added 904 mg Cs_2CO_3 (2.78 mmol, 1.5 equiv) and 841 µL $ClC(C{=}NPh)CF_3$ (5.55 mmol, 3 equiv). When TLC analysis showed complete consumption of the starting material, the mixture was filtered over celite and the filtrate was evaporated. Purification of the crude product by flash column chromatography using EtOAc/PE (1/44 → 1/19) yielded 1.17 mg of imidate **21** (1.60 mmol, 86%) with trace amounts of its β configured epimer. R_f 0.83 (EtOAc/PE, 1/4, v/v); IR (neat, cm^{-1}) 3031, 2920, 1714, 1598, 1489, 1454, 1117, 737, 695; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, T = 333 K) δ 7.40 – 7.17 (m, 17H, H_{arom}), 7.08 (t, *J* = 7.5 Hz, 1H, H_{arom}), 6.79 (d, *J* = 7.6 Hz, 2H, H_{arom}), 6.18 (br s, 1H, H-1), 4.95 (d, *J* = 11.1 Hz, 1H, CH_2 benzyl), 4.74 – 4.55 (m, 5H, CH_2 benzyl), 3.94 – 3.83 (m, 2H, H-3, H-4), 3.82 (br s, 1H, H-2), 3.63 – 3.55 (m, 1H, H-5), 3.49 (dd, *J* = 10.7, 2.6 Hz, 1H, H-6), 3.33 (dd, *J* = 10.7, 6.5 Hz, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC, T = 333 K) δ 143.5, 138.2, 138.0, 137.8 (C_q), 128.8, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 124.4, 119.5 (CH_{arom}), 95.3 (C-1), 78.9 (C-3), 78.1 (C-4), 75.4 (CH_2 benzyl), 74.0 (C-2), 73.9 (C-5), 72.9, 72.7 (CH_2 benzyl), 6.0 (C-6); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$, T = 333 K) δ 95.3 ($J_{C1\text{-}H1}$ = 175.8 Hz, C-1); HRMS $[M+Na]^+$ calcd for $C_{35}H_{33}F_3INO_5Na$ 754.12477, found 754.12482.

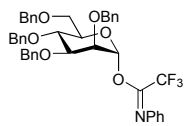


2,3,4-tri-*O*-benzyl-6-deoxy-D-mannopyranose (22): To a solution of 4.04 g iodine **7** (7.04 mmol, 1 equiv) in 35 mL DMSO was added 1.60 g $NaBH_4$ (42.23 mmol, 6 equiv) and the reaction was stirred overnight at 100 °C. The mixture was then allowed to cool to room temperature followed by the addition of 35 mL acetone. After refluxing for 1 hour, the mixture was concentrated and partitioned between EtOAc and water and the organic layer was washed

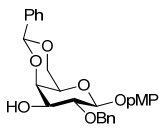
with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, evaporated and coevaporated with toluene. The crude product was dissolved in 35 mL Ac_2O and the pH was adjusted to approximately 1 by the addition of H_2SO_4. After stirring at 80°C for 2 nights, the mixture was neutralized by the addition of triethylamine and concentrated *in vacuo*. The residue was taken up in EtOAc, washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The crude acetate was dissolved in 35 mL THF and 2.09 mL piperidine (21.12 mmol, 3 equiv) was added. After stirring for 3 nights, the mixture was partitioned between EtOAc and water and the organic layer was washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. Flash column chromatography using EtOAc/PE (3/17 → 7/13) gave the title compound **22** (2.49 g, 5.74 mmol, 81% over 3 steps). Spectroscopic data were in accordance with known literature data.[25]



2,3,4-tri-*O*-benzyl-6-deoxy-α-D-mannopyranosyl (*N*-phenyl)trifluoroacetimidate (23): To a solution of 872 mg hemiacetal **22** (2.01 mmol, 1 equiv.) in 9.5 mL acetone and 0.5 mL H_2O were added 981 mg Cs_2CO_3 (3.01 mmol, 1.5 equiv.) and 912 µL ClC(C=NPh)CF_3 (6.02 mmol, 3 equiv.). When TLC analysis showed complete consumption of the starting material, the mixture was filtered over celite and the filtrate was evaporated. Purification of the crude product by flash column chromatography using EtOAc/PE (1/44 → 1/19) yielded 886 mg of the title imidate **23** (1.46 mmol, 73%). R*f* 0.80 (EtOAc/PE, 1/4, v/v); $[\alpha]_D^{22}$ -2 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3036, 1710, 1599, 1498, 1490, 1454, 1116, 730, 693; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.36 – 7.10 (m, 17H, H_{arom}), 7.06 (t, *J* = 7.4 Hz, 1H, H_{arom}), 6.74 (d, *J* = 7.8 Hz, 2H, H_{arom}), 6.10 (br s, 1H, H-1), 4.91 (d, *J* = 11.0 Hz, 1H, CH_2 benzyl), 4.73 – 4.50 (m, 5H, CH_2 benzyl), 3.94 – 3.76 (m, 3H, H-5, H-3, H-2), 3.68 (t, *J* = 9.2 Hz, 1H, H-4), 1.33 (d, *J* = 6.2 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 143.7, 138.5, 138.3, 137.9 (C_q), 129.2, 128.7, 128.4, 128.3, 128.0, 127.9, 127.7, 127.6, 126.3, 124.3, 120.7, 119.5 (CH_{arom}), 96.0 (C-1), 79.8 (C-4), 79.1 (C-3), 75.3 (CH_2 benzyl), 74.1 (C-2), 72.9, 72.7 (CH_2 benzyl), 71.1 (C-5), 18.0 (C-6); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$, T = 333 K) δ 96.0 ($J_{C1\text{-}H1}$ = 175.1 Hz, C-1); HRMS $[M+Na]^+$ calcd for $C_{35}H_{34}F_3NO_5Na$ 628.22813, found 628.22764.

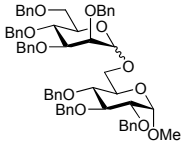


2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl (*N*-phenyl)trifluoroacetimidates (25): Acetyl 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose17 **24** (956 mg, 1.64 mmol) was stirred in a 5% piperidine in THF solution (8 mL) for 3 days. The reaction mixture was diluted with EtOAc, washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude hemiacetal was dissolved in 8 mL acetone and 0.4 mL H_2O, 339 mg K_2CO_3 (2.45 mmol, 1.5 equiv.) and 0.37 mL ClC(C=NPh)CF_3 (2.44 mmol, 1.5 equiv.) were added. After stirring overnight the mixture was partitioned between EtOAc and sat. aq. $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification of the crude product by flash column chromatography (silica was pretreated with triethylamine/PE (1/19 → 0/1)) using toluene/PE (1/1 → 1/0) as eluent yielded 617 mg of the title imidate **25** (0.87 mmol, 53% over 2 steps). R*f* 0.39 (toluene); $[\alpha]_D^{22}$ +9 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3032, 2870, 1714, 1598, 1497, 1490, 1454, 1118, 732, 694; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.37 – 7.14 (m, 22H, H_{arom}), 7.06 (t, *J* = 7.5 Hz, 1H, H_{arom}), 6.73 (d, *J* = 7.7 Hz, 2H, H_{arom}), 6.21 (br s, 1H, H-1), 4.87 (d, *J* = 11.0 Hz, 1H, CH_2 benzyl), 4.71 – 4.48 (m, 7H, CH_2 benzyl), 4.08 (t, *J* = 9.5 Hz, 1H, H-4), 3.97 – 3.85 (m, 2H, H-5, H-3), 3.84 – 3.75 (m, 2H, H-2, H-6), 3.72 (dd, *J* = 11.2, 1.8 Hz, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 143.6, 138.5, 138.3, 137.9 (C_q), 128.7, 128.4, 128.3, 127.9, 127.7, 127.6, 127.4, 124.3, 119.5 (CH_{arom}), 96.0 (C-1), 79.1 (C-3), 75.1 (CH_2 benzyl), 75.0 (C-5), 74.5 (C-4), 73.9 (C-2), 73.5, 72.8 (CH_2 benzyl), 69.2 (C-6); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$, T = 333 K) δ 96.0 ($J_{C1\text{-}H1}$ = 178.1 Hz, C-1); HRMS $[M+Na]^+$ calcd for $C_{42}H_{40}F_3NO_6Na$ 734.26999, found 734.26983.

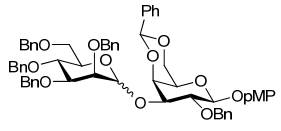


4-Methoxyphenyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (26b):
4-Methoxyphenyl β-D-galactopyranoside[26] (5.47g, 19.1 mmol, 1 equiv) was stirred under argon for 48 hours at room temperature in 100 mL 2,2-dimethoxypropane with a catalytic amount of (±)-10-camphorsulphonic acid. The mixture was

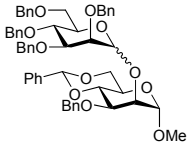
neutralized by the addition of triethylamine and the volatile material was evaporated. The residue was dissolved in 100 mL dry tetrahydrofuran and 9.1 mL benzyl bromide (76 mmol, 4 equiv) and 1.53 g sodium hydride (60% dispersion in oil, 38.2 mmol, 2 equiv) were added and the mixture was stirred at 45 °C under argon until TLC analysis showed complete conversion of the starting material. Methanol and then water were added at 0 °C to destroy the excess of sodium hydride. The mixture was extracted twice with ether, and the combined extracts were dried over $MgSO_4$ and concentrated. A solution of the residue in 100 mL methanol was treated with a catalytic amount of (±)-10-camphorsulphonic acid and the reaction was monitored by TLC. Next, triethylamine was used to neutralize the mixture and the solvent was evaporated. The crude product was filtered through a plug of silica gel using EtOAc/PE (9/1) as the eluent. R_f 0.24 (EtOAc/PE, 17/3, v/v) ^{1}H NMR (400 MHz, $CDCl_3$/MeOD) δ 7.44 – 7.25 (m, 5H, H_{arom}), 7.02 (d, *J* = 9.1 Hz, 2H, H_{arom}), 6.84 (d, *J* = 9.1 Hz, 2H, H_{arom}), 5.02 (d, *J* = 11.1 Hz, 1H, CH_2 benzyl), 4.88 (d, *J* = 7.7 Hz, 1H, H-1), 4.82 (d, *J* = 11.1 Hz, 1H, CH_2 benzyl), 3.96 (d, *J* = 3.3 Hz, 1H, H-4), 3.88 – 3.73 (m, 6H, H-6, CH_3 OMe, H-2), 3.67 (dd, *J* = 9.6, 3.4 Hz, 1H, H-3), 3.59 (t, *J* = 6.0 Hz, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$/MeOD) δ 154.9, 151.2, 138.0 (C_q), 128.1, 127.9, 127.5, 117.8, 114.3 (CH_{arom}), 102.5 (C-1), 79.0 (C-2), 74.8 (CH_2 benzyl), 74.6 (C-5), 72.8 (C-3), 68.5 (C-4), 60.9 (C-6), 55.3 (CH_3 OMe). After evaporation of the solvent, the crude product was dissolved in 45 mL acetonitrile and was treated with 1.93 mL benzaldehyde dimethylacetal (12.82 mmol, 0.67 equiv) and 325 mg *p*-toluenesulfonic acid monohydrate (1.71 mmol, 0.09 equiv). Upon complete conversion the mixture was neutralized by the addition of triethylamine and the solvent was removed. Crystallization from EtOAc/PE yielded 3.31 g of the title compound **26b** (7.13 mmol 37% over 4 steps). R_f 0.39 (EtOAc/PE, 1/1, v/v); mp = 161.1 °C; $[\alpha]_D^{22}$ -38 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3454, 2878, 2361, 2342, 1507, 1455, 1216, 1004, 826, 730; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.59 – 7.23 (m, 10H), 7.06 (d, *J* = 9.0 Hz, 2H, H_{arom}), 6.83 (d, *J* = 9.0 Hz, 2H, H_{arom}), 5.58 (s, 1H, CH benzylidene), 5.05 (d, *J* = 11.2 Hz, 1H, CH_2 benzyl), 4.89 (d, *J* = 7.5 Hz, 1H, H-1), 4.82 (d, *J* = 11.2 Hz, 1H, CH_2 benzyl), 4.36 (d, *J* = 12.3 Hz, 1H, H-6), 4.26 (d, *J* = 3.2 Hz, 1H, H-4), 4.09 (d, *J* = 11.5 Hz, 1H, H-6), 3.94 – 3.81 (m, 2H, H-2, H-3), 3.78 (s, 3H, CH_3 OMe), 3.53 (s, 1H, H-5), 2.56 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 155.4, 151.5, 138.3, 137.5 (Cq), 129.2, 128.4, 128.2, 128.0, 127.8, 126.5, 118.9, 114.5, 103.0 (C-1), 101.5 (CH benzylidene), 79.0 (C-2), 75.3 (CH_2 benzyl), 75.1 (C-4), 72.5 (C-3), 69.1 (C-6), 66.6 (C-5), 55.6 (C-6); HRMS $[M+Na]^+$ calcd for $C_{27}H_{28}O_7Na$ 487.17272, found 487.17223.



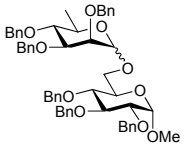
2,3,4,6-Tetra-*O*-benzyl-D-mannopyranosyl-(1→6)-(methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside) (27a): Donor **25** and acceptor **26a** were coupled according to the general glycosylation procedure to yield 204 mg (207 µmol, 94%) of the title compound **27a** as an epimeric mixture (α/β 1/3.5). Spectroscopic data were in accordance with published data.[18]



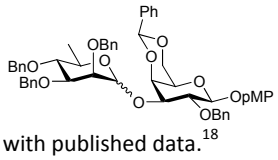
2,3,4,6-Tetra-*O*-benzyl-D-mannopyranosyl-(1→3)-(*p*-methoxyphenyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside) (27b): Donor **6** and acceptor **26b** were coupled according to the general glycosylation procedure to yield 191 mg (194 µmol, 88%) of the title compound **27b** as an epimeric mixture (α/β 1/1). Spectroscopic data were in accordance with published data.[18]



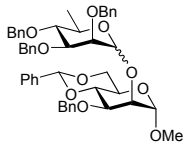
2,3,4,6-Tetra-*O*-benzyl-D-mannopyranosyl-(1→2)-(methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside) (27c): Donor **6** and acceptor **26c** were coupled according to the general glycosylation procedure to yield 195 mg (218 µmol, 99%) of the title compound **27c** as an epimeric mixture (α/β 1/4). Spectroscopic data were in accordance with known literature data.[20]



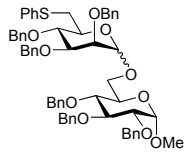
2,3,4-Tri-*O*-benzyl-6-deoxy-D-mannopyranosyl-(1→6)-(methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside) (28a): Donor **23** and acceptor **26a** were coupled according to the general glycosylation procedure to yield 176 mg (200 µmol, 91%) of the title compound **28a** as an epimeric mixture (α/β 1/2.5). Spectroscopic data were in accordance with published data.[18]



2,3,4-Tri-*O*-benzyl-6-deoxy-D-mannopyranosyl-(1→3)-(*p*-methoxyphenyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside) (28b): Donor 23 and acceptor 26b were coupled according to the general glycosylation procedure to yield 169 mg (191 µmol, 87%) of the title compound as an epimeric mixture (α/β 1/1.5). Spectroscopic data were in accordance with published data.[18]



2,3,4-Tri-*O*-benzyl-6-deoxy-D-mannopyranosyl-(1→2)-(methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside) (28c): Donor **23** and acceptor **26c** were coupled according to the general glycosylation procedure to yield 156 mg (198 µmol, 90%) of the title compound **28c** as an epimeric mixture (α/β 1/1). R*f* 0.47, 0.71 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 3030, 2912, 1497, 1454, 1071, 733, 695; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC)[27] δ 7.55 – 7.20 (m, 50H), 5.61 (s, 1H), 5.53 (s, 1H), 5.16 (s, 1H), 5.08 – 4.92 (m, 4H), 4.84 (d, *J* = 12.2 Hz, 1H), 4.77 (d, *J* = 11.8 Hz, 1H), 4.74 – 4.68 (m, 2H), 4.67 – 4.56 (m, 6H), 4.55 – 4.48 (m, 4H), 4.42 (d, *J* = 11.9 Hz, 1H), 4.31 – 4.20 (m, 3H), 4.13 – 4.03 (m, 2H), 4.00 – 3.87 (m, 6H), 3.84 – 3.71 (m, 5H), 3.71 – 3.59 (m, 2H), 3.46 (dd, *J* = 9.4, 3.0 Hz, 1H), 3.39 – 3.30 (m, 7H), 1.38 (d, *J* = 6.1 Hz, 3H), 1.35 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC)[27] δ 138.8, 138.7, 138.6, 138.4, 138.3, 138.1, 137.6, 137.5, 128.8, 128.8, 128.6, 128.4, 128.3, 128.1, 128.0, 127.7, 127.6, 127.5, 127.4, 127.3, 127.1, 126.1, 126.0, 101.6, 101.4, 101.0, 99.8, 99.7, 99.2, 81.8, 80.4, 79.9, 79.2, 79.1, 78.5, 76.0, 75.7, 75.5, 75.4, 75.1, 73.8, 73.5, 73.2, 72.3, 72.1, 71.9, 71.0, 70.7, 68.9, 68.8, 68.5, 63.9, 63.6, 54.9, 54.8, 18.0, 17.9; ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 101.0 ($J_{C\text{-}H}$ = 171 Hz), 99.8 ($J_{C\text{-}H}$ = 171 Hz), 99.7 ($J_{C\text{-}H}$ = 153 Hz), 99.2 ($J_{C\text{-}H}$ = 168 Hz); HRMS $[M+Na]^+$ calcd for $C_{48}H_{52}O_{10}Na$ 811.34527, found 811.34492.



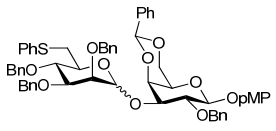
2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-phenyl-6-thio-D-mannopyranosyl-(1→6)-(methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside) (29a): Donor **9** and acceptor **26a** were coupled according to the general glycosylation procedure to yield 196 mg (198 µmol, 90%) of the title compound **29a** as an epimeric mixture (α/β 1/7). R*f* 0.47 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 3029, 2918, 1584, 1497, 1482, 1454, 1069, 735, 696; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.50 – 6.95 (m, 35H, H_{arom}), 5.06 – 4.89 (m, 3H, CH_2 benzyl), 4.89 – 4.72 (m, 4H, CH_2 benzyl), 4.72 – 4.41 (m, 6H, H-1, CH_2 benzyl), 4.16 (dd, *J* = 10.2, 1.4 Hz, 1H, H-6), 4.08 (s, 1H, H-1'), 4.03 (t, *J* = 9.2 Hz, 1H, H-3), 3.85 – 3.72 (m, 2H, H-5, H-4'), 3.70 (d, *J* = 2.7 Hz, 1H, H-2'), 3.51 (dd, *J* = 9.7, 3.5 Hz, 1H, H-2), 3.49 – 3.30 (m, 8H, H-4, H-6, H-3', H-6', H-5', CH_3 OMe), 3.04 (dd, *J* = 13.7, 9.1 Hz, 1H, H-6'); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 138.8, 138.5, 138.2, 138.1, 138.0, 137.9, 137.3 (C_q), 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 125.3 (CH_{arom}), 101.2 (C-1'), 97.7 (C-1), 82.1 (C3, C3'), 79.8 (C-2), 77.6, 77.5 (C-4, C-4'), 75.6 (CH_2 benzyl), 75.2 (C-5', CH_2 benzyl), 74.7, 73.7 (CH_2 benzyl), 73.5 (C-2'), 73.2, 71.4 (CH_2 benzyl), 69.5 (C-5), 68.0 (C-6), 55.0 (CH_3 OMe), 35.3 (C-6'); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 101.2 ($J_{C1'\text{-}H1'}$ = 158.1 Hz, C-1'), 97.7 ($J_{C1\text{-}H1}$ = 166.2 Hz, C-1); Diagnostic peaks from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 3.95 (t, *J* = 9.2 Hz, 0.14H, H-3), 3.27 (s, 0.42H, CH_3 OMe). HRMS $[M+Na]^+$ calcd for $C_{61}H_{64}O_{10}SNa$ 1011.41124, found 1011.41158.

Pre-activation experiment with donor 9 at room temperature: Donor **9** (157 mg, 0.22 mmol, 1 equiv) was coevaporated with toluene, dissolved in 3.0 mL DCM and stirred over 3Å molecular sieves for 30 minutes. The mixture was then cooled to -80 °C after which 21.4 µL TfOH (242 µmol, 1.1 equiv) was added. The mixture was allowed to warm up to room temperature in 15 minutes. Next 153 mg acceptor

26a (0.33 mmol, 1.5 equiv) and 88 mg 2,6-di-*tert*-butyl-4-methylpyridine (429 µmol, 2 equiv) were added in 1.4 mL DCM and the reaction was stirred overnight at room temperature. The reaction was quenched by the addition of 1mL Et_3N. After filtration over celite, the mixture was washed with sat. aq. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by size exclusion chromatography (DCM/MeOH, 1/1, v/v) yielded 169 mg of the coupled product **29a** (171 µmol, 78%, α/β 1/1). NMR data for the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$,HH-COSY, HSQC) δ 7.64 – 6.91 (m, 35H, H_{arom}), 5.00 – 4.94 (m, 2H, CH_2 benzyl), 4.91 (d, *J* = 1.3 Hz, 1H, H-1'), 4.84 – 4.64 (m, 6H, CH_2 benzyl), 4.61 – 4.57 (m, 3H, CH_2 benzyl), 4.51 – 4.45 (m, 2H, H-1, CH_2 benzyl), 3.95 (t, *J* = 9.2 Hz, 1H, H-3), 3.86 – 3.74 (m, 5H, H-2', H-4', H-5', H-3', H-6), 3.69 – 3.58 (m, 2H, H-5, H-6), 3.39 (dd, *J* = 9.6, 3.6 Hz, 1H, H-2), 3.36 – 3.30 (m, 2H, H-6', H-4), 3.27 (s, 3H, CH_3 OMe), 2.99 (dd, *J* = 13.2, 7.5 Hz, 1H, H-6'). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6, 138.4, 138.2, 138.1, 138.0, 137.2 (C_q), 128.9, 128.6, 128.4, 128.3, 128.2, 127.9, 127.8, 127.6, 127.6, 125.3 (CH_{arom}), 97.8 (C-1'), 97.5 (C-1), 82.0 (C-3), 79.9 (C-2), 79.5 (C-2'), 77.7 (C-4, C-4'), 75.7, 75.1, 74.9 (CH_2 benzyl), 74.4 (C-3'), 73.1, 72.5, 71.8 (CH_2 benzyl), 71.0 (C-5'), 69.6 (C-5), 65.6 (C-6), 54.9 (CH_3 OMe), 35.6 (C-6'); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 97.8 ($J_{C1'-H1'}$ = 170 Hz, C-1'), 97.5 (J_{C1-H1} = 170 Hz, C-1).

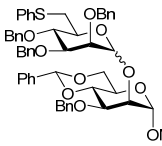
Pre-activation experiment with donor 9 at -80°C: Donor **9** (155 mg, 0.217 mmol, 1 equiv) was coevaporated with toluene, dissolved in 3.5 mL DCM and stirred over 3Å molecular sieves for 30 minutes. The mixture was then cooled to -80 °C after which 21 µL TfOH (239 µmol, 1.1 equiv) was added. The mixture was stirred at -80°C for 15 minutes. Next 303 mg acceptor **26a** (651 µmol, 1.5 equiv) and 90 mg 2,6-di-*tert*-butyl-4-methylpyridine (434 µmol, 2 equiv) were added in 1.0 mL DCM and the reaction was stirred overnight at -60 °C for 3 days. The reaction was quenched by the addition of 1mL Et_3N and the mixture was allowed to warm up to room temperature. After filtration over celite, the mixture was washed with sat. aq. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by size exclusion chromatography (DCM/MeOH, 1/1, v/v) yielded 144 mg of the coupled product **29a** (146 µmol, 67%, α/β 1/4).

Pre-activation experiment with mannoside 38 at room temperature: Mannoside **38** (123 mg, 226 µmol, 1 equiv) and 4.5 mg Ph_2SO (23 µmol, 0.1 equiv) were coevaporated with toluene, dissolved in 3.0 mL DCM and stirred over 3Å molecular sieves for 30 minutes. Triflic anhydride (41 µL, 249 µmol, 1.1 equiv) was added and the mixture was stirred for 1 minute. Next 158 mg acceptor **26a** (0.34 mmol, 1.5 equiv) and 140 mg 2,6-di-*tert*-butyl-4-methylpyridine (680 µmol, 3 equiv) were added in 1.4 mL DCM and the reaction was stirred overnight at room temperature. The reaction was quenched by the addition of 1mL Et_3N. After filtration over celite, the mixture was washed with sat. aq. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by size exclusion chromatography (DCM/MeOH, 1/1, v/v) yielded 94 mg of the coupled product **29a** (95 µmol, 42%, α/β 1/1).

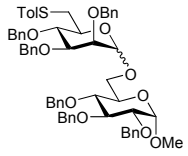


2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-phenyl-6-thio-D-mannopyranosyl-(1→3)-(*p*-methoxyphenyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside) (29b): Donor 9 and acceptor 26b were coupled according to the general glycosylation procedure to yield 194 mg (196 µmol, 89%) of the title compound 29b as an epimeric mixture (α/β 1/11). R_f 0.26, 0.43 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 3032, 2858, 1584, 1506, 1454, 1060, 732, 696; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.74 – 6.65 (m, 34H, H_{arom}), 5.55 (s, 1H, CH benzylidene), 4.99 – 4.83 (m, 5H, H-1, CH_2 benzyl), 4.63 – 4.55 (m, 2H, H-1', CH_2 benzyl), 4.46 – 4.26 (m, 4H, H-6, CH_2 benzyl), 4.24 (d, *J* = 3.4 Hz, 1H, H-4), 4.08 – 3.97 (m, 2H, H-2, H-6), 3.80 – 3.70 (m, 5H, H-4', H-3, CH_3 OMe), 3.68 (d, *J* = 2.8 Hz, 1H, H-2'), 3.44 – 3.30 (m, 3H, H-5, H-5', H-6'), 3.24 (dd, *J* = 9.3, 2.9 Hz, 1H, H-3'), 3.07 (dd, *J* = 14.1, 9.8 Hz, 1H, H-6'); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 155.2, 151.4, 138.5, 138.4, 138.0, 137.9, 137.4 (C_q), 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3, 126.2, 125.3, 118.7, 114.4 (CH_{arom}), 103.0 (C-1), 102.9 (C-1'), 100.5 (CH benzylidene), 82.5 (C-3'), 78.7 (C-2), 78.1 (C-3), 77.5 (C-4'), 75.8 (C-4), 75.5 (C-5'), 75.2, 73.3 (CH_2 benzyl), 72.4 (C-2'), 71.4 (CH_2 benzyl), 68.8 (C-6), 66.6 (C-5), 55.5 (CH_3 OMe), 35.2 (C-6'); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 103.0 (J_{C1-H1} = 162 Hz, C-1), 102.9 ($J_{C1'-H1'}$ = 160 Hz, C-1'); Diagnostic peak from

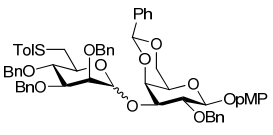
the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 5.43 (s, 0.09H, CH benzylidene); HRMS $[M+Na]^+$ calcd for $C_{60}H_{60}O_{11}Na$ 1011.37485, found 1011.37543.



2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-phenyl-6-thio-D-mannopyranosyl-(1→2)- (methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside) (29c): Donor 9 and acceptor 26c were coupled according to the general glycosylation procedure to yield 172 mg (191 μmol, 87%) of the title compound 29c as an epimeric mixture (α/β 1/5). R_f 0.54, 0.71 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 3033, 2905, 1584, 1497, 1482, 1454, 1072, 736, 696; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.66 – 6.87 (m, 30H, H_{arom}), 5.54 (s, 1H, CH benzylidene), 5.11 – 4.88 (m, 4H, CH_2 benzyl), 4.76 (s, 1H, H-1), 4.69 – 4.48 (m, 4H, H-1', CH_2 benzyl), 4.42 – 4.37 (m, 2H, H-2, CH_2 benzyl), 4.28 – 4.23 (m, 1H, H-6), 4.10 (t, *J* = 9.3 Hz, 1H, H-4), 4.01 – 3.93 (m, 2H, H-2', H-3), 3.86 – 3.76 (m, 3H, H-6, H-4', H-5), 3.49 (dd, *J* = 9.1, 2.9 Hz, 1H, H-3'), 3.46 – 3.37 (m, 2H, H-6', H-5'), 3.34 (s, 3H, CH_3 OMe), 2.95 (dd, *J* = 14.0, 9.5 Hz, 1H, H-6'); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 138.8, 138.6, 138.1, 137.9, 137.5, 137.0 (C_q), 128.8, 128.5, 128.3, 128.1, 128.0, 127.9, 127.5, 127.4, 126.1, 125.3 (CH_{arom}), 101.6 (CH benzylidene), 99.1 (C-1'), 98.8 (C-1), 81.8 (C-3'), 78.3 (C-4), 77.5 (C-4'), 75.2 (C-5'), 75.1, 73.6 (CH_2 benzyl), 73.5 (C-3), 73.2 (C-2'), 72.6 (C-2), 71.0, 70.3 (CH_2 benzyl), 68.8 (C-6), 63.8 (C-5), 54.9 (CH_3 OMe), 35.2 (C-6'); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 99.1 ($J_{C1'-H1'}$ = 155 Hz, C-1'), 98.8 (J_{C1-H1} = 167 Hz, C-1); Diagnostic peaks from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 5.59 (s, 0.21H, CH benzylidene), 3.17 (s, 0.65H, CH_3 OMe); HRMS $[M+Na]^+$ calcd for $C_{54}H_{56}O_{10}SNa$ 919.34864, found 919.34870.

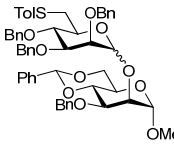


2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-*p*-tolyl-6-thio-D-mannopyranosyl-(1→6)-(methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside) (30a): Donor 11 and acceptor 26a were coupled according to the general glycosylation procedure to yield 190 mg (189 μmol, 86%) of the title compound 30a as an epimeric mixture (α/β 1/5). R_f 0.60 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 3030, 2911, 1497, 1489, 1454, 1070, 732, 694; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.61 – 6.73 (m, 34H, H_{arom}), 5.07 – 4.89 (m, 3H, CH_2 benzyl), 4.89 – 4.72 (m, 4H, CH_2 benzyl), 4.72 – 4.41 (m, 6H, H-1, CH_2 benzyl), 4.19 (dd, *J* = 10.3, 1.9 Hz, 1H, H-6), 4.08 (s, 1H, H-1'), 4.03 (t, *J* = 9.2 Hz, 1H, H-3), 3.85 – 3.71 (m, 2H, H-5, H-4'), 3.70 (d, *J* = 2.9 Hz, 1H, H-2'), 3.52 (dd, *J* = 9.7, 3.5 Hz, 1H, H-2), 3.49 – 3.42 (m, 2H, H-6, H-4), 3.42 – 3.25 (m, 6H, H-3', CH_3 OMe, H-6', H-5'), 3.02 (dd, *J* = 14.0, 9.6 Hz, 1H, H-6'), 2.27 (s, 3H, CH_3 Me); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 138.7, 138.5, 138.1, 137.9, 135.4, 133.4 (C_q), 129.5, 129.4, 129.2, 129.0, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4 (CH_{arom}), 101.1, 97.7, 82.1, 82.0 (C-3, C-3'), 79.7 (C-2), 77.6, 77.4 (C-4, C-4'), 75.6, 75.1 (CH_2 benzyl), 75.1 (C-5'), 74.7, 73.6 (CH_2 benzyl), 73.4 (C-2'), 73.2, 71.4 (CH_2 benzyl), 69.5 (C-5), 67.9 (C-6), 55.0 (CH_3 OMe), 36.0 (C-6'), 20.9 (CH_3 Me); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 101.1 ($J_{C1'-H1'}$ = 154.6 Hz, C-1'), 97.7 (J_{C1-H1} = 167.1 Hz, C-1); Diagnostic peaks from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 3.96 (t, *J* = 9.3 Hz, 0.19H, H-3), 2.26 (s, 0.57H, CH_3 Me); HRMS $[M+Na]^+$ calcd for $C_{62}H_{66}O_{10}SNa$ 1025.42689, found 1025.42706.

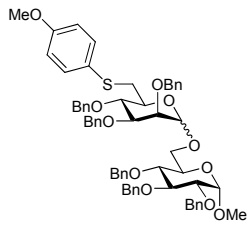


2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-*p*-tolyl-6-thio-D-mannopyranosyl (1→3)-(*p*-methoxyphenyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside) (30b): Donor 11 and acceptor 26b were coupled according to the general glycosylation procedure to yield 124 mg (123 μmol, 56%) of the title compound 30b as an epimeric mixture (α/β 1/8). R_f 0.59 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 3030, 2866, 1505, 1454, 1060, 731, 697; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.74 – 6.70 (m, 33H, H_{arom}), 5.57 (s, 1H, CH benzylidene), 4.98 – 4.84 (m, 5H, CH_2 benzyl, H-1), 4.63 – 4.55 (m, 2H, H-1', CH_2 benzyl), 4.46 – 4.29 (m, 5H, CH_2 benzyl, H-6, H-4), 4.10 – 4.00 (m, 2H, H-2, H-6), 3.80 – 3.70 (m, 5H, H-4', CH_3 OMe, H-3), 3.67 (d, *J* = 2.9 Hz, 1H, H-2'), 3.45 (s, 1H, H-5), 3.37 – 3.27 (m, 2H, H-5', H-6'), 3.23 (dd, *J* = 9.3, 2.9 Hz, 1H, H-3'), 3.04 (dd, *J* = 14.0, 9.9 Hz, 1H, H-6'), 2.29 (s, 3H, CH_3 Me); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ

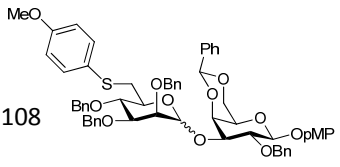
155.3, 151.5, 138.5, 138.0, 135.5, 133.5 (C_q), 129.6, 128.8, 128.7, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 126.3, 118.8, 114.4 (CH_{arom}), 103.1 (C-1), 102.9 (C-1'), 100.6 (CH benzylidene), 82.5 (C-3'), 78.7 (C-2), 78.3 (C-3), 77.7 (C-4'), 75.9 (C-4), 75.3 (C-5'), 75.2, 73.3 (CH_2 benzyl), 72.4 (C-2'), 71.5 (CH_2 benzyl), 68.9 (C-6), 66.7 (C-5), 55.6 (CH_3 OMe), 36.0 (C-6'), 20.9 (CH_3 Me); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 103.1 ($J_{C1\text{-}H1}$ = 158 Hz, C-1), 102.9 ($J_{C1'\text{-}H1'}$ = 158 Hz, C-1'); Diagnostic peaks from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 5.46 (s, 0.13H, CH benzylidene), 2.08 (s, 0.38H, CH_3 Me); HRMS $[M+Na]^+$ calcd for $C_{61}H_{62}O_{11}SNa$ 1025.39050, found 1025.39141.



2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-*p*-tolyl-6-thio-D-mannopyranosyl-(1→2)- (methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside) (30c): Donor 11 and acceptor 26c were coupled according to the general glycosylation procedure to yield 178 mg (196 µmol, 89%) of the title compound 30c as an epimeric mixture (α/β 1/3.5). R_f 0.55, 0.75 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 3032, 2919, 1496, 1454, 1072, 735, 696; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.67 – 7.07 (m, 29H, H_{arom}), 5.66 (s, 1H, CH benzylidene), 5.20 – 5.00 (m, 4H, CH_2 benzyl), 4.87 (s, 1H, H-1), 4.83 – 4.58 (m, 4H, H-1', CH_2 benzyl), 4.54 – 4.47 (m, 2H, CH_2 benzyl, C-2), 4.41 – 4.34 (m, 1H, H-6), 4.20 (t, *J* = 9.3 Hz, 1H, H-4), 4.12 – 4.06 (m, 2H, H-2', H-3), 3.94 – 3.83 (m, 3H, H-6, H-5, H-4'), 3.58 (dd, *J* = 9.2, 2.9 Hz, 1H, H-3'), 3.53 – 3.44 (m, 5H, H-6', H-5', CH_3 OMe), 3.05 (dd, *J* = 13.9, 9.7 Hz, 1H, H-6'), 2.38 (s, 3H, CH_3 Me); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 138.8, 138.6, 138.1, 137.9, 137.5, 135.5, 133.1 (C_q), 129.6, 128.8, 128.6, 128.3, 128.1, 128.0, 127.6, 127.5, 126.1 (CH_{arom}), 101.6 (CH_{arom}), 99.1 (C-1'), 98.8 (C-1), 81.8 (C-3'), 78.3 (C-4), 77.6 (C-4'), 75.3 (CH2 benzyl, C-5'), 73.6 (CH_2 benzyl), 73.5 (C-3), 73.1 (C-2'), 72.5 (C-2), 71.0, 70.3 (CH_2 benzyl), 68.9 (C-6), 63.8 (C-5), 55.0 (CH_3 OMe), 36.0 (C-6'), 20.9 (CH_3 Me); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 99.1 ($J_{C1'\text{-}H1'}$ = 154 Hz, C-1'), 98.8 ($J_{C1\text{-}H1}$ = 168 Hz, C-1); Diagnostic peaks from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 5.71 (s, 0.29H, CH benzylidene), 3.32 (s, 0.88H, CH_3 OMe); HRMS $[M+Na]^+$ calcd for $C_{55}H_{58}O_{10}SNa$ 933.36429, found 933.36435.

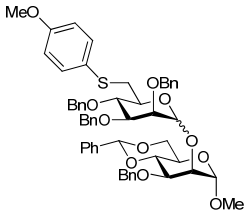


2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-*p*-methoxyphenyl-6-thio-D-mannopyranosyl-(1→6)-(methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside) (31a): Donor 13 and acceptor 26a were coupled according to the general glycosylation procedure to yield 191 mg (187 µmol, 85%) of the title compound 31a as an epimeric mixture (α/β 1/5). R_f 0.52 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 3031, 2908, 1593, 1496, 1454, 1070, 734, 696; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.60 – 6.99 (m, 32H, H_{arom}), 6.86 – 6.59 (m, 2H, H_{arom}), 5.03 (d, *J* = 10.9 Hz, 1H, CH_2 benzyl), 4.97 – 4.88 (m, 2H, CH_2 benzyl), 4.88 – 4.73 (m, 4H, CH_2 benzyl), 4.66 (d, *J* = 12.1 Hz, 1H, CH_2 benzyl), 4.61 – 4.38 (m, 5H, CH_2 benzyl, H-1), 4.18 (dd, *J* = 10.3, 1.8 Hz, 1H, H-6), 4.08 (s, 1H, H-1'), 4.03 (t, *J* = 9.2 Hz, 1H, H-3), 3.87 – 3.69 (m, 6H, H-5, CH_3 OMe, H-4', H-2'), 3.52 (dd, *J* = 9.7, 3.5 Hz, 1H, H-2), 3.49 – 3.42 (m, 2H, H-6, H-4), 3.40 – 3.22 (m, 6H, H-3', CH_3 OMe, H-6', H-5'), 3.00 (dd, *J* = 13.5, 9.0 Hz, 1H, H-6'); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 158.5, 138.8, 138.5, 138.1, 138.0, 137.9 (C_q), 132.2, 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.6, 127.5, 127.4 (CH_{arom}), 127.2 (C_q), 114.4 (CH_{arom}), 101.2 (C-1'), 97.7 (C-1), 82.1 (C-3, C-3'), 79.8 (C-2), 77.6, 77.5 (C-4, C-4'), 75.6 (CH_2 benzyl), 75.1 (C-5', CH_2 benzyl), 74.7, 73.6 (CH_2 benzyl), 73.4 (C-2'), 73.2, 71.4 (CH_2 benzyl), 69.5 (C-5), 68.0 (C-6), 55.2, 55.0 (CH_3 OMe), 37.6 (C-6'); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 101.2 ($J_{C1'\text{-}H1'}$ = 154.9 Hz, C-1'), 97.7 ($J_{C1\text{-}H1}$ = 171.7 Hz, C-1); Diagnostic peak from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 3.96 (t, *J* = 9.2 Hz, 0.20H, H-3); HRMS $[M+Na]^+$ calcd for $C_{62}H_{66}O_{11}SNa$ 1041.42180, found 1041.42186.

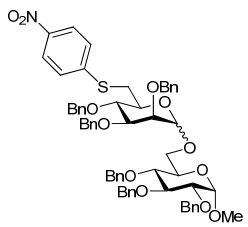


2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-*p*-methoxyphenyl-6-thio-D-mannopyranosyl (1→3)(-*p*-methoxyphenyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside) (31b): Donor 13 and acceptor

26b were coupled according to the general glycosylation procedure to yield 130 mg (128 µmol, 58%) of the title compound 31b as an epimeric mixture (α/β 1/7). R_f 0.33 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 3034, 2858, 1593, 1505, 1495, 1454, 1060, 730, 696; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.81 – 6.69 (m, 33H, H_{arom}), 5.59 (s, 1H, CH benzylidene), 4.97 – 4.84 (m, 5H, H-1, CH_2 benzyl), 4.57 (d, *J* = 11.2 Hz, 2H, H-1', CH_2 benzyl), 4.44 – 4.27 (m, 5H, H-6, H-4, CH_2 benzyl), 4.10 – 4.01 (m, 2H, H-6, H-2), 3.78 – 3.70 (m, 8H, H-3, H-4', 2*CH_3 OMe), 3.67 (d, *J* = 2.9 Hz, 1H, H-2'), 3.48 (s, 1H, H-5), 3.35 – 3.27 (m, 1H, H-5'), 3.25 – 3.19 (m, 2H, H-3', H-6'), 3.03 (dd, *J* = 13.7, 9.4 Hz, 1H, H-6'); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 158.5, 155.3, 151.5, 138.5, 138.1, 138.0, 132.06 (C_q), 132.0, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4 (CH_{arom}), 127.4 (C_q), 126.3, 119.0, 118.8, 114.5, 114.4 (CH_{arom}), 103.1 (C-1), 102.9 (C-1'), 100.7 (CH benzylidene), 82.5 (C-3'), 78.8 (C-2), 78.2 (C-3), 77.5 (C-4'), 75.9 (C-4), 75.5 (C-5'), 75.3, 73.3 (CH_2 benzyl), 72.4 (C-2'), 71.5 (CH_2 benzyl), 68.9 (C-6), 66.7 (C-5), 55.6, 55.3 (CH_3 OMe), 37.5 (C-6'); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 103.1 ($J_{C1\text{-}H1}$ = 159 Hz, C-1), 102.9 ($J_{C1'\text{-}H1'}$ = 158 Hz, C-1'); Diagnostic peaks from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 5.48 (s, 0.12H, CH_3 OMe), 3.58 (s, 0.38H); HRMS $[M+Na]^+$ calcd for $C_{61}H_{62}O_{12}SNa$ 1041.38542, found 1041.38571.

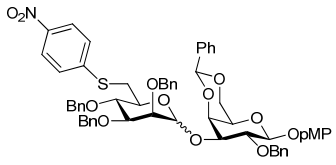


2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-*p*-methoxyphenyl-6-thio-D-mannopyranosyl-(1→2)-(methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside) (31c): Donor 13 and acceptor 26c were coupled according to the general glycosylation procedure to yield 179 mg (194 µmol, 88%) of the title compound 31c as an epimeric mixture (α/β 1/4.5). R_f 0.40, 0.60 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 2910, 1593, 1495, 1454, 1072, 730, 696; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.57 – 7.17 (m, 27H, H_{arom}), 6.82 – 6.69 (m, 2H), 5.55 (s, 1H, CH benzylidene), 5.06 (d, *J* = 12.4 Hz, 1H, CH_2 benzyl), 5.01 – 4.90 (m, 3H, CH_2 benzyl), 4.78 (d, *J* = 0.9 Hz, 1H, H-1), 4.69 – 4.48 (m, 3H, H-1', CH_2 benzyl), 4.43 (dd, *J* = 3.3, 1.4 Hz, 1H, H-2), 4.39 (d, *J* = 11.8 Hz, 1H, CH_2 benzyl), 4.29 – 4.25 (m, 1H, H-6), 4.12 – 4.06 (m, 1H, H-4), 4.01 – 3.95 (m, 2H, H-2', H-3), 3.83 – 3.74 (m, 3H, H-6, H-4', H-5), 3.72 (s, 3H, CH_3 OMe), 3.47 (dd, *J* = 9.2, 3.0 Hz, 1H, H-3'), 3.41 – 3.34 (m, 4H, CH_3 OMe, H-5'), 3.30 (dd, *J* = 13.5, 1.7 Hz, 1H, H-6'), 2.94 (dd, *J* = 13.6, 9.2 Hz, 1H, H-6'); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 158.5, 138.8, 138.6, 138.2, 137.9, 137.5 (C_q), 132.0, 128.5, 128.3, 128.1, 128.0, 127.9, 127.6, 127.5, 127.4, 126.1, 114.5 (CH_{arom}), 101.6 (CH benzylidene), 99.1 (C1'), 98.8 C-1), 81.8 (C-3'), 78.3 (C-4), 77.6 (C-4'), 75.2 (C-5'), 75.1, 73.6 (CH_2 benzyl), 73.5 (C-3), 73.1 (C-2'), 72.5 (C-2), 71.0, 70.3 (CH_2 benzyl), 68.9 (C-6), 63.8 (C-5), 55.2, 55.0 (CH_3 OMe), 37.5 (C-6'); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 99.1 ($J_{C1'\text{-}H1'}$ = 154 Hz, C-1'), 98.8 ($J_{C1\text{-}H1}$ = 168 Hz, C-1); Diagnostic peaks from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 5.61 (s, 022H, CH benzylidene), 3.27 (s, 0.66H, CH_3 OMe); HRMS $[M+Na]^+$ calcd for $C_{55}H_{58}O_{11}SNa$ 949.35920, found 949.35920.

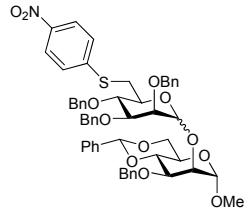


2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-*p*-nitrophenyl-6-thio-D-mannopyranosyl-(1→6)-(methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside) (32a): Donor 15 and acceptor 26a were coupled according to the general glycosylation procedure to yield 180 mg (174 µmol, 79%) of the title compound as 32a an epimeric mixture (α/β 1/7). R_f 0.59 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 3032, 2903, 1578, 1512, 1497, 1454, 1336, 1067, 733, 696; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 8.10 – 7.85 (m, 2H, H_{arom}), 7.50 – 7.09 (m, 32H, H_{arom}), 5.08 – 4.99 (m, 2H, CH_2 benzyl), 4.92 (d, *J* = 12.4 Hz, 1H, CH_2 benzyl), 4.87 – 4.75 (m, 4H, CH_2 benzyl), 4.69 – 4.46 (m, 6H, H-1, CH_2 benzyl), 4.12 – 4.06 (m, 2H, H-1', H-6), 4.02 (t, *J* = 9.2 Hz, 1H, H-3), 3.86 – 3.74 (m, 2H, H-4', H-5), 3.72 (d, *J* = 2.8 Hz, 1H, H-2'), 3.54 – 3.30 (m, 9H, H-2, H-6, H3', H-4, H-6', H-5', CH_3 OMe), 3.04 (dd, *J* = 14.1, 9.1 Hz, 1H, H-6'); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ147.9, 144.7, 138.7, 138.4, 138.2, 137.9, 137.8 (C_q), 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 125.9, 123.7, 123.6 (CH_{arom}), 101.2 (C-1'), 97.7 (C-1), 82.0 (C-3, C-3'), 79.8 (C-2), 77.2 (C-4, C-4'), 75.6, 75.3 (CH_2 benzyl), 74.9 (C-5'), 74.6, 73.8 (CH_2 benzyl), 73.4 (C-2'), 73.2, 71.4 (CH_2 benzyl), 69.5 (C-5),

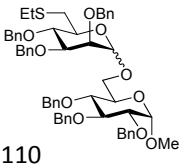
68.1 (C-6), 55.0 (CH_3 OMe), 33.9 (C-6'); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 101.2 ($J_{C1'\text{-}H1'}$ = 156.0 Hz, C-1'), 97.7 ($J_{C1\text{-}H1}$ = 168.1 Hz, C-1); Diagnostic peak from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 3.95 (t, *J* = 9.2 Hz, 0.14H, H-3); HRMS $[M+Na]^+$ calcd for $C_{61}H_{63}NO_{12}SNa$ 1056.39632, found 1056.39636.



2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-*p*-nitrophenyl-6-thio-D-mannopyranosyl-(1→3)-(*p*-methoxyphenyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside) (32b): Donor 15 and acceptor 26b were coupled according to the general glycosylation procedure to yield 207 mg (200 µmol, 91%) of the title compound 32b as an epimeric mixture (α/β 1/4). R_f 0.37 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 2870, 1579, 1506, 1454, 1336, 1060, 730, 696; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 8.05 – 7.96 (m, 2H, H_{arom}), 7.62 – 6.75 (m, 31H, H_{arom}), 5.56 (s, 1H, CH benzylidene), 5.03 – 4.82 (m, 5H, H-1, CH_2 benzyl), 4.65 – 4.59 (m, 2H, H-1', CH_2 benzyl), 4.43 (d, *J* = 11.6 Hz, 1H, CH_2 benzyl), 4.38 – 4.28 (m, 3H, H-6, CH_2 benzyl), 4.26 (d, *J* = 3.4 Hz, 1H, H-4), 4.10 – 3.98 (m, 2H, H-2, H-6), 3.83 – 3.70 (m, 5H, H-4', H-3, CH_3 OMe), 3.69 (d, *J* = 2.8 Hz, 1H, H-2'), 3.43 (s, 1H, H-5), 3.39 – 3.28 (m, 2H, H-5', H-6'), 3.23 (dd, *J* = 9.2, 2.9 Hz, 1H, H-3'), 3.09 – 3.00 (m, 1H, H-6'); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 155.3, 151.4, 147.9, 144.7, 138.4, 138.2, 137.9, 137.8 (C_q), 128.5, 128.4, 128.3, 128.0, 127.9, 127.6, 127.4, 126.2, 125.8, 123.7, 119.1, 118.7, 114.4 (CH_{arom}), 103.1 (C-1), 102.7 (C-1'), 100.7 (CH benzylidene), 82.4 (C-3'), 78.8 (C-2), 78.0 (C-3), 77.1 (C-4'), 75.9 (C-4), 75.3, 75.2 (CH_2 benzyl), 74.9 (C-5'), 73.4 (CH_2 benzyl), 72.3 (C-2'), 71.4 (CH_2 benzyl), 68.8 (C-6), 66.6 (C-5), 55.5 (CH_3 OMe), 33.9 (C-6'); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 103.1 ($J_{C1\text{-}H1}$ = 159 Hz, C-1), 102.7 ($J_{C1'\text{-}H1'}$ = 157 Hz, C-1'); Diagnostic peaks from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 5.45 (s, 0.24H, benzylidene), 2.93 (dd, *J* = 14.1, 9.2 Hz, 1H, H-6'); HRMS $[M+Na]^+$ calcd for $C_{60}H_{59}NO_{13}SNa$ 1056.35993, found 1056.36042.

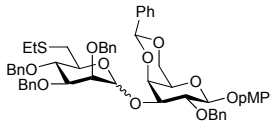


2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-*p*-nitrophenyl-6-thio-D-mannopyranosyl-(1→2)-(methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside) (32c): Donor 15 and acceptor 26c were coupled according to the general glycosylation procedure to yield 187 mg (198 µmol, 90%) of the title compound 32c as an epimeric mixture (α/β 1/4). R_f 0.47 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 2908, 1579, 1512, 1598, 1454, 1336, 1072, 730, 696; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.97 – 7.91 (m, 2H, H_{arom}), 7.56 – 7.14 (m, 27H, H_{arom}), 5.53 (s, 1H, CH benzylidene), 5.06 (dd, *J* = 11.7, 4.6 Hz, 2H, CH_2 benzyl), 4.97 (d, *J* = 12.3 Hz, 1H, CH_2 benzyl), 4.88 (d, *J* = 12.3 Hz, 1H, CH_2 benzyl), 4.73 (d, *J* = 1.1 Hz, 1H, H-1), 4.70 – 4.53 (m, 4H, CH_2 benzyl, H-1'), 4.43 (d, *J* = 11.8 Hz, 1H, CH_2 benzyl), 4.31 (dd, *J* = 3.3, 1.4 Hz, 1H, H-2), 4.29 – 4.24 (m, 1H, H-6), 4.11 – 4.06 (m, 1H, H-4), 4.02 (d, *J* = 2.9 Hz, 1H, H-2'), 3.96 (dd, *J* = 9.9, 3.4 Hz, 1H, H-3), 3.85 (t, *J* = 9.2 Hz, 1H, H-4'), 3.81 – 3.76 (m, 2H, H-5, H-6), 3.53 (dd, *J* = 9.1, 2.9 Hz, 1H, H-3'), 3.46 – 3.36 (m, 2H, H-6', H-5'), 3.34 (s, 3H, CH_3 OMe), 2.92 (dd, *J* = 13.9, 9.2 Hz, 1H, H-6'); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 147.6, 144.7, 138.6, 138.4, 137.9, 137.7, 137.4 (C_q), 128.5, 128.3, 128.2, 128.1, 127.9, 127.5, 127.4, 126.0, 125.6, 123.7 (CH_{arom}), 101.6 (CH benzylidene), 99.4 (C-1'), 99.0 (C-1), 81.7 (C-3'), 78.4 (C-4), 77.2 (C-4'), 75.3 (CH_2 benzyl), 74.8 (C-5'), 73.8 (CH_2 benzyl), 73.7, 73.4, 73.2 (C-3, C-2', C-2), 71.0, 70.7 (CH_2 benzyl), 68.8 (C-6), 63.8 (C-5), 54.9 (CH_3 OMe), 33.8 (C-6'); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 99.4 ($J_{C1'\text{-}H1'}$ = 152 Hz, C-1'), 99.0 ($J_{C1\text{-}H1}$ = 168 Hz, C-1); Diagnostic peaks from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 5.60 (s, 0.25H, CH benzylidene), 3.15 (s, 0.75H, CH_3 OMe); HRMS $[M+Na]^+$ calcd for $C_{54}H_{55}NO_{12}SNa$ 964.33372, found 964.33391.

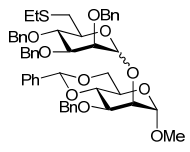


2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-ethyl-6-thio-D-mannopyranosyl-(1→6)-(methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside) (33a): Donor **17** and acceptor **26a** were coupled according to the general glycosylation procedure to yield 166 mg (176 µmol, 80%) of the title compound **33a** as an epimeric mixture (α/β 1/4). R_f 0.48,

0.53 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 3030, 2924, 1497, 1454, 1067, 736, 696; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.44 – 7.15 (m, 30H, H_{arom}), 5.07 – 4.89 (m, 3H, CH_2 benzyl), 4.86 – 4.73 (m, 4H, CH_2 benzyl), 4.70 – 4.43 (m, 6H, H-1, CH_2 benzyl), 4.16 (dd, *J* = 10.3, 1.8 Hz, 1H, H-6), 4.12 (s, 1H, H-1'), 4.02 (t, *J* = 9.2 Hz, 1H, H-3), 3.82 – 3.74 (m, 2H, H-5, H-4'), 3.72 (d, *J* = 2.8 Hz, 1H, H-2'), 3.54 – 3.42 (m, 3H, H-2, H-6, H-4), 3.40 (dd, *J* = 9.3, 2.9 Hz, 1H, H-3'), 3.34 – 3.27 (m, 4H, CH_3 OMe, H-5'), 2.89 (dd, *J* = 13.9, 2.0 Hz, 1H, H-6'), 2.71 (dd, *J* = 14.0, 8.6 Hz, 1H, H-6'), 2.58 (q, *J* = 7.4 Hz, 2H, CH_2 ethyl), 1.18 (t, *J* = 7.4 Hz, 3H, CH_3 ethyl); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 138.7, 138.6, 138.2, 138.0, 137.9 (C_q), 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3 (CH_{arom}), 101.3 (C-1'), 97.7 (C-1), 82.1, 82.0 (C-3, C-3'), 79.7 (C-2), 77.5, 77.4 (C-4, C-4'), 77.1 (C-5'), 75.5 , 75.2, 74.6, 73.6 (CH_2 benzyl), 73.5 (C-2'), 73.2, 71.4 (CH_2 benzyl), 69.6 (C-5), 68.1 (C-6), 54.9 (CH_3 OMe), 33.1 (C-6'), 26.9 (CH_2 ethyl), 14.78 (CH_3 ethyl); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 101.3 ($J_{C1'-H1'}$ = 153.1 Hz, C-1'), 97.7 (J_{C1-H1} = 168.1 Hz, C-1); Diagnostic peaks from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 3.62 (dd, *J* = 11.5, 1.7 Hz, 0.22 H, H-6), 2.47 (q, *J* = 7.3 Hz, 0.44H, CH_2 ethyl); HRMS $[M+Na]^+$ calcd for $C_{57}H_{64}O_{10}SNa$ 963.41124, found 963.41153.

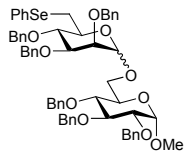


2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-ethyl-6-thio-D-mannopyranosyl-(1→3)-(*p*-methoxyphenyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside) (33b): Donor 17 and acceptor 26b were coupled according to the general glycosylation procedure to yield 178 mg (189 µmol, 86%) of the title compound 33b as an epimeric mixture (α/β 1/3.5). R_f 0.21, 0.29 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) IR (neat, cm^{-1}) 2867, 1506, 1454, 1062, 733, 697; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.62 – 6.78 (m, 29H), 5.62 (s, 1H, CH benzylidene), 4.97 – 4.88 (m, 4H, H-1, CH_2 benzyl), 4.64 – 4.57 (m, 3H, H-1', CH_2 benzyl), 4.44 – 4.30 (m, 5H, H-4, H-6, CH_2 benzyl), 4.10 – 4.02 (m, 2H, H-2, H-6), 3.82 (dd, *J* = 10.0, 3.5 Hz, 1H, H-3), 3.76 – 3.70 (m, 4H, CH_3 OMe, H-4'), 3.68 (d, *J* = 2.9 Hz, 1H, H-2'), 3.51 (s, 1H, H-5), 3.32 – 3.25 (m, 1H, H-5'), 3.23 (dd, *J* = 9.3, 2.9 Hz, 1H, H-3'), 2.87 (dd, *J* = 13.7, 2.0 Hz, 1H, H-6'), 2.71 (dd, *J* = 13.7, 9.2 Hz, 1H, H-6'), 2.57 (q, *J* = 7.4 Hz, 2H, CH_2 ethyl), 1.21 (t, *J* = 7.4 Hz, 3H, CH_3 ethyl); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 155.3, 151.5, 138.5, 138.5, 138.1, 138.0 (C_q), 128.4, 128.3, 128.1, 128.0, 127.9, 127.6, 127.5, 126.3, 118.8, 114.4 (CH_{arom}), 103.1 (C-1), 102.9 (C-1'), 100.7 (CH benzylidene), 82.5 (C-3'), 78.7 (C-2), 78.4 (C-3), 77.5 (C-4'), 76.4 (C-4), 76.1 (C-5'), 75.2, 73.3 (CH_2 benzyl), 72.4 (C-2'), 71.5 (CH_2 benzyl), 68.9 (C-6), 66.7 (C-5), 55.6 (CH_3 OMe), 33.5 (C-6'), 26.8 (CH_2 ethyl), 14.9 (CH_3 ethyl); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 103.1 (J_{C1-H1} = 159 Hz, C-1), 102.9 ($J_{C1'-H1'}$ = 158 Hz, C-1'); Diagnostic peaks from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 5.46 (s, 0.29H, CH benzylidene), 2.32 (q, *J* = 7.4 Hz, 0.57H, CH_2 ethyl), 1.00 (t, *J* = 7.4 Hz, 0.86H, CH_3 ethyl); HRMS $[M+Na]^+$ calcd for $C_{56}H_{60}O_{11}SNa$ 963.37485, found 963.37521.

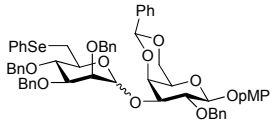


2,3,4-Tri-*O*-benzyl-6-deoxy-6-*S*-ethyl-6-thio-D-mannopyranosyl-(1→2)-(methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside) (33c): Donor 17 and acceptor 26c were coupled according to the general glycosylation procedure to yield 146 mg (172 µmol, 78%) of the title compound 33c as an epimeric mixture (α/β 1/1.5). R_f 0.40, 0.59 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 2926, 1718, 1497, 1454, 1075, 738, 697; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ7.54 – 7.18 (m, 25H, H_{arom}), 5.54 (s, 1H, CH benzylidene), 5.09 – 4.85 (m, 2H, CH_2 benzyl), 4.79 (d, *J* = 0.8 Hz, 1H), 4.71 – 4.50 (m, 6H, H-1', CH_2 benzyl), 4.43 (d, *J* = 11.8 Hz, 1H, CH_2 benzyl), 4.39 (dd, *J* = 3.4, 1.5 Hz, 1H, H-2), 4.28 – 4.21 (m, 1H, H-6), 4.13 – 4.05 (m, 1H, H-4), 4.02 – 3.95 (m, 2H, H-2', H-3), 3.88 – 3.74 (m, 3H, H-4', H-5, H-6), 3.50 (dd, *J* = 9.3, 3.0 Hz, 1H, H-3'), 3.41 – 3.33 (m, 4H, H-5', CH_3 OMe), 2.99 – 2.89 (m, 1H, H-6'), 2.73 – 2.65 (m, 1H, H-6'), 2.55 (q, *J* = 7.4 Hz, 2H, CH_2 ethyl), 1.15 (t, *J* = 7.4 Hz, 3H, CH_3 ethyl); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 138.8, 138.7, 138.3, 137.5 (C_q), 128.5, 128.3, 128.1, 128.0, 127.6, 127.5, 126.1 (CH_{arom}), 101.6 (CH benzylidene), 99.0 (C-1'), 98.7 (C-1), 81.9 (C-3'), 78.5 (C-4), 77.4 (C-4'), 76.9 (C-5'), 75.2, 73.7 (CH_2 benzyl), 73.6, 73.5 (C-2', C-3), 72.8 (C-2), 71.1, 70.7 (CH_2 benzyl), 68.9 (C-6), 63.9 (C-5), 55.0 (CH_3 OMe), 33.5 (C-6'), 26.9 (CH_2 ethyl), 14.8 (CH_3 ethyl); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 99.0 ($J_{C1'-H1'}$ = 154 Hz, C-1'), 98.7 (J_{C1-H1} = 167 Hz, C-1);

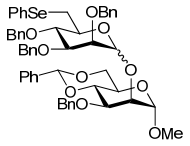
Diagnostic peaks from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 5.61 (s, 0.65H, CH benzylidene), 1.24 (t, *J* = 7.5 Hz, 1.95H, CH_3 ethyl); HRMS $[M+Na]^+$ calcd for $C_{50}H_{56}O_{10}SNa$ 871.34864, found 871.34859.



2,3,4-Tri-*O*-benzyl-6-deoxy-6-*Se*-phenyl-6-seleno-D-mannopyranosyl-(1→6)-(methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside) (34a): Donor 19 and acceptor 26a were coupled according to the general glycosylation procedure to yield 226 mg (218 µmol, 99%) of the title compound 34a as an epimeric mixture (α/β 1/7). R_f 0.47 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 3030, 2910, 1580, 1497, 1454, 1069, 731, 694; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.70 – 6.94 (m, 35H, H_{arom}), 5.03 (d, *J* = 10.9 Hz, 1H, CH_2 benzyl), 4.99 – 4.89 (m, 2H, CH_2 benzyl), 4.88 – 4.73 (m, 4H, CH_2 benzyl), 4.70 – 4.39 (m, 6H, H-1, CH_2 benzyl), 4.18 (br d, *J* = 9.9 Hz, 1H, H-6), 4.10 (s, 1H, H-1'), 4.04 (t, *J* = 9.2 Hz, 1H, H-3), 3.86 – 3.72 (m, 2H, H-5, H-4'), 3.71 (d, *J* = 2.3 Hz, 1H, H-2'), 3.52 (dd, *J* = 9.6, 3.4 Hz, 1H, H-2), 3.50 – 3.24 (m, 8H, H-6, H-4, H-5', H-3', CH_3 OMe, H-6'), 3.08 (dd, *J* = 12.5, 9.5 Hz, 1H, H-6'); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 138.7, 138.4, 138.1, 138.0, 137.9, 137.8 (C_q), 131.6, 131.4 (CH_{arom}), 131.2 (C_q), 128.8, 128.7, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 126.2 (CH_{arom}), 101.1 (C-1'), 97.6 (C-1), 82.0 (C-3, C-3'), 79.7 (C-2), 78.3 (C-4'), 77.4 (C-4), 75.7 (C-5'), 75.5, 75.1, 74.5, 73.6 (CH_2 benzyl), 73.4 (C-2'), 73.1, 71.4 (CH_2 benzyl), 69.4 (C-5), 67.9 (C-6), 54.9 (CH_3 OMe), 29.4 (C-6'); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 101.2 ($J_{C1'-H1'}$ = 154 Hz, C-1'), 97.6 (J_{C1-H1} = 169.0 Hz, C-1); Diagnostic peaks from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 3.97 (t, *J* = 9.2 Hz, 0.15H); HRMS $[M+Na]^+$ calcd for $C_{61}H_{64}O_{10}SeNa$ 1059.35569, found 1059.35680.

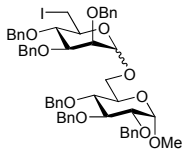


2,3,4-Tri-*O*-benzyl-6-deoxy-6-*Se*-phenyl-6-seleno-D-mannopyranosyl-(1→3)-(*p*-methoxyphenyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside) (34b): Donor 19 and acceptor 26b were coupled according to the general glycosylation procedure to yield 210 mg (203 µmol, 96%) of the title compound 34b as an epimeric mixture (α/β 1/10). R_f 0.24, 0.38 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 3034, 2867, 1578, 1506, 1454, 1059, 731, 695; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.62 – 6.73 (m, 34H, H_{arom}), 5.55 (s, 1H, CH benzylidene), 4.99 – 4.82 (m, 5H, H-1, CH_2 benzyl), 4.59 (d, *J* = 13.5 Hz, 2H, H-1', CH_2 benzyl), 4.47 – 4.25 (m, 5H, H-4, H-6, CH_2 benzyl), 4.11 – 3.96 (m, 2H, H-6, H-2), 3.80 – 3.66 (m, 6H, H-4', H-3, CH_3 OMe, H-2'), 3.44 – 3.33 (m, 2H, H-5, H-5'), 3.30 (br d, *J* = 11.3 Hz, 1H, H-6'), 3.24 (dd, *J* = 9.2, 2.4 Hz, 1H, H-3'), 3.10 (dd, *J* = 12.2, 10.2 Hz, 1H, H-6'); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 155.2, 151.4, 138.5, 138.4, 138.0, 137.9 (C_q), 131.6, 131.2, 128.9, 128.3, 128.2, 128.1, 127.9, 127.8, 127.6, 127.4, 126.2, 118.7, 114.4 (CH_{arom}), 103.0 (C-1), 102.9 (C-1'), 100.5 (CH benzylidene), 82.4 (C-3'), 78.7 (C-2), 78.4, 78.3 (C-3, C-4'), 75.9 (C-4), 75.7 (C-5'), 75.2, 73.3 (CH_2 benzyl), 72.5 (C-2'), 71.4, 68.8 (CH_2 benzyl), 66.6 (C-6), 55.5 (CH_3 OMe), 29.6 (C-6'); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 103.0 (J_{C1-H1} = 160 Hz, C-1), 102.9 ($J_{C1'-H1'}$ = 159 Hz, C-1'); Diagnostic peak from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 5.43 (s, 0.10H, CH benzylidene); HRMS $[M+Na]^+$ calcd for $C_{60}H_{60}O_{11}SeNa$ 1059.31931, found 1059.32029.

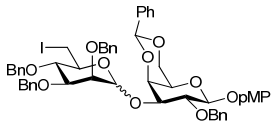


2,3,4-Tri-*O*-benzyl-6-deoxy-6-*Se*-phenyl-6-seleno-D-mannopyranosyl-(1→2)-(methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside) (34c): Donor 19 and acceptor 26c were coupled according to the general glycosylation procedure to yield 191 mg (202 µmol, 92%) of the title compound 34c as an epimeric mixture (α/β 1/3). R_f 0.45, 0.64 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 3034, 2909, 1580, 1497, 1454, 1073, 735, 696; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.56 – 7.12 (m, 30H, H_{arom}), 5.55 (s, 1H, CH benzylidene), 5.07 (d, *J* = 12.4 Hz, 1H, CH_2 benzyl), 5.01 – 4.88 (m, 3H, CH_2 benzyl), 4.78 (s, 1H, H-1), 4.67 (d, *J* = 12.3 Hz, 1H, CH_2 benzyl), 4.63 – 4.48 (m, 3H, H-1', CH_2 benzyl), 4.44 – 4.38 (m, 2H, H-2, CH_2 benzyl), 4.28 – 4.23 (m, 1H, H-6), 4.13 – 4.07 (m, 1H, H-4), 4.01 – 3.95 (m, 2H, H-2', H-3), 3.85 – 3.77 (m, 3H, H-6, H-4', H-5), 3.51 –

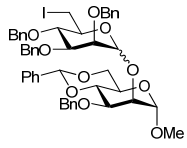
3.43 (m, 2H, H-3', H-5'), 3.40 – 3.33 (m, 4H, CH_3 OMe, H-6'), 3.01 (dd, *J* = 12.4, 9.6 Hz, 1H, H-6'); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 138.8, 138.6, 138.2, 137.9, 137.5 (C_q), 131.4 (CH_{arom}), 131.1 (C_q), 129.0, 128.5, 128.3, 128.1, 128.0, 127.9, 127.6, 127.4, 126.1 (CH_{arom}), 101.6 (CH benzylidene), 99.0 (C-1'), 98.7 (C-1), 81.8 (C-3'), 78.4 (C-4), 78.3 (C-4'), 75.9 (C-5'), 75.2, 73.7 (CH_2 benzyl), 73.6 (C-3), 73.4 (C-2'), 72.6 (C-2), 71.1, 70.5 (CH_2 benzyl), 68.8 (C-6), 63.8 (C-5), 55.0 (CH_3 OMe), 29.5 (C-6'); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 99.0 ($J_{C1'-H1'}$ = 154 Hz, C-1'), 98.7 (J_{C1-H1} = 168 Hz, C-1); Diagnostic peaks from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 5.60 (s, 0.33H, CH benzylidene), 3.24 (s, 1H, CH_3 OMe), 3.09 (dd, *J* = 12.4, 9.5 Hz, 0.33H, H-6'); HRMS $[M+Na]^+$ calcd for $C_{54}H_{56}O_{10}SeNa$ 967.29309, found 967.29351.



2,3,4-Tri-*O*-benzyl-6-deoxy-6-iodo-D-mannopyranosyl-(1→6)-(methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside) (35a): Donor **21** and acceptor **26a** were coupled according to the general glycosylation procedure to yield 186 mg (185 μmol, 84%) of the title compound **35a** as an epimeric mixture (α/β 1/7). R_f 0.49 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 3032, 2872, 1497, 1454, 1066, 908, 728, 695; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.64 – 7.09 (m, 30H, H_{arom}), 5.03 (d, *J* = 10.9 Hz, 1H, CH_2 benzyl), 4.98 – 4.90 (m, 2H, CH_2 benzyl), 4.87 – 4.74 (m, 4H, CH_2 benzyl), 4.70 – 4.48 (m, 5H, H-1, CH_2 benzyl), 4.43 (d, *J* = 11.9 Hz, 1H, CH_2 benzyl), 4.27 (dd, *J* = 10.3, 1.7 Hz, 1H, H-6), 4.12 (s, 1H, H-1'), 4.04 (t, *J* = 9.2 Hz, 1H, H-3), 3.88 – 3.79 (m, 1H, H-5), 3.71 (d, *J* = 2.8 Hz, 1H, H-2'), 3.67 (t, *J* = 9.0 Hz, 1H, H-4'), 3.55 – 3.42 (m, 4H, H-2, H-6', H-6, H-4), 3.39 (dd, *J* = 9.2, 2.9 Hz, 1H, H-3'), 3.34 (s, 3H, CH_3 OMe), 3.20 (dd, *J* = 7.9, 4.5 Hz, 2H, H-5', H-6'); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 138.6, 138.3, 138.1, 137.9, 137.7 (C_q), 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4 (CH_{arom}), 101.2 (C-1'), 97.6 (C-1), 82.0 (C-3), 81.6 (C-3'), 79.6 (C-2), 78.0 (C-4'), 77.5 (C-4), 75.6 (C-5'), 75.5, 75.2, 74.6, 73.6 (CH_2 benzyl), 73.3 (C-2'), 73.2, 71.4 (CH_2 benzyl), 69.4 (C-5), 68.3 (C-6), 55.0 (CH_3 OMe), 5.5 (C-6'); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 101.2 ($J_{C1'-H1'}$ = 155.0 Hz, C-1'), 97.6 (J_{C1-H1} = 168.4 Hz, C-1); Diagnostic peak from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 3.30 (s, 0.43H, CH_3 OMe); HRMS $[M+Na]^+$ calcd for $C_{55}H_{59}IO_{10}Na$ 1029.30451, found 1029.30480.

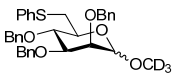


2,3,4-Tri-*O*-benzyl-6-deoxy-6-iodo-D-mannopyranosyl-(1→3)-(*p*-methoxyphenyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside) (35b): Donor 21 and acceptor 26b were coupled according to the general glycosylation procedure to yield 210 mg (209 μmol, 95%) of the title compound 35b as an epimeric mixture (α/β 1/6). R_f 0.24, 0.39 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 3030, 2866, 1506, 1454, 1059, 732, 696; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.66 – 6.73 (m, 29H, H_{arom}), 5.65 (s, 1H, CH benzylidene), 4.98 – 4.84 (m, 5H, H-1, CH_2 benzyl), 4.61 – 4.56 (m, 2H, H-1', CH_2 benzyl), 4.53 (d, *J* = 3.4 Hz, 1H, H-4), 4.49 – 4.30 (m, 4H, H-6, CH_2 benzyl), 4.13 – 4.04 (m, 2H, H-6, H-2), 3.85 (dd, *J* = 10.0, 3.4 Hz, 1H, H-3), 3.75 (s, 3H, CH_3 OMe), 3.70 – 3.63 (m, 2H, H-2', H-4'), 3.57 – 3.50 (m, 2H, H-6', H-5), 3.25 (dd, *J* = 9.2, 3.0 Hz, 1H, H-3'), 3.23 – 3.14 (m, 2H, H-5', H-6'); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 155.3, 151.5, 138.5, 138.3, 138.0, 137.8 (C_q), 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.5, 126.3, 118.8, 114.4 (CH_{arom}), 103.1 (C-1, C-1'), 100.6 (CH benzylidene), 82.2 (C-3'), 78.7, 78.6 (C-2, C-3), 78.0 (C-4'), 76.0 (C-4), 75.6 (C-5'), 75.3 (2*CH_2 benzyl), 73.4 (CH_2 benzyl), 72.5 (C-2'), 71.5 (CH_2 benzyl), 68.9 (C-6), 66.7 (C-5), 55.6 (CH_3 OMe), 6.5 (C-6'); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 103.1 (J_{C1-H1} = 160 Hz, C-1, $J_{C1'-H1'}$ = 158 Hz, C-1'); Diagnostic peak from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 5.45 (s, 0.16H, CH benzylidene); HRMS $[M+Na]^+$ calcd for $C_{54}H_{55}IO_{11}Na$ 1029.26813, found 1029.26818.



2,3,4-Tri-*O*-benzyl-6-deoxy-6-iodo-D-mannopyranosyl-(1→2)-(methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside) (35c): Donor **21** and acceptor **26c** were coupled according to the general glycosylation procedure to yield 175 mg (191 μmol, 87%) of the title compound **35c** as an epimeric mixture (α/β 1/3).

R_f 0.45, 0.71 (EtOAc/PE, 1/3, v/v); IR (neat, cm^{-1}) 3032, 2916, 1497, 1454, 1073, 735, 696; NMR data of the major β-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.59 – 7.19 (m, 25H, H_{arom}), 5.55 (s, 1H, CH benzylidene), 5.06 (d, *J* = 12.4 Hz, 1H, CH_2 benzyl), 4.98 (dd, *J* = 11.3, 5.1 Hz, 3H, CH_2 benzyl), 4.81 (s, 1H, H-1), 4.73 – 4.57 (m, 3H, H-1', CH_2 benzyl), 4.55 – 4.48 (m, 2H, H-2, CH_2 benzyl), 4.40 (d, *J* = 11.9 Hz, 1H, CH_2 benzyl), 4.29 – 4.25 (m, 1H, H-6), 4.13 – 4.03 (m, 1H, H-4), 4.04 – 3.97 (m, 2H, H-2', H-3), 3.86 – 3.71 (m, 3H, H-5, H-6, H-4'), 3.55 (dd, *J* = 10.3, 1.6 Hz, 1H, H-6'), 3.50 (dd, *J* = 9.2, 2.9 Hz, 1H, H-3'), 3.37 (s, 3H, CH_3 OMe), 3.32 – 3.25 (m, 1H, H-5'), 3.23 – 3.16 (m, 1H, H-6'); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 138.77, 138.5, 137.9, 137.7, 137.5 (Cq), 128.5, 128.4, 128.3, 128.1, 128.0, 127.6, 127.5, 126.1 (CH_{arom}), 101.6 (CH benzylidene), 98.8 (C-1'), 98.5 (C-1), 81.4 (C-3'), 78.3 (C-4), 78.0 (C-4'), 76.0 (C-5'), 75.3, 73.7 (CH_2 benzyl), 73.5 (C-3), 73.2 (C-2'), 72.4 (C-2), 71.0, 70.5 (CH_2 benzyl), 68.8 (C-6), 63.8 (C-5), 55.0 (CH_3 OMe), 5.7 (C-6'); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 98.8 ($J_{C1'-H1'}$ = 154 Hz, C-1'), 98.5 (J_{C1-H1} = 168 Hz, C-1); Diagnostic peaks from the α-linked product: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 5.62 (s, 0.32H, CH benzylidene), 3.34 (s, 1H, CH_3 OMe); HRMS $[M+Na]^+$ calcd for $C_{48}H_{51}IO_{10}Na$ 937.24173, found 937.24191.



Methyl (*d*3) 2,3,4-tri-*O*-benzyl-6-deoxy-6-*S*-phenyl-6-thio-D-mannopyranoside (37) (NMR tube experiment)**:** Donor **9** (38 mg, 53 µmol, 1 equiv) was coevaporated with toluene and transferred with 0.6 mL CD_2Cl_2 to a dry NMR tube capped with a septum. The temperature was lowered to -80°C, 4.7 µL triflic acid (53 µmol, 1 equiv) was added, the tube was shaken thoroughly and NMR spectra were recorded (crude sulfonium species **36**: ^{1}H NMR (400 MHz, CD_2Cl_2, HH-COSY, HSQC, T = 193 K) δ 7.89 – 7.03 (m, 20H, H_{arom}), 5.87 (d, *J* = 2.3 Hz, 1H, H-1), 5.74 (d, *J* = 7.4 Hz, 1H, H-5), 4.82 (d, *J* = 11.7 Hz, 1H, CH_2 benzyl), 4.75 – 4.63 (m, 3H, CH_2 benzyl), 4.59 – 4.51 (m, 3H, CH_2 benzyl, H-6), 4.21 (t, *J* = 3.4 Hz, 1H, H-2), 3.94 (app s, 1H, H-3), 3.91 – 3.89 (m, 1H, H-4), 3.71 (dd, *J* = 13.0, 7.5 Hz, 1H, H-6); ^{13}C NMR (100 MHz, CD_2Cl_2, HH-COSY, HSQC, T = 193 K) δ 137.4, 137.3, 136.9 (C_q), 135.5, 131.7, 130.9, 129.7, 129.5, 129.4, 129.3, 129.1, 129.1, 128.9, 128.8, 128.6, 128.5, 128.4, 128.2 (CH_{arom}), 127.0 (C_q), 126.7, 125.9, 121.2 (CH_{arom}), 105.2 (C-1), 82.4 (C-5), 75.6 (C-4), 75.2 (CH_2 benzyl), 74.6 (C-2), 74.0 (C-3), 73.2, 72.8 (CH_2 benzyl), 52.4 (C-6)). Next 25 µL MeOH-*d*4 was added, the tube was shaken thoroughly and was kept at room temperature overnight to give the crude title compound **26** as a mixture of anomers (α/β 3.5:1)[28]. NMR data of the major α-linked product: ^{1}H NMR (400 MHz, CD_2Cl_2, HH-COSY, HSQC) δ 7.50 – 6.95 (m, 20H, H_{arom}), 4.97 (d, *J* = 11.1 Hz, 1H, CH_2 benzyl), 4.76 – 4.64 (m, 3H, CH_2 benzyl, H-1), 4.64 – 4.53 (m, 3H, CH_2 benzyl), 3.91 – 3.71 (m, 4H, H-3, H-4, H-2, H-5), 3.42 (dd, *J* = 13.4, 1.7 Hz, 1H, H-6), 3.02 (dd, *J* = 13.4, 8.6 Hz, 1H, H-6); ^{13}C NMR (100 MHz, CD_2Cl_2, HH-COSY, HSQC) δ 139.1, 138.9, 138.8, 137.7 (C_q), 130.6, 129.7, 129.6, 129.5, 129.4, 129.1, 128.9, 128.7, 128.6, 128.5, 128.3, 128.2 , 126.5, 126.2 (CH_{arom}), 99.4 (C-1), 80.6 (C-3), 78.3 (C-4), 75.7 (C-2, CH_2 benzyl), 73.5, 72.5 (CH_2 benzyl), 71.6 (C-5), 36.3 (C-6). Diagnostic peak from the β-linked product: ^{1}H NMR (400 MHz, CD_2Cl_2, HH-COSY, HSQC) δ 4.32 (s, H-1); ^{13}C NMR (150 MHz, CD_2Cl_2, HH-COSY, HSQC) δ 103.1 (0.29C, C-1).[28]

Control experiments to exclude acid catalyzed anomerisation:

1)

Compound **29a** (144 mg, 0.15 mmol) and TTBP (72 mg, 0.29 mmol, 2 eq) were dissolved in DCM-d_2 (1 mL). TfOH (13 µL, 0.15 mmol, 1 eq) was added and the mixture was stirred for a period of 5 days. NMR spectroscopy of the mixture did not indicate any change in the composition of the mixture.

2)

Dimer **29a** (126 mg, 0.13 mmol) was dissolved in 2.5 mL DCM and stirred over 3Å molecular sieves for 30 minutes. The mixture was then cooled to -80 °C after which TfOH (0.025 mmol) in DCM (0.1 ml) was added and the reaction was stirred overnight at -80 °C. The reaction was quenched by the addition of 0.6 mL Et_3N at -80 °C. After filtration over celite, the mixture was washed with sat. aq. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. NMR spectroscopy of the mixture did not indicate any anomerisation.

References and notes

1. Original publication: Christina, A. E.; van der Es, D.; Dinkelaar, J.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. *Chem. Commun.* **2012**, *48*, 2686–2688
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23. (a) Isomerisation of the β-product into the α-product does not occur under these conditions, excluding this as a pathway leading to the α-product; (b) While the formation of **25** from **8** was instanteneous, the condensation reactions required overnight, excluding direct intermolecular substitution of the activated imidates. See experimental section for more details.
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27. Complete assignment of the peaks is omitted due to a 1:1 mixture of anomers.
28. Due to overlapping peaks in ^{1}H spectrum, the anomeric ratio was based on integration of the ^{13}C spectrum.

Chapter 5b

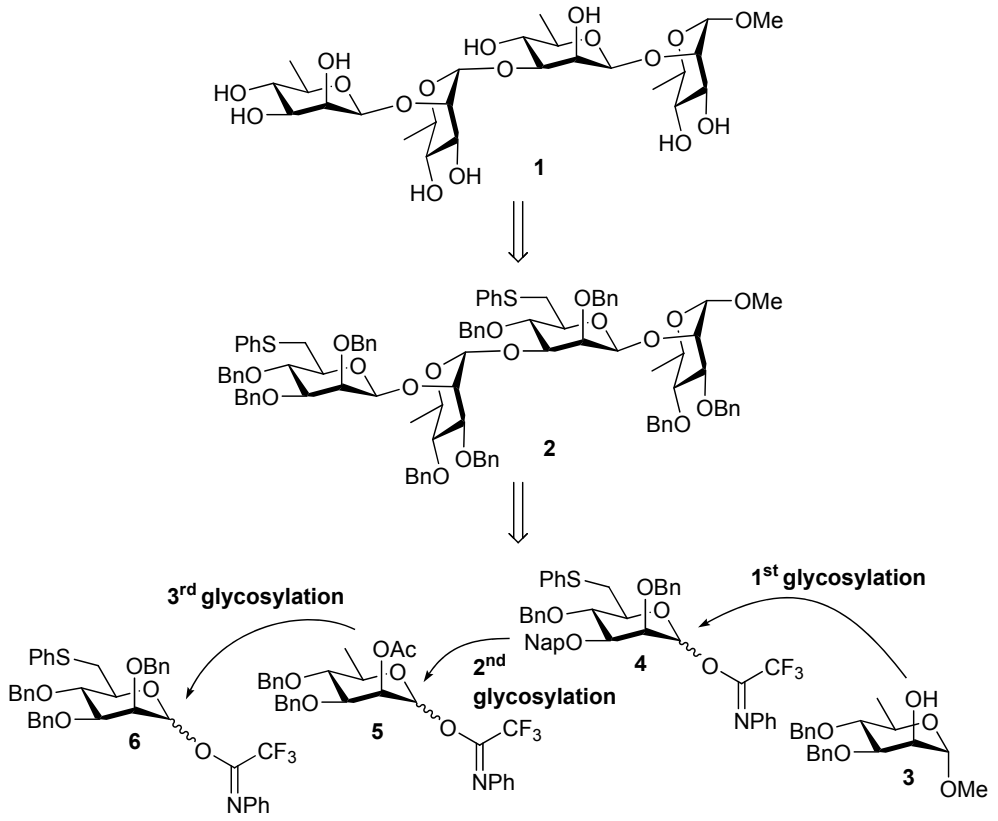
β-Rhamnosides from 6-Thio Mannosides[1]

Introduction

It was shown in the previous chapter that mannosyl donors equipped with a thiophenyl ether at C-6 are efficient 1,2-*cis*-mannosylating agents. It was hypothesized that upon activation of such a donor, a bridged sulfonium ion is formed that exists in equilibrium with the more reactive oxocarbenium ion-triflate anion pair conformers $^{3}H_{4}$ and $^{4}H_{3}$ (section a, scheme 1). The spatial orientation of the ring substituents in the $^{3}H_{4}$ conformer renders this species more favorable than its $^{4}H_{3}$ counterpart. The axially oriented $\sigma_{C1\text{-}H1}$ bond allows for hyperconjugative stabilization of the cation, the axial C-3 and C-4 substituents exert a minimal electron-withdrawing effect[2] while simultaneously permitting donation of electron density from the heteroatom lone pairs into the electron-deficient oxocarbenium ion[3] and the sulfur lone pair electrons of the *pseudo* axial C-5 methylene thioether stabilize the anomeric positive charge in a similar donative way. Whereas nucleophilic attack on both the bicyclic sulfonium ion and the $^{4}H_{3}$ oxocarbenium ion-triflate anion pair lead to α-linked products, the $^{3}H_{4}$ conformer is approached from the diastereotopic face that lead, via a chair-like transition state, to a product having a anomeric β-configuration. When the hypothesis was put to the test, 1,2-*cis* configured products were indeed found with good selectivity. This finding paved the way for an application of C-6 thiophenyl ether mannosyl donors in the

synthesis of complex rhamnose containing oligosaccharides, for desulfurization of β-6-thio mannoses can provide the corresponding β-rhamnose residues in a straightforward manner.[4,5] Therefore, tetrasaccharide **1**, containing alternating α- and β-D-rhamnosides, was chosen as a synthetic target (Figure 1). This oligosaccharide represents the general backbone structure (two repeating units) of the O-specific polysaccharide of the LPS of the phytopathogen *Xanthomonas campestris pathovar campestris*,[6] the causative agent of one of the most devastating diseases affecting cruciferous crops such as cabbage, cauliflower and broccoli. Retrosynthetic analysis (Figure 1) indicates that the target tetrasaccharide **1** can be accessed from fully protected compound **2** by desulfurization and debenzylation. Precursor **2** can in turn be assembled from monomeric building blocks **3**-**6**.[7]

Figure 1



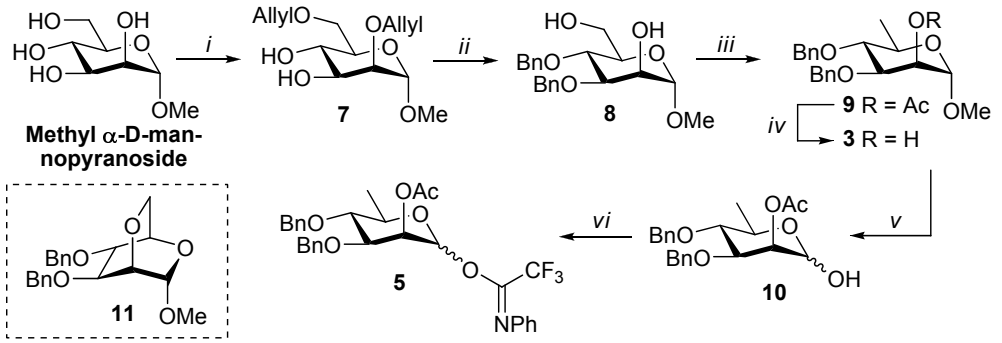
Retrosynthetic analysis of an assembly of backbone tetrasaccharide **1** from *Xanthomonas campestris*.

Results and Discussion

Glycosyl acceptor **3** and rhamnosyl donor **5** were synthesized from methyl α–D-mannopyranoside following the route depicted in Scheme 1. Protection of the C-3 and C-4

hydroxyls with a cyclic diketal using 2,3-butadione, allylation of the remaining hydroxyls and subsequent cleavage of the diketal gave diol **7** in 53% yield. Dibenzylation of this diol gave a crude fully protected mannoside that was converted to diol **8** by deprotection of both allyl groups in a two-step procedure: isomerization under basic conditions and ensuing acidic cleavage. Next the primary hydroxyl was deoxygenated by first converting it to an iodide. Sodium borohydride reduction at elevated temperatures gave crude alcohol **3**. At this stage the alcohol could not be separated from bicyclic sideproduct **11**, brought about by intramolecular displacement of the intermediate C-6 iodide. Therefore the mixture was subjected to acylating conditions with acetic anhydride in pyridine. Acetate **9** could be readily separated from sideproduct **11** and was converted to alcohol **3** under Zemplén conditions. Alcohol **3** was transformed to hemiacetal **10** in 3 steps, which entailed trifluoroacetic acid mediated hydrolysis of the methyl acetal function,[8] diacetylation of the intermediate lactol and selective anomeric deacetylation of the crude diacetate. Finally, installment of an anomeric *N*-phenyltrifluoroacetimidate under mildly basic conditions afforded glycosyl donor **5**.

Scheme 1

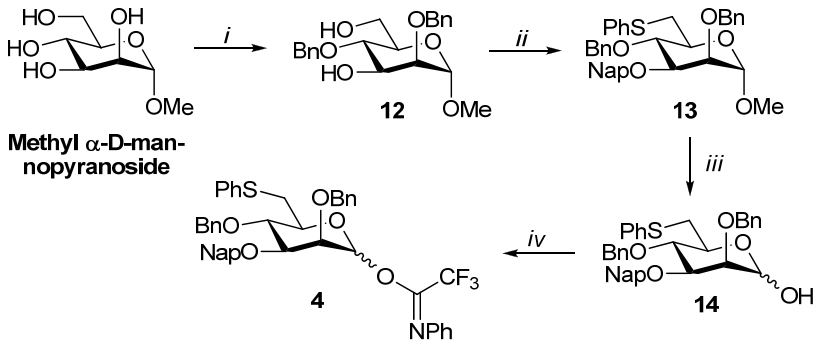


Reagents and conditions: (*i*) (1) butadione, CSA; (2) allylBr, NaH; (3) TFA/H_2O (9:1), 53% over 3 steps; (*ii*) (1) BnBr, NaH; (2) KOtBu, DMF, reflux; (3) MeOH, cat *p*-TsOH, 80%; (*iii*) (1) Ph_3P, imidazole, I_2, THF, 70°C; (2) $NaBH_4$, 100 °C; (3) Ac_2O, pyridine, 63% over 3 steps (with 18% of **11**); (*iv*) NaOMe, MeOH, 95%; (*v*) (1) H_2O/TFA (5:2); (2) Ac_2O, pyridine; (3) piperidine, THF, 86% over 3 steps; (*vi*) $CF_3C(=NPh)Cl$, Cs_2CO_3, acetone, H_2O, 59%.

The synthesis of 6-*S*-phenyl mannosyl donor **4** started with the selective disilylation of the C-6 and C-3 hydroxyls of methyl α-D-mannopyranoside using TBSCl in DMF (Scheme 2). The resulting crude diol was dibenzylated. Ensuing tetrabutyl ammonium fluoride mediated desilylation gave diol **12** in 60% over 3 steps. Next, the primary hydroxyl was converted into an iodide and the iodide was displaced by treatment with thiophenol. The crude alcohol was protected in the form of 2-naphthylmethylether giving mannoside **13** in 77% over 3 steps. Treatment of a solution of **13** in neat acetic anhydride with a catalytic amount of sulfuric acid followed by deacetylation of the resulting anomeric acetate led to hemiacetal **14**. Reaction of

this lactol with 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride under basic conditions furnished donor **4**.

Scheme 2



Reagents and conditions: (*i*) (1) TBSCl, imidazole, DMF; (2) BnBr, NaH, DMF; (3) TBAF, THF, 60% over 3 steps; (*ii*) (1) Ph_3P, imidazole, I_2, toluene, 70°C; (2) PhSH, DiPEA. DMF; (3) NapBr, NaH. DMF, 77% over 3 steps; (*iii*) (1) cat. H_2SO_4, Ac_2O; (2) piperidine, THF (77% over 2 steps); (*iv*) $CF_3C(=NPh)Cl$, Cs_2CO_3, acetone, H_2O, 94%.

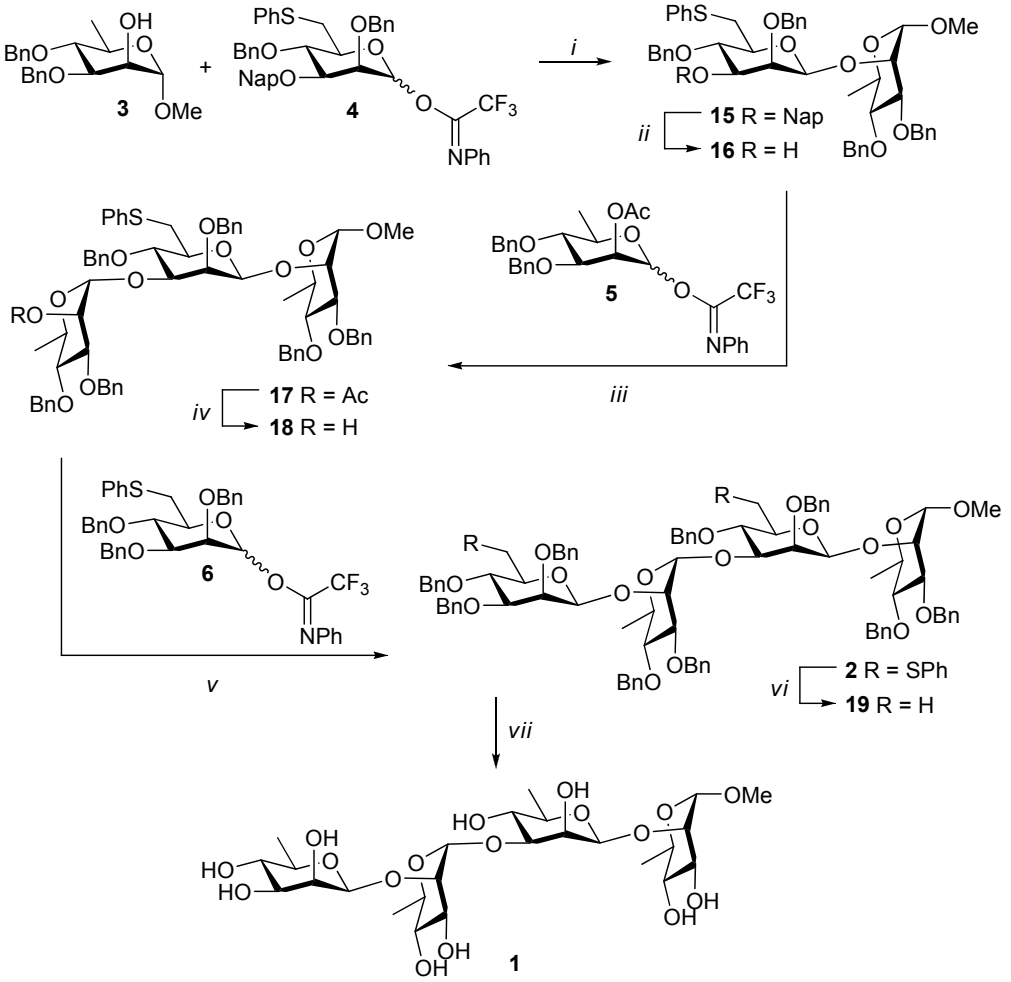
Since mannosyl donor **6** had been synthesized previously,[9] the stage was now set for the application of these building blocks in the construction of tetrasaccharide **1**. Rhamnosyl acceptor **3** and 6-*S*-phenyl mannoside **4** were condensed to give disaccharide **15** in 76% yield, highlighting the β-directing capacities of the 6-*S*-phenyl group in donor **4** (Scheme 3). Removal of the 2-methylnaphthyl ether liberated the C-3'-OH, which was glycosylated with rhamnoside **5** to provide the α-linked trimer **17**, by virtue of the participating acetyl function in donor **5**. Deacetylation of **17** then set the stage for the introduction of the second β-mannosidic bond. Reaction of the trimer acceptor and mannosyl donor **6** at -60 ^{o}C led to the formation of the target tetramer **2**, which was obtained as a mixture of anomers, in which the desired β-isomer prevailed (82%, α/β = 1 : 3). This result shows that also elaborate acceptors can be β-mannosylated with productive selectivity. Desulfurization of tetramer **2** under the agency of Raney-nickel proceeded uneventfully to deliver the perbenzylated tetrarhamnoside **19** in 96% yield. Reductive removal of all benzyl ethers completed the synthesis of tetramer **1**.

Conclusion

A backbone tetrasaccharide containing alternating α- and β-d-rhamnosides was synthesized. Key feature of the synthesis was the use of a C-6 thiophenyl ether mannosyl building block as a 1,2-*cis* selective glycosyl donor. The two glycosylations towards β-linked

products proceeded in good yield. In one of these two condensation, towards a disaccharide, no product resulting from 1,2-trans glycosylation was isolated. The other union, towards

Scheme 3

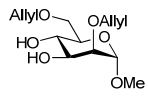


Reagents and conditions: (*i*) cat. TfOH, DCM, -80°C, 76%; (*ii*) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DCM, H_2O, 60%; (*iii*) cat. TfOH, DCM, 0°C, 84%; (*iv*) NaOMe, MeOH, 98%; (*v*) cat. TfOH, DCM, -60°C, 82%, α/β = 1 : 3; (*vi*) Raney-nickel, H_2O, MeOH, 96%; (*vii*) Pd/C, H_2, $^tBuOH/H_2O$, 85%.

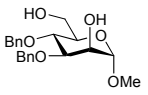
the target tetrasaccharide, yielded a mixture in which the desired β-isomer prevailed (α/β = 1 : 3). The C-6 thiophenyl ethers were desulfurized to give their deoxy counterparts. These results show that C-6 thiophenyl ether mannosyl donors can be used as 1,2-*cis* selective donor building blocks in the synthesis of complex β-rhamnose containing oligosaccharides.

Experimental section

General Procedures: All chemicals were used as received. Trifluoromethanesulfonic anhydride (Tf_2O) was distilled from P_2O_5 and stored in a Schlenk flask. TLC analysis was conducted on silica gel-coated aluminum TLC sheets (Merck, silica gel 60, F_{245}). Compounds were visualized by UV absorption (245 nm), by spraying with 20% H_2SO_4 in ethanol or with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ 25 g/L, $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ 10 g/L, 10% H_2SO_4 in H_2O followed by charring at ~140 °C. Flash chromatography was performed on silica gel (Screening Devices, 40-63 µm 60Å, www.screeningdevices.com) using technical grade, distilled solvents. NMR spectra were recorded on a Bruker AV400. For solutions in $CDCl_3$ chemical shifts (δ) are reported relative to tetramethylsilane (^1H) or $CDCl_3$ (^{13}C). Peak assignments were made based on HH-COSY and HSQC measurements. Optical rotation was measured using a Propol automatic polarimeter. The IR absorbance was recorded using a Shimadzu FTIR-83000 spectrometer. Mass analysis was performed using a PE/SCIEX API 165 with an Electrospray Interface (Perkin-Elmer).

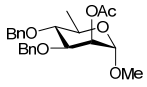


Methyl 2,6-di-*O*-allyl-α-D-mannopyranoside (7): To a stirred solution of 5.0 g methyl α-D-mannopyranoside (25.75 mmol, 1 equiv) in 50 mL methanol were added 11.3 mL trimethyl orthoformate (103.0 mmol, 4 equiv), 2.46 mL butane-2,3-dione (28.32 mmol, 1.1 equiv) and 598 mg (±)-camphorsulfonic acid (2.57 mmol, 0.1 equiv). The reaction was stirred under refluxing conditions overnight, cooled to ambient temperature and quenched by the addition of 1.79 mL Et_3N (12.88 mmol, 0.5 equiv). After concentration of the mixture and coevaporation with toluene, the residue was dissolved in 50 mL *N*,*N*-dimethylformamide and 6.67 mL ally bromide (77.13 mmol, 3 equiv) and 3.09 g NaH (60% dispersion in mineral oil, 77.13 mmol, 3 equiv) were added. The reaction was stirred overnight and was subsequently quenched by the addition of 6.25 mL of MeOH. The mixture was partitioned between water and diethyl ether. The organic layer was washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and water. Next, 100 mL TFA/H_2O (9/1, v/v) was added and the reaction was stirred for 30 min. Another 40 mL of water was added and the mixture was concentrated *in vacuo* and coevaporated with toluene. Flash column chromatography using EtOAc/PE (1/1 → 3/2) gave the title compound **7** (3.73 g, 13.60 mmol, 53% over 3 steps). R_f 0.21 (EtOAc/PE, 3/2, v/v); $[\alpha]_D^{22}$ +21 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3372, 2912, 1136, 1051; ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 6.01 – 5.82 (m, 2H, CH allyl), 5.34 – 5.22 (m, 2H, CH_2 allyl), 5.22 – 5.12 (m, 2H, CH_2 allyl), 4.76 (d, *J* = 1.2 Hz, 1H, H-1), 4.21 – 4.00 (m, 4H, CH_2 allyl), 3.82 – 3.57 (m, 8H, H-2, H-3, H-4, H-5, H-6, OH), 3.36 (s, 3H, CH_3 OMe); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 134.5, 134.2 (CH allyl), 117.4, 116.7 (CH_2 allyl), 98.1 (C-1), 77.2 (C-2), 72.2, 71.8 (CH_2 allyl), 71.1 (C-3), 70.7 (C-4), 69.7 (C-6), 68.6 (C-5), 54.5 (CH_3 OMe); HRMS $[M+Na]^+$ calcd for $C_{13}H_{22}O_6Na$ 297.13086, found 297.13077.

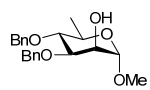


Methyl 3,4-di-*O*-benzyl-α-D-mannopyranoside (8): To a solution of 4.22 g methyl 2,6-di-*O*-allyl-α-D-mannopyranoside **7** (15.38 mmol, 1 equiv) in 60 mL DMF were added 5.52 mL benzyl bromide (46.15 mmol, 3 equiv) and 1.85 g NaH (60% in mineral oil, 46.15 mmol, 3 equiv). The reaction was stirred overnight at room temperature and quenched by the addition of 3.73 mL MeOH. The mixture was partitioned between Et_2O and water and the organic layer was washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The residue was coevaporated with toluene and dissolved in 60 mL DMF. 3.55 g sodium tert-butoxide (36.93 mmol, 2.4 equiv) was added and the mixture was stirred overnight at 120 °C. After cooling to ambient temperature, the mixture was partitioned between Et_2O and water and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in 60 mL MeOH and 293 mg *p*-toluenesulfonic acid monohydrate (1.54 mmol, 0.1 equiv) was added. When TLC analysis showed complete consumption of the starting material, the reaction mixture was neutralized by the addition of 1.07 mL Et_3N and the solvent was removed under vacuum. Flash column chromatography using EtOAc/PE (3/7 → 1/0) gave the title compound **8** (461 g, 12.31 mmol, 80% over 2 steps). R_f 0.20 (EtOAc/PE, 7/3, v/v); $[\alpha]_D^{22}$ +49 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3388, 2918, 1454, 1064, 737, 698; ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.39 – 7.22 (m, 10H, H_{arom}), 4.88 (d, *J* = 10.9 Hz, 1H, CH_2 benzyl),

4.74 (d, *J* = 1.3 Hz, 1H, H-1), 4.72 – 4.63 (m, 3H, CH_2 benzyl), 4.00 (dd, *J* = 3.0, 1.7 Hz, 1H, H-2), 3.94 (t, *J* = 9.5 Hz, 1H, H-4), 3.85 (dd, *J* = 9.3, 3.2 Hz, 1H, H-3), 3.82 (d, *J* = 1.5 Hz, 2H, H-6), 3.60 (dt, *J* = 9.7, 2.8 Hz, 1H, H-5), 3.28 (s, 3H, CH_3 OMe), 3.22 (s, 2H, OH); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 138.3, 137.8 (C_q), 128.3, 128.2, 127.7, 127.6, 127.5 (CH_{arom}), 100.2 (C-1), 79.7 (C-3), 75.0 (CH_2 benzyl), 73.7 (C-4), 71.8 (CH_2 benzyl), 71.4 (C-5), 68.2 (C-2), 61.5 (C-6), 54.7 (CH_3 OMe); HRMS $[M+Na]^+$ calcd for $C_{21}H_{26}O_6Na$ 397.16216, found 397.16153.

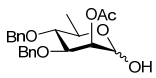


Methyl 2-*O*-acetyl-3,4-di-*O*-benzyl-6-deoxy-α-D-mannopyranoside (9): 2.99 g Diol **8** (7.97 mmol, 1 equiv) was dissolved in 40 mL toluene and argon was bubbled through the mixture for 15 minutes. To this solution 3.14 g Ph_3P (11.98 mmol, 1.5 equiv), 1.09 g imidazole (15.97 mmol, 2 equiv) and 2.84 g I_2 (11.18 mmol, 1.4 equiv) were added and the reaction was stirred at 70 °C for 90 minutes. The reaction was quenched by adding sat. aq. $Na_2S_2O_3$. The mixture was diluted with EtOAc and the organic phase was washed with sat. aq. $Na_2S_2O_3$, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The residue was coevaporated with toluene and dissolved in 40 mL DMSO. To this solution 1.81 g $NaBH_4$ (47.82 mmol, 6 equiv) was added and the reaction was stirred at 100 °C overnight. 20 mL Acetone was added and the reaction was stirred at 100 °C for another 15 min. The flask was allowed to cool to room temperature and the mixture was partitioned between water and EtOAc. The organic layer was washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The residue was filtered through a plug of silica gel using EtOAc/PE (1/3) as the eluent. After evaporation of the solvent, the crude mixture was dissolved in 30 mL pyridine and 10 mL acetic anhydride was added. The reaction was stirred overnight and quenched with MeOH. Removal of the solvents and coevaporation with toluene gave a crude mixture that was purified by flash column chromatography using EtOAc/toluene (1/19). This yielded the title compound **9** (2.00 g, 4.99 mmol, 63% over 3 steps) as the major product. Rf 0.65 (EtOAc/PE, 3/7, v/v); $[\alpha]_D^{22}$ +7 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2910, 1747, 1454, 1370, 1233, 1078, 698; ^{1}H NMR (300 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.46 – 7.06 (m, 10H, H_{arom}), 5.37 (dd, *J* = 3.4, 1.8 Hz, 1H, H-2), 4.91 (d, *J* = 10.9 Hz, 1H, CH_2 benzyl), 4.67 (d, *J* = 11.2 Hz, 1H, CH_2 benzyl), 4.62 – 4.58 (m, 2H, H-1, CH_2 benzyl), 4.49 (d, *J* = 11.2 Hz, 1H, CH_2 benzyl), 3.91 (dd, *J* = 9.3, 3.5 Hz, 1H, H-3), 3.80 – 3.65 (m, 1H, H-5), 3.43 (t, *J* = 9.4 Hz, 1H, H-4), 3.30 (s, 3H, CH_3 OMe), 2.11 (s, 3H, CH_3 Ac), 1.33 (d, *J* = 6.2 Hz, 3H, H-6); ^{13}C NMR (75 MHz, $CDCl_3$, HH-COSY, HSQC) δ 170.1 (C=O), 138.3, 137.9 (C_q), 128.2, 128.1, 127.8, 127.7, 127.5, 127.4 (CH_{arom}), 98.5 (C-1), 79.8 (C-4), 77.8 (C-3), 75.1 (CH_2 benzyl), 71.5 (CH_2 benzyl), 68.7 (C-2), 67.3 (C-5), 54.5 (CH_3 OMe), 20.8 (CH_3 Ac), 17.8 (C-6); HRMS $[M+Na]^+$ calcd for $C_{23}H_{28}O_6Na$ 423.17781, found 423.17768; Methyl 2,6-anhydro-3,4-di-*O*-benzyl-α-D-mannopyranoside **11** was isolated as a side product (509 mg, 1.43 mmol, 18%). Rf 0.40 (EtOAc/PE, 1/3, v/v); $[\alpha]_D^{22}$ +3 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2880, 1454, 1113, 737, 696; ^{1}H NMR (300 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.38 – 7.16 (m, 10H, H_{arom}), 5.04 (d, *J* = 2.7 Hz, 1H, H-1), 4.63 – 4.53 (m, 3H, CH_2 benzyl), 4.46 (d, *J* = 11.8 Hz, 1H, CH_2 benzyl), 4.09 – 4.03 (m, 2H, H-3, H-5), 3.99 – 3.89 (m, 2H, H-2, H-6), 3.70 (dd, *J* = 9.7, 0.7 Hz, 1H, H-6), 3.55 – 3.52 (m, 1H, H-4), 3.42 (s, 3H, CH_3 OMe); δ ^{13}C NMR (75 MHz, $CDCl_3$, HH-COSY, HSQC) δ 137.7, 137.7 (C_q), 128.1, 127.6, 127.5, 127.4 (CH_{arom}), 99.8 (C-1), 79.9 (C-4), 77.5 (C-3), 70.5, 69.9 (CH_2 benzyl), 68.3 (C-5), 67.8 (C-2), 65.8 (C-6), 55.2 (CH_3 OMe); HRMS $[M+Na]^+$ calcd for $C_{21}H_{24}O_5Na$ 379.15160, found 379.15176.

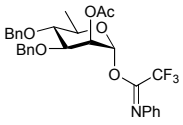


Methyl 3,4-di-*O*-benzyl-6-deoxy-α-D-mannopyranoside (3): A catalytic amount of NaOMe (54 mg, 1.00 mmol, 0.2 equiv) was added to a solution of 2.00 g mannopyranoside **9** (4.99 mmol, 1 equiv) and the solution was stirred overnight at room temperature. 286 µL AcOH (4.99 mmol, 1 equiv) was added and the solvent was removed *in vacuo*. The residue was partitioned between EtOAc and water and the organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated, yielding the title alcohol **3** as a colorless oil (1.70 g, 4.74 mmol, 95%). Rf 0.28 (EtOAc/PE, 3/7, v/v); $[\alpha]_D^{22}$ +44 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3462, 2908, 1454, 1056, 974, 735, 696; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.39 – 7.20 (m, 10H, H_{arom}), 4.87 (d, *J* = 11.0 Hz, 1H, CH_2 benzyl), 4.68 – 4.58 (m, 4H, H-1, CH_2 benzyl), 3.98 (d, *J* = 1.3 Hz, 1H, H-2), 3.80 (dd, *J* = 9.1, 3.2 Hz, 1H, H-3), 3.73 – 3.64 (m, 1H, H-5), 3.46 (t, *J* = 9.3 Hz, 1H, H-4), 3.28 (s, 3H, CH_3 OMe), 2.91 (s, 1H, OH), 1.31 (d, *J* = 6.3 Hz, 3H, H-6); ^{13}C NMR (100

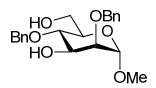
MHz, $CDCl_3$, HH-COSY, HSQC) δ 138.2, 137.7 (C_q), 128.2, 128.1, 127.6, 127.6, 127.6, 127.4 (CH_{arom}), 99.9 (C-1), 79.7 (C-3, C-4), 75.0 (CH_2 benzyl), 71.6 (CH_2 benzyl), 68.1 (C-2), 67.0 (C-55), 54.4 (CH_3 OMe), 17.7 (C-6); HRMS $[M+Na]^+$ calcd for $C_{21}H_{26}O_5Na$ 381.16725, found 381.16720.



2-*O*-Acetyl-3,4-di-*O*-benzyl-6-deoxy-D-mannopyranose (10): Methyl 3,4-di-*O*-benzyl-6-deoxy-α-D-mannopyranoside **3** (509 mg, 1.42 mmol, 1 equiv) was refluxed for 1 hour in 7 mL H_2O/TFA (5/2, v/v) and subsequently coevaporated with toluene. The crude product was stirred in 8 mL pyridine/Ac_2O (3/1, v/v) overnight. After quenching by the addition of MeOH, the mixture was evaporated and partitioned between EtOAc and water. The organic layer was washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. Next, the residue was dissolved in 8 mL THF/piperidine (7/1, v/v) and was stirred overnight. The reaction mixture was diluted by the addition of EtOAc and washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. Flash column chromatography using EtOAc/PE (1/4 → 2/3) gave the title compound **10** (474 mg, 1.23 mmol, 86% over 3 steps). R_f 0.24 (EtOAc/PE, 3/7, v/v); IR (neat, cm^{-1}) 3384, 2935, 1736, 1454, 1370, 1232, 1052, 736, 697; NMR data of the major anomer (α): ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 5.36 (s, 1H, H-2), 5.09 (s, 1H, H-1), 4.91 (d, *J* = 10.8 Hz, 1H, CH_2 benzyl), 4.69 (d, *J* = 11.3 Hz, 1H, CH_2 benzyl), 4.61 (d, *J* = 10.9 Hz, 1H, CH_2 benzyl), 4.53 (d, *J* = 11.2 Hz, 1H, CH_2 benzyl), 4.04 – 3.93 (m, 2H, H-3, H-5), 3.48 – 3.41 (m, 1H, H-4), 2.14 (s, 3H, CH_3 Ac), 1.30 (d, *J* = 6.2 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 170.5 (C=O Ac), 138.3, 137.9 (C_q), 128.3, 128.0, 127.9, 127.7, 127.6 (CH_{arom}), 92.3 (C-1), 78.8 (C-4), 77.4 (C-3), 75.3 (CH_2 benzyl), 71.7 (CH_2 benzyl), 69.4 (C-2), 67.7 (C-5), 21.1 (CH_3 Ac), 18.0 (C-6); HRMS $[M+Na]^+$ calcd for $C_{22}H_{26}O_6Na$ 409.16216, found 409.16195.

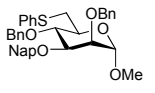


2-*O*-acetyl-3,4-di-*O*-benzyl-6-deoxy-D-mannopyranosyl *N*-phenyltrifluoroacetimidate (5): To a solution of 554 mg hemiacetal **10** (1.43 mmol, 1 equiv) in 8 mL acetone/H_2O (19/1, v/v) were added 513 mg Cs_2CO_3 (1.58 mmol, 1.1 equiv) and 434 µL $ClC(C=NPh)CF_3$ (2.87 mmol, 2.0 equiv). The mixture was stirred for 2 days at ambient temperature, evaporated slightly and filtered over celite. After evaporation the crude product was purified by flash column chromatography using EtOAc/toluene (0/1→3/97) with 1% triethylamine to give 469 mg (841 µmol, 59%) of the title imidate as a mixture of epimers. R_f 0.51 (EtOAc/PE, 1/9, v/v); IR (neat, cm^{-1}) 3032, 1748, 1718, 1598, 1490, 1453, 1370, 1334, 1208, 1162, 1112, 751, 694; NMR data of the major anomer (α): ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, T = 333 K) δ 7.63 – 6.60 (m, 15H, H_{arom}), 6.09 (s, 1H, H-1), 5.48 – 5.43 (m, 1H, H-2), 4.90 (d, *J* = 11.0 Hz, 1H, CH_2 benzyl), 4.70 (d, *J* = 11.2 Hz, 1H, CH_2 benzyl), 4.63 (d, *J* = 11.0 Hz, 1H, CH_2 benzyl), 4.57 (d, *J* = 11.2 Hz, 1H, CH_2 benzyl), 3.95 (dd, *J* = 9.3, 3.4 Hz, 1H, H-3), 3.92 – 3.84 (m, 1H, H-5), 3.50 (t, *J* = 9.4 Hz, 1H, H-4), 2.10 (s, 3H, CH_3 Ac), 1.34 (d, *J* = 6.2 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC, T = 333 K) δ 169.8 (C=O), 143.4, 138.4, 137.7 (C_q), 128.8, 128.4, 128.2, 128.0, 127.9, 127.7, 124.5, 119.5 (CH_{arom}), 94.7 (C-1), 79.4 (C-4), 77.5 (C-3), 75.4 (CH_2 benzyl), 72.3 (CH_2 benzyl), 70.7 (C-5), 67.9 (C-2), 20.7 (CH_3 Ac), 18.0 (C-6); HRMS $[M-(OC(N=Ph)CF_3)]^+$ calcd for $C_{22}H_{25}O_5$ 369.16965, found 369.16964.

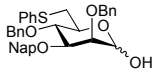


Methyl 2,4-di-*O*-benzyl-α-D-mannopyranoside (12): To a mixture of 996 mg methyl α-D-mannopyranoside (5.13 mmol, 1 equiv) in 25 mL DMF were added 1.22 g imidazole (17.95 mmol, 3.5 equiv) and 2.32 g TBSCl (15.39 mmol, 3 equiv). After 2 hours of stirring, TLC analysis showed complete consumption of the starting material. The reaction was quenched by the addition of 375 µL MeOH. The mixture was partitioned between H_2O and Et_2O and the aqueous layer was extracted. The combined organic phases were washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was coevaporated with toluene and subsequently dissolved in 25 mL of DMF. To this solution 1.84 mL BnBr (15.39 mmol, 3 equiv) and 616 mg NaH (60% in mineral oil, 15.39 mmol, 3 equiv) were added. After stirring at ambient temperature overnight, the reaction was quenched with 2.08 mL MeOH, taken up in Et_2O and washed with 5% aq. LiCl and brine. After drying over $MgSO_4$, filtration and concentration

under reduced pressure, the residue was dissolved in 5 mL THF and treated with 20.52 mL 1.0 M TBAF (in THF, 20.52 mmol, 4 equiv). The mixture was stirred for 2 hours and subsequently partitioned between EtOAc and H_2O. The water layer was further extracted with EtOAc and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography using EtOAc/PE (2/3 → 1/1) afforded the target compound **12** (1.16 g, 3.10 mmol, 60% over 3 steps). R_f 0.33 (EtOAc/PE, 1/1, v/v); $[\alpha]_D^{22}$ +20 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3446, 2906, 1454, 1028, 698; ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.38 – 7.22 (m, 10H, H_{arom}), 4.88 (d, *J* = 11.2 Hz, 1H, CH_2 Bn), 4.72 (d, *J* = 1.3 Hz, 1H, H-1), 4.69 (d, *J* = 11.8 Hz, 1H, CH_2 Bn), 4.64 (d, *J* = 11.2 Hz, 1H, CH_2 Bn), 4.58 (d, *J* = 11.8 Hz, 1H, CH_2 Bn), 4.02 – 3.93 (m, 1H, H-3), 3.84 (dd, *J* = 11.8, 2.5 Hz, 1H, H-6), 3.76 (dd, *J* = 11.8, 3.8 Hz, 1H, H-6), 3.73 – 3.63 (m, 2H, H-2, H-4), 3.60 – 3.54 (m, 1H, H-5), 3.29 (s, 3H, CH_3 OMe), 2.49 (d, *J* = 8.6 Hz, 1H, OH), 2.36 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ138.4, 137.7 (C_q Ph), 128.6, 128.5, 128.1, 128.0, 127.9, 127.8 (CH_{arom}), 98.3 (C-1), 78.4 (C-2), 76.4 (C-4), 74.9, 73.2 (CH_2 Bn), 71.7 (C-3), 71.3 (C-5), 62.2 (C-6), 54.9 (CH_3 OMe); HRMS $[M+Na]^+$ calcd for $C_{21}H_{26}O_6Na$ 397.16216, found 397.16050.

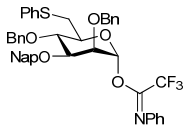


Methyl 2,4-di-*O*-benzyl-6-deoxy-3-(2-napthylmethyl)-6-thiophenyl-α-D-mannopyranoside (13): Argon was bubbled through a solution of 1.16 g methyl 2,4-di-*O*-benzyl-α-D-mannopyranoside (3.10 mmol, 1 equiv) in 20 mL toluene. Next, 1.22 g triphenylphosphine (4.65 mmol, 1.5 equiv), 422 mg imidazole (6.20 mmol, 2.0 equiv) and 1.10 g iodine (4.34 mmol, 1.4 equiv) were added and the mixture was stirred for 3 hours at 70 °C. The reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$ and the organic phase was diluted with EtOAc. Washing with H_2O and brine, drying ($MgSO_4$), filtration and evaporation afforded the crude product, which was dissolved in 15 mL of DMF. To this solution 1.10 mL DiPEA (6.20 mmol, 2 equiv) and 475 µL thiophenol (4.65 mmol, 1.5 equiv) were added. After stirring at ambient temperature for 1 hour, TLC-MS analysis showed complete consumption of the starting material and the emergence of the desired product. The reaction was diluted with Et_2O, washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was dissolved in 15 mL DMF and 1.37 g 2-(bromomethyl)naphthalene (6.20 mmol, 2 equiv) and 248 mg NaH (60% in mineral oil, 6.20 mmol, 2 equiv) were added. After stirring overnight, the mixture was partitioned between H_2O and Et_2O and the aqueous layer was extracted. The combined organic phases were washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography using EtOAc/PE (1/19 → 1/9) afforded the title compound **13** (1.46 g, 2.40 mmol, 77% over 3 steps). R_f 0.42 (EtOAc/PE, 1/6, v/v); $[\alpha]_D^{22}$ +6 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2908, 1454, 1064, 733; ^1H NMR (300 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 7.83 – 7.65 (m, 4H, H_{arom}), 7.50 – 7.02 (m, 18H, H_{arom}), 5.01 (d, *J* = 11.2 Hz, 1H, CH_2 Bn), 4.73 – 4.72 (m, *J* = 2.4 Hz, 5H, CH_2 Bn, CH_2 Nap, H-1), 4.64 (d, *J* = 11.2 Hz, 1H, CH_2 Bn), 3.97 – 3.69 (m, 4H, H-3, H-4, H-2, H-5), 3.48 – 3.40 (m, 1H, H-6), 3.27 (s, 3H, CH_3 OMe), 3.05 (dd, *J* = 13.4, 8.6 Hz, 1H, H-6); ^{13}C NMR (75 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 138.3, 138.1, 137.0, 135.8, 133.2, 132.8 (C_q Ph), 128.7, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 126.1, 126.0, 125.7, 125.6, 125.5 (CH_{arom}), 98.7 (C-1), 80.1 (C-3), 77.8 (C-4), 75.1 (CH_2 Bn), 74.51 (C-2), 72.6 (CH_2 Bn), 71.9 (CH_2 Nap), 71.0 (C-5), 54.6 (CH_3 OMe), 35.7 (C-6); HRMS $[M+Na]^+$ calcd for $C_{38}H_{38}O_5SNa$ 629.23322, found 629.23180.

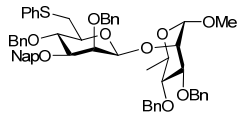


2,4-Di-*O*-benzyl-6-deoxy-3-(2-napthylmethyl)-6-thiophenyl-D-mannopyranose (14): A catalytic amount of concentrated sulphuric acid was added to a solution of 1.21 g methyl 2,4-di-*O*-benzyl-6-deoxy-3-(2-napthylmethyl)-6-thiophenyl-α-D-mannopyranoside **13** (1.99 mmol, 1 equiv) in 10 mL acetic anhydride at 0 °C. The reaction was quenched by the addition of triethylamine after 7 hours of stirring at 0 °C. The mixture was partitioned between H_2O and EtOAc and the organic layer was washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was dissolved in 10 mL THF and 590 µL piperidine (5.97 mmol, 3 equiv) was added. After stirring overnight, the mixture was partitioned between H_2O and EtOAc and the aqueous layer was washed with aq. 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography using

EtOAc/toluene (0/1 → 1/19) gave the title compound **14** (902 mg, 1.52 mmol, 77% over 2 steps). R_f 0.23 (EtOAc/PE, 1/4, v/v); IR (neat, cm^{-1}) 3403, 3060, 2926, 1454, 1069, 732; NMR data of the major anomer: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 7.81 – 7.65 (m, 4H, H_{arom}), 7.45 – 7.04 (m, 18H, H_{arom}), 5.19 (dd, *J* = 3.1, 1.7 Hz, 1H, H-1), 5.00 (d, *J* = 11.1 Hz, 1H, CH_2 Bn), 4.70 (s, 2H, CH_2 Nap), 4.66 (s, 2H, CH_2 Bn), 4.62 (d, *J* = 11.2 Hz, 1H, CH_2 Bn), 4.11 – 4.03 (m, 1H, H-5), 4.00 (dd, *J* = 9.2, 2.8 Hz, 1H, H-3), 3.89 (t, *J* = 9.3 Hz, 1H, H-4), 3.80 – 3.76 (m, 1H, H-2), 3.58 (d, *J* = 3.6 Hz, 1H, OH), 3.42 (dd, *J* = 13.5, 1.9 Hz, 1H, H-6), 3.04 (dd, *J* = 13.6, 8.5 Hz, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 138.5, 138.4, 137.1, 136.0, 133.4, 133.1 (C_q), 129.1, 129.0, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 126.5, 126.3, 126.0, 125.8 (CH_{arom}), 92.6 (C-1), 79.8 (C-3), 78.0 (C-4), 75.4 (CH_2 Bn), 75.1 (C-2), 72.8 (CH_2 Bn), 72.3 (C-1), 71.3 (C-5), 35.9 (C-6); HRMS $[M+Na]^+$ calcd for $C_{37}H_{36}O_5SNa$ 615.21757 found 615.21714.

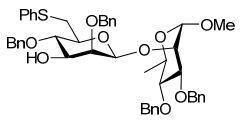


2,4-Di-*O*-benzyl-6-deoxy-3-(2-napthylmethyl)-6-thiophenyl-D-mannopyranosyl *N*-phenyltrifluoroacetimidate (4): To a solution of 902 mg hemiacetal **14** (1.52 mmol, 1 equiv) in 8 mL acetone/H_2O (19/1, v/v) were added 545 mg Cs_2CO_3 (1.67 mmol, 1.1 equiv) and 632 mg ClC(C=NPh)CF_3 (3.04 mmol, 2.0 equiv). The mixture was stirred overnight at ambient temperature, evaporated slightly and filtered over Celite. After evaporation the crude product was purified by flash column chromatography using EtOAc/PE (1/19→1/9) with 1% triethyamine to give 1.10 g (1.43 mmol, 94%) of the title imidate **4** as a mixture of epimers. R_f 0.65 (EtOAc/PE, 3/17, v/v); IR (neat, cm^{-1}) 3063, 1718, 1117, 694; NMR data of the major anomer : ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, T = 333K) δ 7.84 – 7.68 (m, 4H, H_{arom}), 7.50 – 6.99 (m, 21H, H_{arom}), 6.67 (d, *J* = 7.5 Hz, 2H, H_{arom}), 6.15 (s, 1H, H-1), 4.95 (d, *J* = 11.2 Hz, 1H, CH_2 Bn/Nap), 4.80 (d, *J* = 11.9 Hz, 1H, CH_2 Bn/Nap), 4.72 (d, *J* = 11.9 Hz, 1H, CH_2 Bn/Nap), 4.67 – 4.58 (m, 3H, CH_2 Bn/Nap), 4.03 – 3.90 (m, 3H, H-5, H-4, H-3), 3.82 (t, *J* = 2.3 Hz, 1H, H-2), 3.42 – 3.34 (m, 1H, H-6), 3.06 (dd, *J* = 13.7, 7.1 Hz, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC, T= 333K) δ 143.5, 138.3, 137.8, 136.8, 135.6, 133.4, 133.2 (C_q), 129.8, 129.3, 128.8, 128.7, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 126.7, 126.3, 126.2, 126.1, 126.0, 125.9, 124.3, 119.4 (CH_{arom}), 95.4 (C-1), 79.4 (C-3), 77.1 (C-4/C-5), 75.2 (CH_2 Bn/Nap) , 74.1 (C-4/C-5, C-2), 72.9 (CH_2 Bn/Nap), 36.4 (C-6); HRMS $[M-(OC(N=Ph)CF_3)]^+$ calcd for $C_{37}H_{35}O_4S$ 575.22506, found 575.22512.

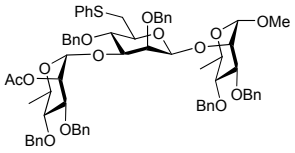


2,4-Di-*O*-benzyl-6-deoxy-3-(2-napthylmethyl)-6-thiophenyl-β-D-mannopyranosyl-(1→2)-(methyl 3,4-di-*O*-benzyl-6-deoxy-α-D-mannopyranoside) (15): Imidate donor 4 (367 mg, 481 µmol, 1 equiv) and 258 mg acceptor 3 (721 µmol, 1.5 equiv) were co-evaporated together with toluene. Freshly distilled DCM (7 mL) and 3Å activated molecular sieves were added and the mixture was stirred under argon for 30 min at room temperature. The mixture was cooled to -80 °C and 386 µL of a well-shaken 0.25 M solution of TfOH in DCM (0.2 equiv) was added. After stirring for 4 nights at -80 °C, 1 mL of Et_3N was added, the mixture was filtered over Celite and the solvent was removed under reduced pressure. The epimeric mixture could be separated by flash column chromatography using EtOAc/toluene (0/1 → 1/19) giving the title β-linked disaccharide 15 (341 mg, 366 µmol, 76%) R_f 0.30 (EtOAc/PE, 3/17, v/v); $[\alpha]_D^{22}$ -32 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3030, 2900, 1454, 1068, 732, 696; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.84 – 7.67 (m, 4H, H_{arom}), 7.58 – 7.05 (m, 28H, H_{arom}), 5.12 (d, *J* = 12.0 Hz, 1H, CH_2 Bn/Nap), 5.06 (d, *J* = 11.1 Hz, 1H, CH_2 Bn/Nap), 5.02 (d, *J* = 11.6 Hz, 1H, CH_2 Bn/Nap), 4.95 (d, *J* = 12.1 Hz, 1H, CH_2 Bn/Nap), 4.91 (d, *J* = 11.0 Hz, 1H, CH_2 Bn/Nap), 4.71 – 4.62 (m, 3H, H-1, CH_2 Bn/Nap), 4.56 – 4.50 (m, 4H, H-1', CH_2 Bn/Nap), 4.38 (dd, *J* = 3.1, 2.0 Hz, 1H, H-2), 4.04 (d, *J* = 3.0 Hz, 1H, H-2'), 3.93 (dd, *J* = 9.0, 3.3 Hz, 1H, H-3), 3.82 (t, *J* = 9.2 Hz, 1H, H-4'), 3.74 – 3.65 (m, 1H, H-5), 3.53 (dd, *J* = 9.2, 3.0 Hz, 1H, H-3'), 3.48 (t, *J* = 9.2 Hz, 1H, H-4), 3.45 – 3.39 (m, 2H, H-5', H-6'), 3.33 (s, 3H, CH_3 OMe), 2.93 (dd, *J* = 13.9, 9.6 Hz, 1H, H-6'), 1.28 (d, *J* = 6.2 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 139.0, 138.6, 138.5, 138.2, 137.0, 135.4, 133.1, 132.9 (C_q), 128.8, 128.6, 128.4, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 127.7, 127.6, 127.5, 127.4, 127.0, 126.2, 126.0, 125.8, 125.6, 125.4 (CH_{arom}), 99.3 (C-1'), 97.9 (C-1), 81.6 (C-3'), 79.7 (C-4), 77.7, 77.6 (C-3, C-4'), 75.2 (CH_2 Bn/Nap), 75.0 (C-5', CH_2 Bn/Nap), 73.8 (CH_2 Bn/Nap), 73.2 (C-2'), 71.8 (C-2), 70.8

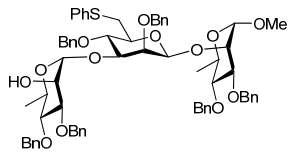
(CH_2 Bn/Nap), 69.9 (CH_2 Bn/Nap), 67.4 (C-5), 54.7 (CH_3 OMe), 35.4 (C-6'), 18.2 (C-6); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 99.3 ($J_{C1'\text{-}H1'}$ = 153.9 Hz, C-1'), 97.9 ($J_{C1\text{-}H1}$ = 166.1 Hz, C-1); HRMS $[M+Na]^+$ calcd for $C_{58}H_{60}O_9SNa$ 955.38503, found 955.38453.



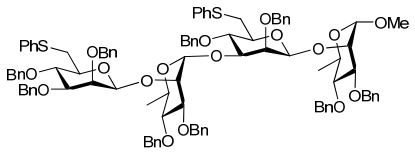
2,4-di-*O*-benzyl-6-deoxy-6-thiophenyl-β-D-mannopyranosyl-(1→2)-(methyl 3,4-di-*O*-benzyl-6-deoxy-α-D-mannopyranoside) (16): To a solution of 140 mg disaccharide **15** (150 µmol, 1 equiv) in 5 mL DCM was added 0.1 mL H_2O and 68 mg 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (300 µmol, 2 equiv). After 1 hour the reaction was quenched by the addition of sat. aq. $NaHCO_3$ and the layers were separated. The aqueous phase was extracted with DCM and the combined organic fractions were dried over $MgSO_4$, filtered and concentrated. Flash column chromatography using EtOAc/toluene (1/9 → 1/4) gave alcohol **16** (71 mg, 89 µmol, 60%). R_f 0.25 (EtOAc/PE, 3/7, v/v); $[\alpha]_D^{22}$ +38 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3526, 3030, 2902, 1454, 1067, 736, 697; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) 7.47 (dd, *J* = 7.6, 1.7 Hz, 2H, H_{arom}), 7.43 (dd, *J* = 6.6, 2.9 Hz, 2H, H_{arom}), 7.34 – 7.08 (m, 21H, H_{arom}), 5.20 (d, *J* = 11.2 Hz, 1H, CH_2 Bn), 5.02 – 4.96 (m, 2H, CH_2 Bn), 4.86 (d, *J* = 11.0 Hz, 1H, CH_2 Bn), 4.71 (d, *J* = 1.6 Hz, 1H, H-1), 4.68 (d, *J* = 11.2 Hz, 1H, CH_2 Bn), 4.63 (s, 1H, H-1'), 4.57 (d, *J* = 11.2 Hz, 1H, CH_2 Bn), 4.52 (d, *J* = 11.5 Hz, 1H, CH_2 Bn), 4.47 (d, *J* = 11.0 Hz, 1H, CH_2 Bn), 4.39 (dd, *J* = 3.2, 2.0 Hz, 1H, H-2), 3.92 (dd, *J* = 9.1, 3.4 Hz, 1H, H-3), 3.88 (d, *J* = 3.8 Hz, 1H, H-2'), 3.73 – 3.63 (m, 2H, H-5, H-3'), 3.48 – 3.36 (m, 4H, H-4, H-4', H-5', H-6'), 3.35 (s, 3H, CH_3 OMe), 2.90 (dd, *J* = 13.3, 8.3 Hz, 1H, H-6'), 2.62 (s, 1H, OH), 1.25 (d, *J* = 6.2 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 139.0, 138.4, 138.2, 138.1, 136.9 (C_q), 128.8, 128.7, 128.4, 128.2, 128.1, 128.0, 127.9, 127.7, 127.5, 127.1, 125.5 (CH_{arom}), 99.3 (C-1'), 97.9 (C-1), 79.7 (C-4, C-4'), 77.8 (C-3), 77.5 (C-2'), 75.1, 74.9, 74.8 (CH_2 Bn), 74.4 (C-5'), 74.1 (C-3'), 71.9 (C-2), 70.1 (CH_2 Bn), 67.4 (C-5), 54.8 (CH_3 OMe), 35.4 (C-6'), 18.2; ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 99.3 ($J_{C1'\text{-}H1'}$ = 154.3 Hz, C-1'), 97.9 ($J_{C1\text{-}H1}$ = 166.2 Hz, C-1); HRMS $[M+Na]^+$ calcd for $C_{47}H_{52}O_9SNa$ 815.32243, found 815.32190.



2-*O*-acetyl-3,4-di-*O*-benzyl-6-deoxy-α-D-mannopyranosyl-(1→3)-2,4-di-*O*-benzyl-6-deoxy-6-thiophenyl-β-D-mannopyranosyl-(1→2)-(methyl 3,4-di-*O*-benzyl-6-deoxy-α-D-mannopyranoside) (17): Imidate donor 5 (173 mg, 311 µmol, 1.7 equiv) and 142 mg acceptor 16 (179 µmol, 1 equiv) were co-evaporated together with toluene. Freshly distilled DCM (3 mL) and 3Å activated molecular sieves were added and the mixture was stirred under argon atmosphere for 30 min at room temperature. The mixture was cooled to 0 °C and 100 µL of a well-shaken 0.62 M solution of TfOH in DCM (0.35 equiv) was added. After stirring for 15 min at 0 °C, 250 µL Et_3N was added and the solvent was removed under reduced pressure. Flash column chromatography using EtOAc/toluene (1/19 → 3/17) gave the title trisaccharide 17 (175 mg, 151 µmol, 84%). R_f 0.50 (EtOAc/PE, 3/7, v/v); $[\alpha]_D^{22}$ -5 (c 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3032, 2908, 1743, 1454, 1233, 1070, 736, 697; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 7.51 – 7.09 (m, 35H, H_{arom}), 5.46 (apparent s, 1H, H-2''), 5.15 (d, *J* = 11.5 Hz, 1H, CH_2 Bn), 5.05 (app s, 1H, H-1''), 4.99 (d, *J* = 11.5 Hz, 1H, CH_2 Bn), 4.93 (d, *J* = 11.2 Hz, 1H, CH_2 Bn), 4.89 – 4.81 (m, 2H, CH_2 Bn), 4.75 – 4.69 (m, 2H, H-1, CH_2 Bn), 4.68 – 4.59 (m, 3H, H-1', CH_2 Bn), 4.56 – 4.45 (m, 4H, CH_2 Bn), 4.38 (app s, 1H, H-2), 3.98 – 3.86 (m, 3H, H-3'', H-3, H-2'), 3.81 – 3.74 (m, 2H, H-4', H-5''), 3.71 – 3.64 (m, 2H, H-5, H-3'), 3.45 – 3.33 (m, 6H, H-4'', H-4, H-5', CH_3 OMe), 3.30 (d, *J* = 13.5 Hz, 1H, H-6'), 2.82 (dd, *J* = 13.5, 9.4 Hz, 1H, H-6'), 2.08 (s, 3H, CH_3 Ac), 1.27 (t, *J* = 5.7 Hz, 6H, H-6'', H-6); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 170.1 (C=O Ac), 139.0, 138.7, 138.6, 137.9, 137.7, 136.8 (C_q), 128.8, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 127.1, 125.6 (CH_{arom}), 99.6 (C-1''), 99.2 (C-1'), 98.0 (C-1), 80.3 (C-3'), 79.9 (C-4), 79.7 (C-4''), 78.4 (C-4'), 77.8 (C-2', C-3''), 77.5 (C-3), 75.4, 75.1 (CH_2 Bn), 74.9 (C-5'), 74.4 (CH_2 Bn), 71.9 (CH_2 Bn), 71.7 (C-2), 70.0 (CH_2 Bn), 69.1 (C-2''), 68.4 (C-5''), 67.5 (C-5), 54.8 (CH_3 OMe), 35.3 (C-6'), 21.0 (CH_3 Ac), 18.1 (C-6, C-6''); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 99.6 ($J_{C1''\text{-}H1''}$ = 171.7 Hz, C-1''), 99.2 ($J_{C1'\text{-}H1'}$ = 154.5 Hz, C-1'), 98.0 ($J_{C1\text{-}H1}$ = 171.7 Hz, C-1); HRMS $[M+Na]^+$ calcd for $C_{69}H_{76}O_{14}SNa$ 1183.48480, found 1183.48542.

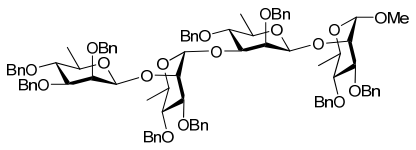


3,4-Di-*O*-benzyl-6-deoxy-α-D-mannopyranosyl-(1→3)-2,4-di-*O*-benzyl-6-deoxy-6-thiophenyl-β-D-mannopyranosyl-(1→2)-(methyl 3,4-di-*O*-benzyl-6-deoxy-α-D-mannopyranoside) (18): To a solution of 175 mg (151 µmol, 1 equiv) trisaccharide 17 in 3 mL MeOH was added 20 mg NaOMe (377 µmol, 2.5 equiv) and the mixture was stirred overnight at ambient temperature. The reaction was quenched with 43 µL acetic acid (755 µmol, 5 equiv) and the solvent was evaporated. The crude mixture was partitioned between EtOAc and H_2O. The organic phase was washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. Flash column chromatography using EtOAc/toluene (1/4 → 3/7) gave the title alcohol 18 (165 mg, 147 µmol, 98%). Rf 0.33 (EtOAc/PE, 2/3, v/v); $[\alpha]_D^{22}$ +27 (c 0.66, CH_2Cl_2); IR (neat, cm^{-1}) 2928, 1454, 1074, 697; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 7.53 – 7.06 (m, 35H, H_{arom}), 5.16 (d, *J* = 11.5 Hz, 1H, CH_2 benzyl), 5.11 (d, *J* = 1.6 Hz, 1H, H-1''), 5.00 (d, *J* = 11.5 Hz, 1H, CH_2 benzyl), 4.92 – 4.82 (m, 2H, CH_2 benzyl), 4.76 – 4.59 (m, 7H, H-1, H-1', CH_2 benzyl), 4.55 – 4.44 (m, 3H, CH_2 benzyl), 4.38 (dd, *J* = 3.0, 2.1 Hz, 1H, H-2), 4.03 – 3.97 (m, 1H, H-2''), 3.93 – 3.87 (m, 2H, H-3, H-3'), 3.85 (dd, *J* = 9.1, 3.2 Hz, 1H, H-3''), 3.82 – 3.72 (m, 2H, H-5'', H-4'), 3.72 – 3.63 (m, 2H, H-2', H-5), 3.49 – 3.28 (m, 7H, H-4'', H-4, H-5', CH_3 OMe, H-6'), 2.86 (dd, *J* = 13.4, 9.2 Hz, 1H, H-6'), 2.41 (d, *J* = 1.8 Hz, 1H, OH), 1.26 – 1.25 (d, *J* = 6.1 Hz, 6H, H-6, H-6''); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 139.1, 138.6, 138.5, 137.9, 137.7, 136.8 (C_q), 128.9, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.6, 127.5, 127.4, 127.0, 125.6 (CH_{arom}), 101.2 (C-1''), 99.3 (C-1'), 98.0 (C-1), 80.6 (C-2'), 79.9, 79.8, 79.7 (C-3'', C-4'', C-4), 78.4 (C-4'), 77.9 (C-3), 77.6 (C-3'), 75.4 (CH_2 benzyl), 75.1 (CH_2 benzyl), 75.0 (CH_2 benzyl), 74.8 (C-5'), 74.3 (CH_2 benzyl), 72.3 (CH_2 benzyl), 71.8 (C-2), 70.0 (CH_2 benzyl), 69.0 (C-2''), 68.0 (C-5''), 67.5 (C-5), 54.8 (CH_3 OMe), 35.3 (C-6'), 18.1 (C-6, C-6''); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 101.2 ($J_{C1''\text{-}H1''}$ = 170.2 Hz, C-1''), 99.3 ($J_{C1'\text{-}H1'}$ = 154.1 Hz, C-1'), 98.0 ($J_{C1\text{-}H1}$ = 166.7 Hz, C-1); HRMS $[M+Na]^+$ calcd for $C_{67}H_{74}O_{13}SNa$ 1141.47423, found 1141.47440.

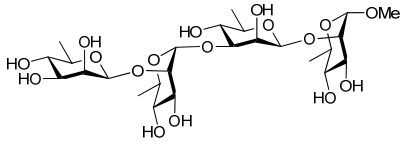


2,3,4-tri-*O*-benzyl-6-deoxy-6-thiophenyl-β-D-mannopyranosyl-(1→2)-3,4-di-*O*-benzyl-6-deoxy-α-D-mannopyranosyl-(1→3)-2,4-di-*O*-benzyl-6-deoxy-6-thiophenyl-β-D-mannopyranosyl-(1→2)-(methyl 3,4-di-*O*-benzyl-6-deoxy-α-D-mannopyranoside) (2): Imidate donor 6 (70 mg, 98 µmol, 1.5 equiv) and 73 mg acceptor 18 (65 µmol, 1.0 equiv) were co-evaporated together with toluene. Freshly distilled DCM (1 mL) and 3Å activated molecular sieves were added and the mixture was stirred under argon for 30 min at room temperature. The mixture was cooled to -60 °C and a solution of 13 µmol of TfOH in 0.1 mL DCM (0.2 equiv) was added. After stirring for 3 nights at -60 °C, 0.5 mL of Et_3N was added, the mixture was filtered over celite and the solvent was removed under reduced pressure. The epimeric mixture (α/β 1:3) could be separated by flash column chromatography using EtOAc/toluene (1/99 → 3/97) giving the title tetrasaccharide 2 (60 mg, 36 µmol, 55%). Rf 0.26 (EtOAc/toluene, 1/19, v/v); $[\alpha]_D^{22}$ -12 (c 0.6, CH_2Cl_2); IR (neat, cm^{-1}) 2932, 1454, 1364, 1074, 1028, 737, 697; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 7.77 – 6.79 (m, 55H, H_{arom}), 5.12 (d, *J* = 1.1 Hz, 1H, H-1''), 5.08 – 4.97 (m, 5H, CH_2 benzyl), 4.93 – 4.84 (m, 2H, CH_2 benzyl), 4.84 – 4.74 (m, 3H, CH_2 benzyl), 4.71 (d, *J* = 1.5 Hz, 1H, H-1), 4.60 (s, 1H, H-1'), 4.59 – 4.43 (m, 7H, CH_2 benzyl), 4.39 (dd, *J* = 3.0, 2.0 Hz, 1H, H-2), 4.36 – 4.32 (m, 1H, H-2''), 4.30 (d, *J* = 12.2 Hz, 1H, CH_2 benzyl), 3.95 (dd, *J* = 9.1, 3.2 Hz, 1H, H-3''), 3.91 (dd, *J* = 9.0, 3.4 Hz, 1H, H-3), 3.85 (d, *J* = 1.5 Hz, 1H, H-2'), 3.81 (s, 1H, H-1'''), 3.79 – 3.72 (m, 3H, H-4', H-3', H-2'''), 3.71 – 3.61 (m, 2H, H-5, H-5''), 3.56 (t, *J* = 9.2 Hz, 1H, H-4'''), 3.46 – 3.33 (m, 6H, H-4, H-4'', H-5', CH_3 OMe), 3.31 – 3.19 (m, 2H, H-6''', H-6'), 2.89 (dd, *J* = 9.1, 3.0 Hz, 1H, H-3'''), 2.84 – 2.64 (m, 3H, H-6', H-5''', H-6'''), 1.27 (d, *J* = 6.3 Hz, 3H, H-6), 1.22 (d, *J* = 6.1 Hz, 3H, H-6''); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 139.0, 138.8, 138.7, 138.6, 138.5, 138.3, 138.1, 137.9, 137.2, 136.6 (C_q), 128.8, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.5, 127.4, 127.2, 127.0, 126.0, 125.5, 125.2 (CH_{arom}), 99.4 (C-1'''), 99.2 (C-1'), 99.0 (C-1''), 97.9 (C-1), 81.0 (C-3'''), 79.7 (C-4), 79.6 (C-4''), 78.5, 78.4 (C-3', C-4'), 77.8 (C-3), 77.5 (C-3'', C-4''), 77.14 (C-2'), 75.1, 74.9 (CH_2 benzyl, C-5'), 74.8 (CH_2 benzyl), 74.6 (C-5'''), 74.4, 73.8 (CH_2 benzyl), 73.3 (C-2'''), 72.3 (C-2''), 71.6 (C-2), 70.6, 70.0 (CH_2 benzyl), 68.4 (C-5''), 67.5 (C-

5), 54.8 (CH_3 OMe), 34.9 (C-6'), 34.6 (C-6'''), 18.5 (C-6''), 18.2 (C-6); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 99.4 ($J_{C1'''\text{-}H1'''}$ = 155.0 Hz, C-1'''), 99.2 ($J_{C1'\text{-}H1'}$ = 154.6 Hz, C-1'), 99.0 ($J_{C1''\text{-}H1''}$ = 168.4 Hz, C-1''), 97.9 ($J_{C1\text{-}H1}$ = 165.8 Hz, C-1); HRMS $[M+Na]^+$ calcd for $C_{100}H_{106}O_{17}S_2Na$ 1666.67972, found 1666.68036.



2,3,4-tri-*O*-benzyl-6-deoxy-β-D-mannopyranosyl-(1→2)-3,4-di-*O*-benzyl-6-deoxy-α-D-mannopyranosyl-(1→3)-2,4-di-*O*-benzyl-6-deoxy-β-D-mannopyranosyl-(1→2)-(methyl 3,4-di-*O*-benzyl-6-deoxy-α-D-mannopyranoside) (19): To a solution of tetrasaccharide 2 (9.2 mg, 5.6 µmol) were added 300 mg Raney nickel 2800 (slurry in H_2O) and 3 mL of MeOH. The mixture was allowed to reflux under H_2 atmosphere overnight. Filtration over celite gave the crude product, which was purified by flash column chromatography using EtOAc/toluene (1/9) giving the title tetrarhamnoside 19 (7.7 mg, 5.4 µmol, 96%). R_f 0.30 (EtOAc/toluene, 1/9, v/v); $[\alpha]_D^{22}$ -58 (c 0.15, CH_2Cl_2); IR (neat, cm^{-1}) 2934, 1454, 1364, 1074, 735, 697; ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 7.50 – 7.02 (m, 45H, H_{arom}), 5.13 – 5.07 (m, 2H, H-1'', CH_2 benzyl), 5.00 (d, *J* = 12.1 Hz, 1H, CH_2 benzyl), 4.96 – 4.79 (m, 6H, CH_2 benzyl), 4.77 – 4.68 (m, 3H, H-1, CH_2 benzyl), 4.65 – 4.56 (m, 3H, H-1', CH_2 benzyl), 4.50 – 4.42 (m, 5H, CH_2 benzyl), 4.35 – 4.30 (m, 2H, H-2, CH_2 benzyl), 4.20 – 4.17 (m, 1H, H-2''), 4.02 (s, 1H, H-1'''), 3.92 (dd, *J* = 9.0, 3.2 Hz, 1H, H-3''), 3.90 – 3.84 (m, 2Hm H-2', H-3), 3.78 (d, *J* = 3.0 Hz, 1H, H-2'''), 3.76 – 3.59 (m, 4H, H-5'', H-3', H-5, H-4'), 3.53 – 3.38 (m, 3H, H-4''', H-4'', H-4), 3.38 – 3.29 (m, 4H, CH_3 OMe, H-5'), 3.05 (dd, *J* = 9.4, 3.1 Hz, 1H, H-3'''), 2.82 – 2.72 (m, 1H, H-5'''), 1.31 – 1.20 (m, 12H, H-6, H-6', H-6'', H-6'''); ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ 139.0, 138.9, 138.7, 138.5, 138.4, 138.3 (C_q), 128.5, 128.3, 128.2, 128.1, 127.9, 127.6, 127.5, 127.4, 127.3, 127.2, 126.2 (CH_{arom}), 99.8 (C-1'''), 99.3 (C-1'', C-1'), 98.2 (C-1), 81.2 (C-3'''), 80.5 (C-4'), 79.9, 79.8, 79.7 (C-4'', C-4, C-4'''), 79.4 (C-3'), 78.0, 77.9, 77.8 (C-3, C-2', C-3''), 75.1, 74.9, 74.8, 74.5, 74.3 (CH_2 benzyl), 73.8 (CH_2 benzyl, C-2'''), 73.3 (C-2'''), 72.0 (C-2, C-5'), 71.6 (C-5'''), 70.7, 70.6, 70.4 (CH_2 benzyl), 68.4 (C-5''), 67.6 (C-5), 54.7 (CH_3 OMe), 18.5, 18.1, 17.9, 17.8 (C-6, C-6', C-6'', C-6'''); ^{13}C-HMBC NMR (100 MHz, $CDCl_3$) δ 99.8 ($J_{C1'''\text{-}H1'''}$ = 152.1 Hz, C-1'''), 99.3 ($J_{C1''\text{-}H1''}$ = 167.3 Hz, C-1''), 99.3 ($J_{C1'\text{-}H1'}$ = 153.6 Hz, C-1'), 98.2 ($J_{C1\text{-}H1}$ = 165.3 Hz, C-1); HRMS $[M+Na]^+$ calcd for $C_{88}H_{98}O_{17}Na$ 1449.66962, found 1449.67083.



6-deoxy-β-D-mannopyranosyl-(1→2)-6-deoxy-α-D-mannopyranosyl-(1→3)-6-deoxy-β-D-mannopyranosyl-(1→2)-(methyl 6-deoxy-α-D-mannopyranoside) (1): A solution of 7.7 mg (5.4 µmol) tetramer 19 in 5 mL ^{t}BuOH/H_2O (7/3, v/v) was purged with argon for 15 minutes. Next half a teaspoon of palladium on activated charcoal was added and the mixture was stirred overnight under hydrogen atmosphere. Filtration over Celite and subsequent lyophilisation afforded 2.8 mg of the pure title compound 1 (4.6 µmol, 85%). ^{1}H NMR (600 MHz, D_2O, HH-COSY, HSQC, HMBC) δ 5.12 (d, *J* = 1.2 Hz, 1H, H-1''), 4.79 (d, *J* = 1.2 Hz, 1H, H-1), 4.72 (s, 1H, H-1'), 4.70 (s, 1H, H-1'''), 4.22 (dd, *J* = 3.2, 1.7 Hz, 1H, H-2''), 4.10 – 4.07 (m, 2H, H-2', H-2), 4.00 (d, *J* = 3.2 Hz, 1H, H-2'''), 3.87 – 3.83 (m, 2H, H-3'', H-5''), 3.71 (dd, *J* = 9.8, 3.4 Hz, 1H, H-3), 3.69 – 3.62 (m, 2H, H-5, H-3'), 3.59 – 3.56 (m, 1H, H-3'''), 3.50 – 3.36 (m, 9H, H-4', H-4'', H-4, H-5', CH_3 OMe, H-4''', H-5'''), 1.32 – 1.27 (m, 12H, H-6, H-6', H-6'', H-6'''); ^{13}C NMR (150 MHz, D_2O, HH-COSY, HSQC, HMBC) δ 101.1 (C-1''), 99.5 (C-1''', C-1), 99.2 (C-1'), 81.7 (C-3'), 78.3 (C-2''), 78.1 (C-2), 73.5 (C-3''', C-4, C-4''), 73.3 (C-5'''), 73.1 (C-5'), 72.9 (C-4'''), 72.2 (C-4'), 71.9 (C-2'''), 71.8 (C-2'), 70.6 (C-3), 70.5 (C-3''), 70.3 (C-5''), 69.6 (C-5), 55.8 (CH_3 OMe), 17.7, 17.6, 17.5 (C-6, C-6', C-6'', C-6'''); ^{13}C-HMBC NMR (150 MHz, D_2O) δ 101.1 ($J_{C1''\text{-}H1''}$ = 170.6 Hz, C-1''), 99.5 ($J_{C1'''\text{-}H1'''}$ = 159.8 Hz, C-1'''), 99.5 ($J_{C1\text{-}H1}$ = 170.6 Hz, C-1), 99.2 ($J_{C1'\text{-}H1'}$ = 160.0 Hz, C-1'); HRMS $[M+Na]^+$ calcd for $C_{25}H_{44}O_{17}Na$ 639.24707, found 639.24695.

References and notes

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7. Obviously, the anomeric configuration of these building blocks is irrelevant to the strategy.
8. When a catalytic amount of sulfuric acid in acetic anhydride was used for the conversion of the methyl glycoside in **3** to a lactol, the 4-*O*-benzyl group was cleaved as well.
9. See Chapter 5a for details.

Chapter 6

Summary and Future Prospects

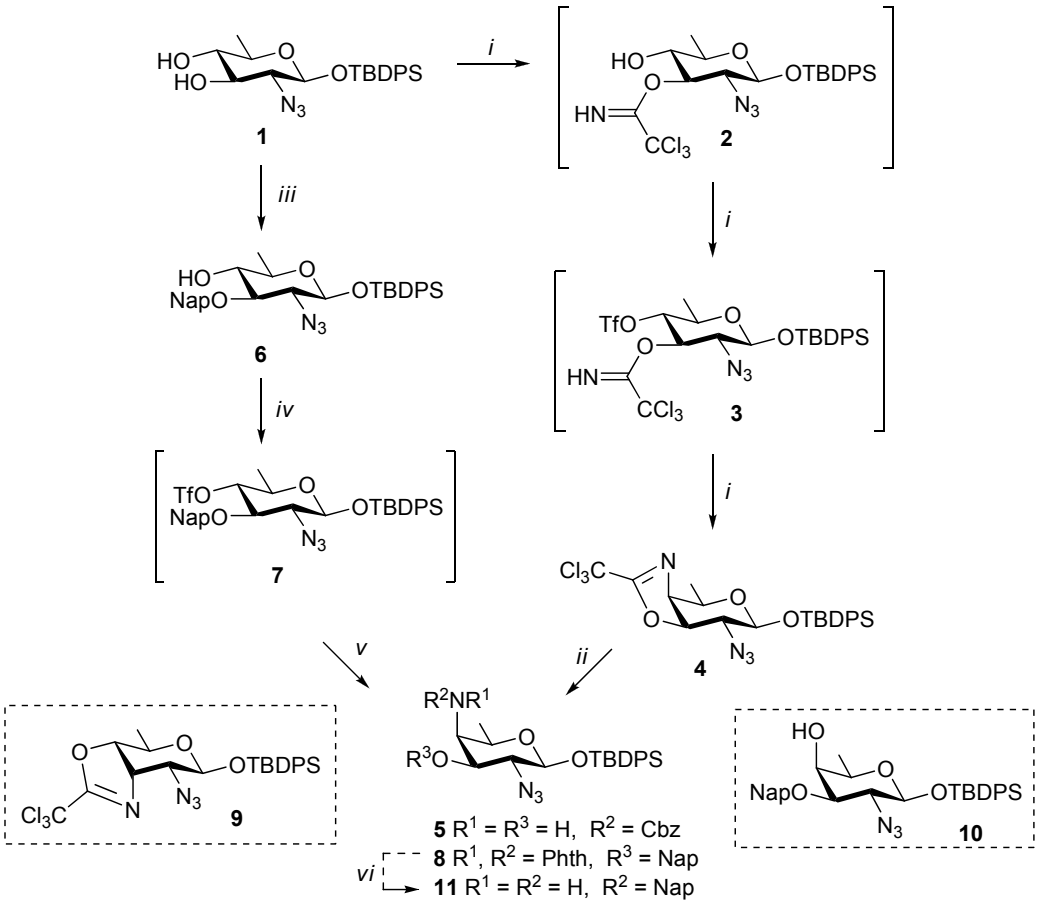
Outline and Perspectives

One of the most challenging aspects in synthetic carbohydrate chemistry is the stereoselective introduction of glycosidic linkages.[1] The introduction of 1,2-*trans* bonds is considered a straightforward matter. Equipping a glycosyl donor with an acyl functionality on the C-2 position leads to the formation of a transient acyloxonium ion upon activation. This directs the glycosylation event towards the 1,2-*trans* product. The synthesis of 1,2-*cis* configured bonds is more difficult and to this end various methods have been brought forward. By means of selected examples, recently introduced strategies for the stereoselective introduction of glycosidic bonds are described in **Chapter 1**.

In **Chapter 2** a synthesis of an orthogonally protected 2-acetamido-4-amino-2,4,6-trideoxy-D-galactose (AAT) building block is outlined. The unprotected progenitor hereof cannot be isolated from natural sources. The developed route of synthesis starts from D-glucosamine. Key features of the route are the regioselective installment of a C-3-*O*-imidate functionality, which is followed by the introduction of a C-4-triflate and subsequent oxazoline formation (**1**→**4** in Scheme 1). Even though treatment of diol **1** with trichloroacetonitrile at low temperature in the presence of DBU leads to the preferential formation of C-3-*O*-imidate **2**, the di-imidate and the C-4-*O*-imidate are also formed. The latter imidate, undergoing a

similar conversion as its C-3 counterpart **1**, eventually leads to the formation of the *allo*-configured sideproduct **9**. Due to structural similarities, the separation of oxazolines **4** and **9** by column chromatography is laborious and mixed fractions were occasionally encountered.

Scheme 1



Reagents and conditions: (i) Cl_3CCN, DBU, DCM, -13°C then Tf_2O, pyridine then DiPEA (**4**: 63%, **9**: 24%); *(ii)* (1) AcOH, H_2O, EtOAc; (2) *N*-(benzyloxycarbonyloxy)succinimide, triethylamine, DCM (**5**: 75%); (*iii*) (1) Bu_2SnO, toluene, reflux for 2 hours; (2) 2-(Bromomethyl)naphthalene, TBAI, toluene (57%); (iv) Tf_2O, pyridine, DCM; (v) potassium phthalimide, DMF (**8**: 48%, **10**: 26%); (*vi*) $H_2NCH_2CH_2NH_2$, BuOH.

With the aim to develop more straightforward procedures for this part of the route towards an AAT building block, a different approach inspired by a route developed by Pedersen *et al.*[2] was attempted (Scheme 1). Diol **1** was converted to C-3-*O*-methylnaphthyl ether **6** *via* an intermediate stannyl ether. Straightforward column chromatography allowed the procurement of pure regioisomer **6** in 57%. Conversion of the remaining alcohol to triflate **7** and subsequent nucleophilic displacement by a phthalimide furnished galactoside **8**

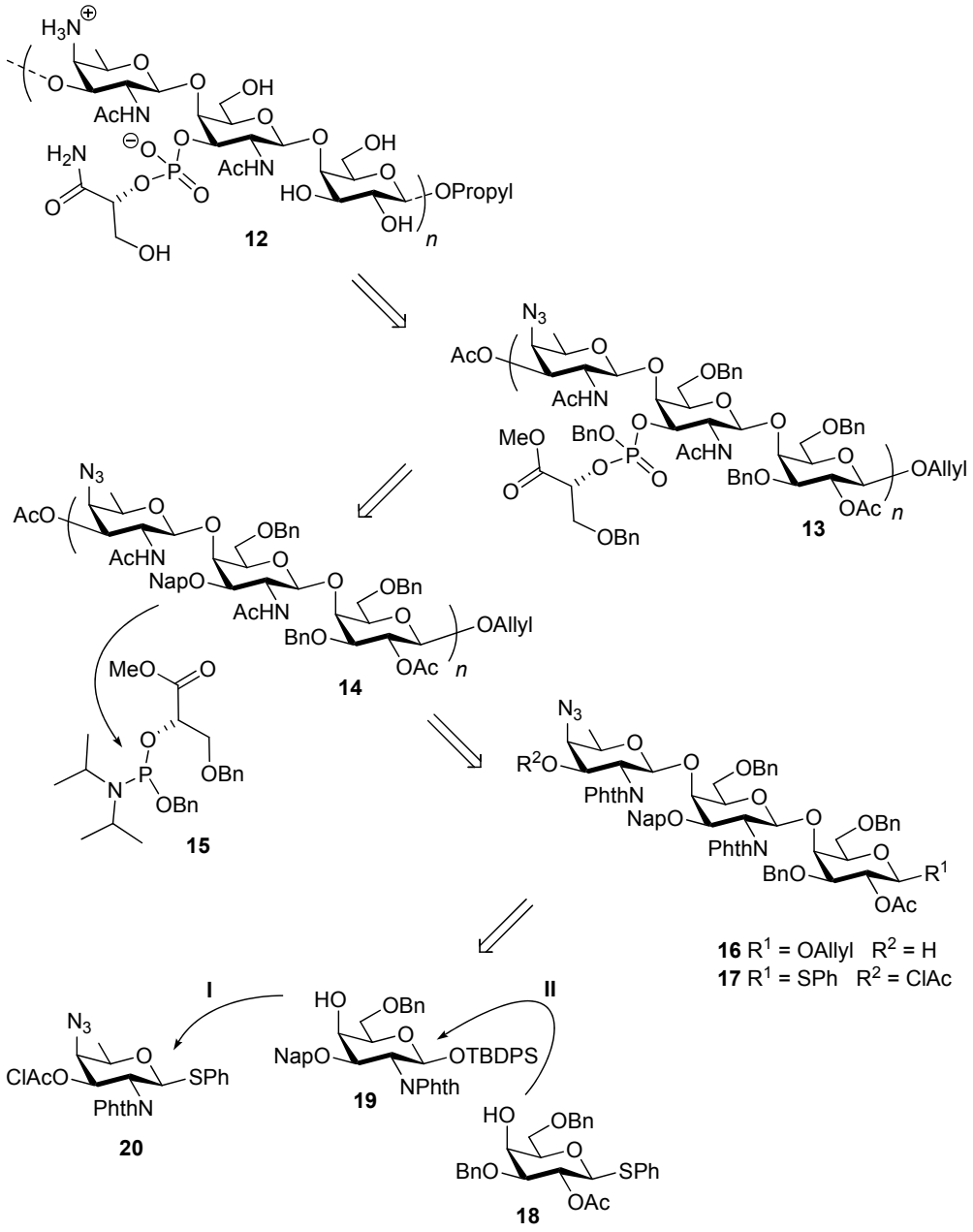
in 48% yield. Although this alternative route is lower-yielding than the initial sequence, it does provide an appropriately configured building block in a practically straightforward manner. Furthermore, sideproduct **10**, resulting from substitution of triflate **7** by water, was obtained in 26%. This indicates that there is ample room for improvement of the efficiency. After deprotection of the phthalimide, the resulting amine **11** can be functionalized as pleased.

Recently, AAT was identified as a constituent of a polysaccharide found in the human opportunistic pathogen *Providencia alcalifaciens*.[3] Deseases that are associated with *Providencia* strains include urinary tract infections and enteric diseases such as travelers' diarrhea. The repeating unit structure of the polysaccharide is depicted in Scheme 2 (compound **12**) and consists of a trisaccharide branched with a d-glyceramide (GroAN) 2-phosphatyl group: [→4)-(d-GroAN-2-P-3-)-β-d-GalNAc-(1→4)-β-D-Gal-(1→3)-β-d-FucNAc4N-(1→].

All three glycosidic linkages are of the 1,2-*trans* type and can thus be introduced by means of a participating C-2 acyl functionality. Retrosynthetic analysis shows that the fully deprotected target structure **12** can be accessed from protected oligosaccharide **13** by hydrogenation and conversion of the methylester to an amide with concomitant deacetylation (Scheme 2). Oligosaccharide **13** can be obtained by deprotection of the 2-naphtylmethyl ethers in **14**, coupling of the resulting alcohols with phosphoramidite **15** and ensuing oxidation of the intermediate phosphite triester. Oligosaccharide **14** can be obtained by the repetitive extension of acceptor **16** with donor **17** followed by dechloroacetylation of the growing chain. Trisaccharide **16** can in turn be accessed by glycosylation of trisaccharide **17** with allyl alcohol and subsequent dechloroacetylation. Trisaccharide **17** can be synthesized by the union of AAT imidate donor **20** and protected galactoside **19**, two step conversion of the anomeric TBDPS group to an *N*-phenyltrifluoroacetimidoyl group and an acid catalyzed coupling of the resulting disaccharide donor with alcohol **18**. Imidate donor **20** is accessible by chloroacetylation of its known C3-OH analogue.[4]

Chapter 3 describes a modular approach towards the synthesis of all possible trimer repeating units of the type 1 capsular polysaccharide of *Streptococcus pneumonia*, Sp1. The trisaccharide repeats are composed of two galacturonic acid monomers and an AAT residue. All monomeric constituents are linked through *cis*-glycosidic bonds. The difficulty associated with the efficient stereoselective introduction of the α-galacturonic acid bonds was overcome by employing galacturonic acid-[3,6]-lactone building blocks. These synthons performed well when used as donor galactosides and also showed to be reactive acceptor glycosides, when equipped with a free hydroxyl function. All three frame-shifted trimer repeats were constructed *via* highly stereoselective glycosylation reactions, with one exception. The epimeric mixture of trisaccharides, formed in the non-selective glycosylation event, could be readily separated after global deprotection using High Performance Anion Exchange Chromatography (HPAEC).

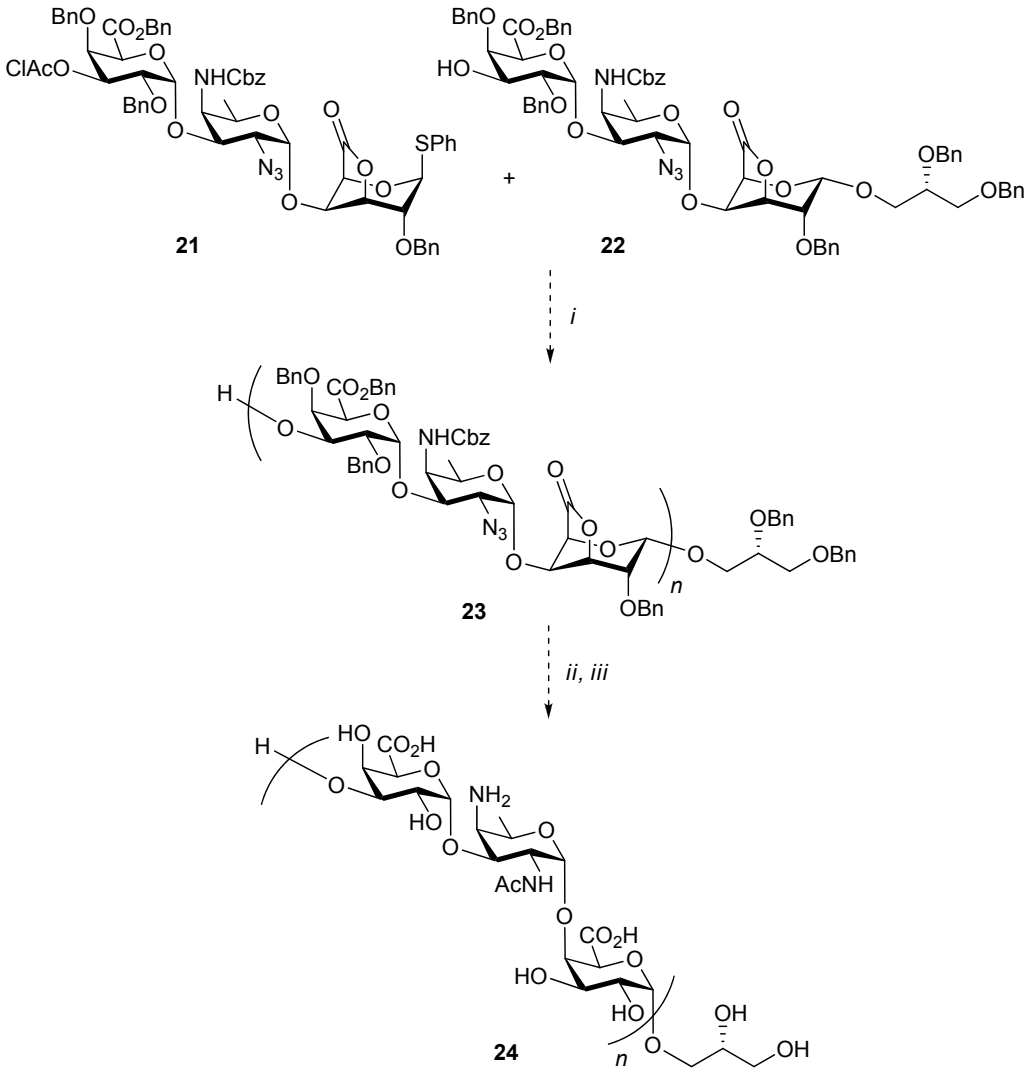
Scheme 2



Retrosynthetic analysis of a trisaccharide from *Providencia alcalifaciens*.

Now that efficient routes toward trisaccharide donor **21** and trisaccharide acceptor **22** have been developed, the synthesis of longer fragments lies within reach (Scheme 3).

Scheme 3



Reagents and conditions: (*i*) n times: (1) **21**, Ph_2SO, Tf_2O, DCM, TTBP, -60°C then acceptor **22**; (2) thiourea, EtOH, pyridine, 65°C; (*ii*) AcSH/pyridine (1/1 v/v); (*iii*) TMSONa, DCM, then H_2/Pd(C), *t*BuOH, H_2O, HCl.

Successive block couplings of trisaccharide thioglycoside donor **21** onto acceptor **22**, followed by dechloroacetylation of the resulting oligosaccharide can give protected oligomers **23**. In view of the varying results obtained with similar glycosylations, as shown in Chapter 3, it is well conceivable that this 1,2-*cis* block coupling strategy will need substantial optimization. Data obtained in Chapter 4, however, suggests that favoring the formation of an intermediate anomeric β-triflate is beneficial for the creation of a 1,2-*cis* linkage. All attempts to steer the selectivity might provide valuable clues that lead to a deeper

mechanistic understanding. Besides exerting the glycosylation at various temperatures, different promoter systems like *para*-nitrophenylsulfenyl triflate (*p*-NO_2PhSOTf),[5] *N*-phenylthio-ε-caprolactam-TMSOTf[6] (or its tolyl derivative)[7] or dimethyl(methylthio)sulfonium triflate (DMTST)[8] can be used. Judging from the insights gained in Chapter 4, it is advisable to use these promotors in a pre-activation glycosylation protocol. The addition of more triflic acid (and a hindered base, such as TTBP) might also promote the formation of an anomeric β-triflate. Furthermore, altering the nucleophilicity of acceptor **22** through the formation of a stannyl ether might influence the stereochemical outcome of the glycosylation. Next, oligosaccharide **23** can be converted to the fully deprotected oligosaccharide **24**. A treatment with thiolacetic acid and pyridine can convert the azides to acetamides. The lactone bridges can be opened with TMSONa. Finally, hydrogenolysis of the remaining benzyl ester, benzyloxy carbamate and benzyl groups can provide the fully deprotected target oligosaccharide.

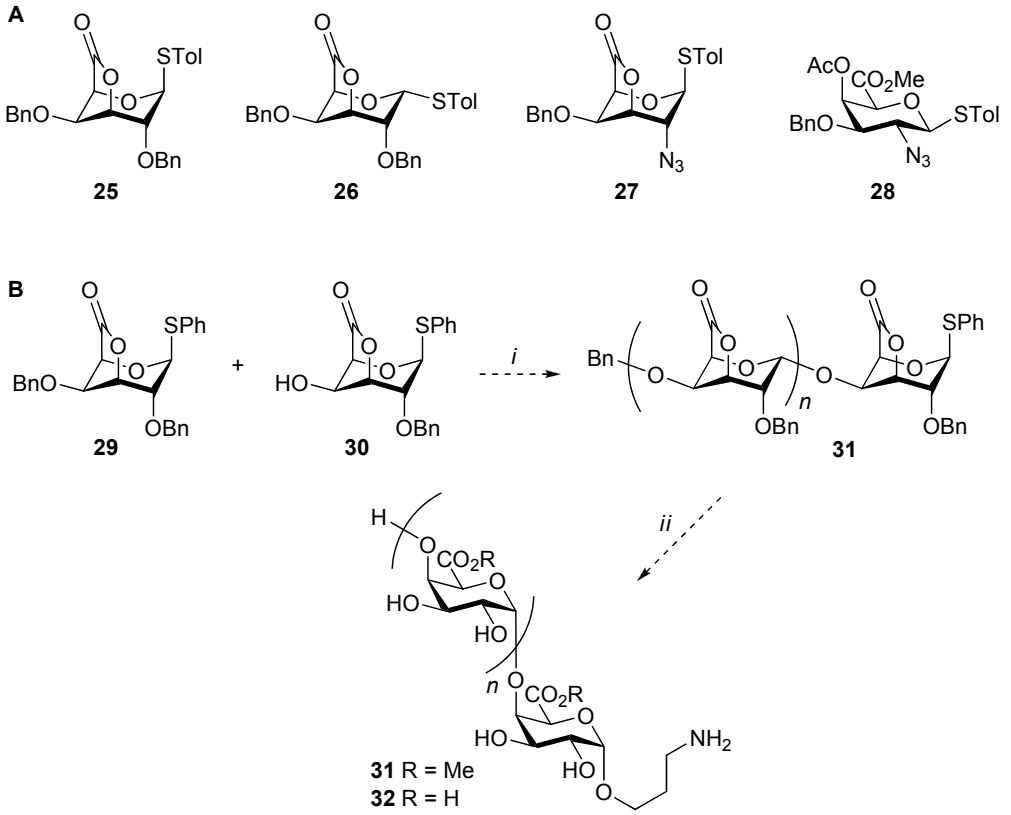
Chapter 4 describes a study of the reactivity and stereoselectivity of a galacturonic acid-3,6-lactone thioglycosyl donor in comparison with protected galacturonic acid and galactose donors using a series of competition experiments and condensation reactions with different thiophilic activator systems. It was revealed that the relative reactivity of different thioglycosides depends on the activator system used and that *p*-nitrophenylsulfenyl triflate shows, in an in situ protocol, overall attenuated reactivity differences with respect to the commonly used *N*-iodosuccinimide-triflic acid promoter system. With respect to the stereoselectivity of the studied galacturonic acid-3,6-lactone thioglycosyl donor, it was revealed that a pre-activation based glycosylation system gives rise to an α-selective glycosylation process, whereas an *in-situ* activation protocol leads to the formation of the β-product with good selectivity. It was hypothesized that these opposing stereoselectivities are the result of different product-forming intermediates. Where pre-activation of the donor leads to the formation of an intermediate β-triflate, which is substituted in a concerted fashion to provide the α-product, an $^3H_4$ oxocarbenium ion like species is substituted in the *in situ* activation experiment to provide the β-linked product.

It has thus been established in Chapter 4 that the relative reactivity of different thioglycosides depends on the type of activator system. A more direct relationship between the galacturonic acid-3,6-lactone thioglycosyl donor reactivity and the used promoter requires more data. This can be attained by running more competition experiments using different promoter systems, such as: IDCP,[9] *para*-nitrophenylsulfenyl triflate (*p*-NO_2PhSOTf),[5] *N*-phenylthio-ε-caprolactam-TMSOTf[6] (or its tolyl derivative)[7] or dimethyl(methylthio)sulfonium triflate (DMTST).[8]

To gain more insight in the reactivity of different glycosyl donors more building blocks can be incorporated in the investigated series. Three examples (**26**-**28**) are provided in Scheme 4A. Thioglycosyl donor **26** is the α-thioglycosyl counterpart of the studied galacturonic acid-3,6-lactone β-thioglycosyl donor **25**. Most of the donors described in Chapter 4 reside in the $^1C_4$ conformation and bear an equatorially oriented aglycon. Although expulsion of the aglycon upon activation of the donor is expected to occur more rapidly in

the case of donor **25** due to a better orbital overlap of the O5 lone pairs with the $\sigma^*_{C1\text{-}S}$, the equatorially oriented aglycon in **26** should be more prone to react with the promoter, owing to its increased accessibility. This reactivity difference can be assessed by indirect reactivity comparison using two separate competition experiments with a competing donor, such as **28**, since both galacturonic acid-3,6-lactone thioglycosyl donors **25** and **26** will give the same dimer upon reaction with an identical acceptor.

Scheme 4



Reagents and conditions: (*i*) n times: **29**, *p*-NO_2PhSOTf, -60°C then acceptor **30**; (*ii*) (1) TMSONa, DCM or MeOH, *p*-TsOH then H_2/Pd(C), *t*BuOH, H_2O, HCl.

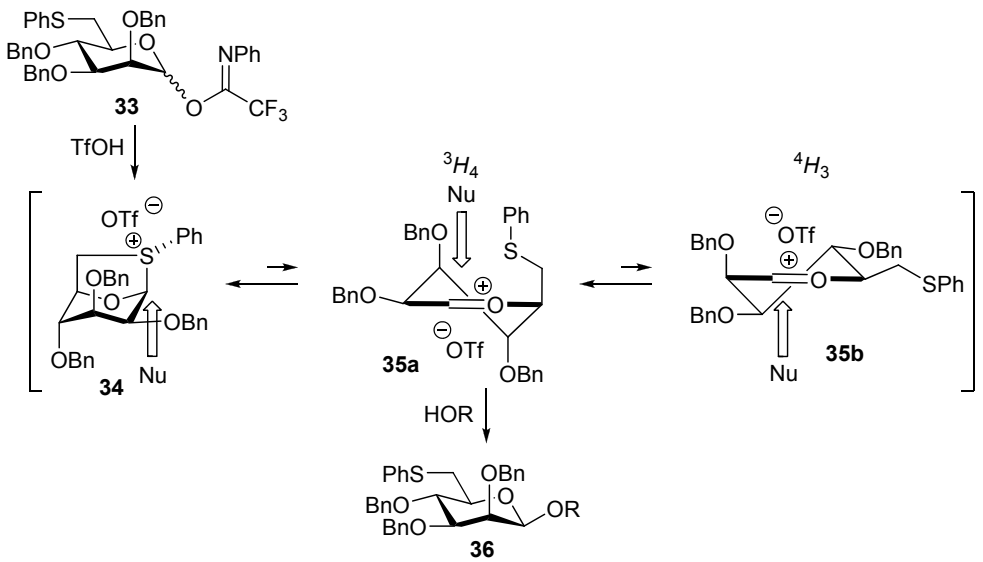
The effect of an azide functionality at the C2 position of galacturonic acid lactone **27** and galacturonic acid ester **28** is of interest as well, in particular since 2-acetamido-2-deoxy-galacturonic acid residues are found in several natural polysaccharides.[10]

Considerable experience has been gained concerning the glycosylations with donors **25** and **29**, the construction of pectin fragments **31**/**32** can be attempted (Scheme 4B). In a preliminary experiment donor **29** and acceptor **30** were coupled using Ph_2SO/Tf_2O as a promoter system. This led to the procurement of dimeric lactone **31** (n=1), albeit in low yield.

Furthermore a large excess of donor **29** had to be used to obtain this result. Usage of *para*-nitrophenylsulfenyl triflate (*p*-NO_2PhSOTf) as activator employing a pre-activation based protocol can provide a means to increase the efficiency of this glycosylation. A repetition of this coupling can give larger structures. The reason why this proposal elongates the chain from the reducing to the non-reducing end stems from the observation that the spacer-capped α-linked galacturonic acid lactone acceptors are intrinsically labile. Coupling of oligosaccharide **31** onto a suitable spacer, azidopropanol for example, hydrolysis or methanolysis of the lactone bridges followed by catalytic hydrogenation provides the target pectin oligosaccharides **31**/**32**.

Chapter 5a describes the application of a panel of C-6 thioether mannosyl donors, a C-6-selenoether donor and a C-6-iodide *N*-phenyltrifluoroacetimidate mannosyl donor in a series of condensation reactions. While all of these donors preferentially provided 1,2-*cis* linked disaccharides, a 2,3,4-tri-*O*-benzyl-6-deoxy-6-*S*-phenyl-6-thio-D-mannopyranosyl donor **33** showed the best potential as a 1,2-*cis*-mannosylating agent (Scheme 5). Variable temperature NMR experiments showed the formation of bridged sulfonium ion **34** upon activation of donor **33**. The stereoselectivity in the *cis*-mannosylation reaction can be rationalized with a Curtin-Hammett kinetic scenario in which the quasi-stable bicyclic $^{1}C_4$-sulfonium ion intermediate **34** is in equilibrium with the more reactive and β-selective mannosyl $^{3}H_4$-oxocarbenium ion and its α-selective $^{3}H_4$-conformer **35b**. Oxocarbenium ion **35a** places all ring-substituents in an electronically favorable position.

Scheme 5

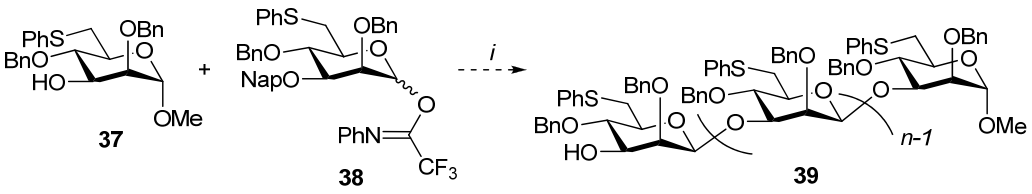


Mechanistic rationale for the formation of 1,2-*cis* mannosidic linkages from a C-6 thioether mannosyl donor.

The applicability of the 1,2-*cis*-mannosylating agent described above is the subject of **Chapter 5b**. Upon condensation of 6-thio-6-deoxy-mannosyl donors reductive removal of the 6-thio functionality provides 1,2-*cis* rhamnosides. Following this methodology a backbone tetrasaccharide containing alternating α- and β-D-rhamnosides was synthesized.

During the assembly of the tetrameric backbone, it was observed that the second glycosylation towards β-linked products proceeded less selective than the first one (completely β-selective versus a 1/3 α/β ratio). To investigate the influence of an elongating C-6 thiophenyl ether acceptor on the stereoselectivity of the glycosylations, the modular synthesis depicted in Scheme 6 is proposed.

Scheme 6



Reagents and conditions: (*i*) n times: (1) **38** and elongating **37**, cat. TfOH, DCM, -80°C; (2) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DCM, H_2O.

In conclusion, the development and application of different methods for the construction of 1,2-cis glycosidic bonds has been described in this thesis.

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Samenvatting

Een van de uitdagingen in de synthetische koolhydraatchemie is de stereoselectieve introductie van glycosidische bindingen. De voorwaarden voor de invoering van 1,2-*trans* bindingen zijn inmiddels vastgesteld. Door het uitrusten van een glycosyldonor met een acyl-functionaliteit op de C-2 positie wordt bij activering van de donor een instabiel acyloxonium ion intermediair gevormd, die de glycosylering naar het 1,2-*trans* product stuurt. De synthese van 1,2-*cis* geconfigureerde bindingen is echter gecompliceerder en blijft het onderwerp van onderzoek. **Hoofdstuk 1** behandelt geselecteerde voorbeelden van recentelijk geïntroduceerde strategieën voor de stereoselectieve introductie van glycosidische bindingen.

In de celwand van bacteriën komt een grote verscheidenheid van bijzondere monosacchariden voor. Omdat deze monosacchariden niet in voor onderzoek bruikbare hoeveelheden uit de natuur te isoleren zijn, wordt er veel aandacht besteed aan de synthese van deze zeldzame monosacchariden. In **hoofdstuk 2** wordt een synthese van een orthogonaal beschermd 2-acetamido-4-amino-2,4,6-tridesoxy-D-galactose (AAT) bouwsteen beschreven, uitgaande van D-glucosamine. De belangrijkste kenmerken van deze synthese zijn de regioselectieve installatie van een C-3-*O*-imidaat functionaliteit, welke wordt gevolgd door de introductie van een C-4-triflaat en de daaropvolgende vorming van een oxazoline.

Hoofdstuk 3 beschrijft een modulaire aanpak van de synthese van alle mogelijke repeterende trisacchariden van het type 1 capsulaire polysaccharide van *Streptococcus pneumonia*, Sp1. De repeterende trisacchariden, die bestaan uit twee galacturonzuur residuen en een AAT residu, zijn verbonden door middel van *cis*-glycosidische bindingen. Een efficiënte stereoselectieve introductie van de α-galacturonzuur bindingen werd bewerkstelligd door gebruik te maken van beschermde galacturonzuur-[3,6]-lacton bouwstenen. In de onderzochte glycosyleringsreacties bleken deze lactonen niet alleen efficiënte donor galactosiden te zijn, maar konden zij ook worden toegepast als reactieve acceptor glycosiden wanneer deze voorzien waren van een vrije hydroxyl-functie. Twee trimeren konden worden bereid via stereoselectieve glycosyleringsreacties, terwijl de laatste

koppeling van het derde trimeer resulteerde in een anomeer mengsel. Het gewenste zuivere trisaccharide kon worden verkregen omdat het epimere mengsel na globale ontscherming gemakkelijk kon worden gescheiden door middel van anionenuitwisselingschromatografie.

Hoofdstuk 4 beschrijft een studie naar de reactiviteit en stereoselectiviteit van een galacturonzuur-[3,6]-lacton thioglycosyl donor middels een reeks van competitie experimenten met galacturonzuur en galactose donoren en (conceptueel) verschillende thiofiele activatorsystemen. Uit de competitie experimenten bleek dat de relatieve reactiviteit van verschillende thioglycosides afhankelijk is van het gebruikte activatorsysteem, waarbij *para*-nitrophenylsulfenyltriflaat over het algemeen kleinere reactiviteitsverschillen liet zien vergeleken met het veel gebruikte *N*-joodsuccinimide-triflaatzuur systeem. Uit het onderzoek naar de stereoselectiviteit van de bestudeerde galacturonzuur-3,6-lacton thioglycosyl donor kwam naar voren dat een op pre-activatie gebaseerde glycosyleringsprocedure leidt tot een α-selectief glycosyleringsproces, terwijl een *in situ*-activeringsprotocol leidt tot de vorming van het β-product. Deze tegengestelde stereoselectiviteiten kunnen verklaard worden met behulp van verschillende product-vormende intermediairen. Waar pre-activatie van de donor leidt tot de vorming van een intermediair β-triflaat, dat met inversie wordt gesubstitueerd om het α-product te geven, wordt een $^{3}H_{4}$ oxocarbenium ion-achtig deeltje in het *in situ*-activeringsexperiment zodanig gesubstitueerd dat het β-gekoppelde product wordt gevormd.

Hoofdstuk 5a beschrijft de evaluatie van een aantal mannosyl N-phenyltrifluoroacetimidaat donoren, voorzien van verschillende C-6 thioethers, een C-6-selenoether en een C-6-jodid, in een reeks condensatiereacties. Hoewel alle donoren hoofdzakelijk 1,2-*cis* gekoppelde disacchariden opleverden, was een 2,3,4-tri-*O*-benzyl-6-desoxy-6-*S*-fenyl-6-thio-D-mannopyranosyl het meeste veelbelovende 1,2-*cis*-mannosylerend agens. Variabele temperatuur NMR experimenten toonden, direct na activatie van deze C-6 thiofenyl mannopyranosyl donor, de vorming van een gebrugd sulfonium ion aan. De stereoselectiviteit in de *cis*-mannosyleringsreactie kan worden gerationaliseerd middels een Curtin-Hammett kinetisch scenario, waarin het quasi-stabiele bicyclische $^{1}C_{4}$-sulfonium ion intermediair in evenwicht is met het reactievere en β-selectieve mannosyl $^{3}H_{4}$-oxocarbenium ion, die alle ring substituenten in een elektronisch gunstige positie plaatst. De toepasbaarheid van het hierboven beschreven 1,2-cis-mannosylerend agens is het onderwerp van **hoofdstuk 5b**. Na condensatie van 6-thio-6-deoxy-mannosyl donoren kunnen door reductie 1,2-*cis* rhamnosides worden verkregen. Volgens deze methode werd een tetrasaccharide gesynthetiseerd, welke afwisselend α-en β-D-rhamnosides bevat.

List of Publications

Synthesis and application of carbohydrate-derived morpholine amino acids

Grotenbreg, G. M.; Christina, A. E.; Buizert, A. E. M.; van der Marel, G. A.; Overkleeft, H.S.; Overhand, M. *J. Org. Chem.* **2004**, *69*, 8331-8339.

Diastereoselective synthesis of novel iminosugar-containing UDP-Galf mimics: potential inhibitors of UDP-Gal mutase and UDP-Gal*f* transferases

Liautard, V.; Christina, A. E.; Desvergnes, V.; Martin, O. R. *J. Org. Chem.* **2006**, *71*, 7337-7345.

Galacturonic acid lactones in the synthesis of all trisaccharide repeating units of the zwitterionic polysaccharide Sp1

Christina, A. E.; van den Bos, L. J.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. *J. Org. Chem.* **2011**, *76*, 1692–1706.

β-Rhamnosides from 6-thio mannosides

Christina, A. E.; van der Es, D.; Dinkelaar, J.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. *Chem. Commun.* **2012**, *48*, 2686–2688

Multigram-scale synthesis of an orthogonally protected 2-acetamido-4-amino-2,4,6-trideoxy-D-galactose (AAT) building block

Christina, A. E.; Blas Ferrando, V. M.; de Bordes, F.; Spruit, W. A.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *Carb. Res.* **2012**, *356*, 282-287.

Uronic acids in oligosaccharide and glycoconjugate synthesis

Codée, J. D. C.; Christina, A. E.; Walvoort, M. T. C.; Overkleeft, H. S.; van der Marel, G. A. *Top. Curr. Chem.* **2011**, *301*, 253-289.

On the reactivity and selectivity of galacturonic acid lactones

Christina, A. E.; Muns, J. A.; Olivier, J. Q. A.; Visser, L.; Hagen, B., van den Bos, L. J.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *Eur. J. Org. Chem.* doi: 10.1002/ejoc.201200717.

Curriculum Vitae

Alphert Enzio Christina werd op 14 oktober 1981 geboren te Vlaardingen. In 2000 behaalde hij zijn gymnasium-diploma aan scholengemeenschap Spieringshoek te Schiedam en in datzelfde jaar begon hij met de studie Scheikunde aan de Universiteit Leiden. Zijn hoofdvaksstage verrichtte hij in de Bio-organische synthese groep onder leiding van prof. dr. H. S. Overkleeft en prof. dr. G. A. van der Marel. Het onderzoek behelsde de synthese van morpholine aminozuren uit pentose suikers in het kader van de ontwikkeling van nieuwe antibiotica gebaseerd op gramicidine S. Tevens deed hij als onderdeel van de doctoraal studie onderzoek aan de Universiteit van Orléans in de groep van prof. dr. O. R. Martin. Dit onderzoek was gericht op de stereoselectieve synthese van β-imino-C-glucosides als potentiële inhibitoren van uridinedifosfaat(UDP)-galactose mutase en UDP-galactofuranose transferases, essentiële enzymen voor de proliferatie van mycobacteria, waaronder *Mycobacterium tuberculosis*. Het doctoraal examen werd in 2006 behaald.

Aansluitend heeft Alphert deelgenomen aan een onderzoeksproject aan de Universiteit van Lyon in de groep van prof. dr. P. Strazewski. Hier werkte hij aan de synthese van conformationeel vastgelegde puromycine-analoga.

Van augustus 2007 tot november 2011 werd als assistent-in-opleiding aan de Universiteit Leiden het in dit proefschrift beschreven onderzoek uitgevoerd in de Bio-organische synthese groep. Dit gebeurde onder begeleiding van prof. dr. G. A. van der Marel, dr. J. D. C. Codée en prof. dr. H. S. Overkleeft. Tussentijds gaf Alphert verscheidene poster presentaties op de jaarlijkse congressen van NWO te Lunteren. Ook gaf hij een lezing tijdens een congres georganiseerd door de KNCV Organische Chemie Divisie en NWO-CW studiegroepen (Ontwerp en Synthese, Coördinatie Chemie en Homogene Katalyse, Biomoleculaire Chemie en Structuur en Reactiviteit) te Wageningen en tijdens het 16th European Carbohydrate Symposium te Sorrento, Italië (2011).

Van november 2011 tot juli 2012 werkte hij als onderzoekschemicus bij Syncom B. V. te Groningen.