Chemical synthesis of fragments of streptococcal cell wall polysaccharides

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Chapter 2

Chemical Synthesis of Fragments of the Multiantennary Group-Specific Polysaccharide of Group B *Streptococcus*

Introduction

July is international Group B *Strep* awareness month indicating that infections by Group B *Streptococcus* (GBS) remain a significant global public health problem.[1] GBS, also known as *Streptococcus agalactiae*, is a β-hemolytic gram-positive bacterium, and the most common cause of neonatal septicemia and meningitis, which are life-threatening for newborn babies.[2] A recent report estimates that 147 000 stillbirths and infant deaths annually are caused by GBS.[3] It was identified as a human pathogen in 1930s,[4] and is also a crucial cause of severe disease for susceptible individuals, such as pregnant women, immunocompromised patients and the elderly.

Intrapartum antibiotic strategies can lead to a significant decrease in early-onset disease (EOD, less than 7 days age), but have no effect on late-onset disease (LOD, 7 – 90 days of age). Until now, there is no vaccine commercially available to prevent GBS infections,[5] although clinical trials are ongoing. Novartis (now GSK) has developed and commenced a phase II clinical trial to evaluate the safety and immunogenicity in healthy pregnant women of a conjugate vaccine (NCT02046148), targeting GBS serotypes Ia, Ib and III. MinervaX has commenced phase I trials to investigate the safety and immunogenicity of a protein based vaccine in non-pregnant women among of 18 - 40 years old (NCT02459262).[5a, 6]

Bacterial cell-surface coated carbohydrates play a significant role in binding events and recognition by the immune system.[7] Bacterial cell wall polysaccharides (CWPS) are excellent targets to use in carbohydrate-based antibacterial vaccine.[8] As early as in 1938, Rebecca Lancefield demonstrated that the infection of mice by GBS could be prevented using CWPS-specific rabbit sera.[9] At least 10 different GBS serotypes can be distinguished on the basis of their capsular polysaccharide (CPS) structure, including type Ia, Ib, II, III, IV, V, VI, VII, VIII and IX.[10] Different CPSs have been explored in conjugate vaccines, but none have shown cross reactivity to other serotypes, even though the structure of some of the CPSs are highly similar.

The structure of the multiantennary group-specific polysaccharide (GBC, Fig. 1a) was first isolated from a type Ia GBS strain and reported by Jennings et al. in 1988.[11] The structure of GBC is assembled of numerous L-rhamnose and three other monosaccharides: D-galactose, D-*N*-acetylglucosamine and D-glucitol, with phosphate diesters joining the different subunits. Because of their immunological significance and due to the fact that bacterial polysaccharides are often not be obtained in sufficient purity and quantity, the chemical synthesis of bacterial oligosaccharides for vaccine purposes has drawn considerable attention in the fields of glycobiology.[8, 12] The chemical synthesis of the repeating units of serotypes Ia[13], Ib[13c], II[14], III[15] and V[16], have been published in the last 10 years by the groups of Adamo, Guo and Gao. Although the structure of GBC has been known for a long time, at present, only a trisaccharide[17] and tetrasaccharide[18] of the rhamnose moiety of the common antigen have been synthesized, and the role of this unique carbohydrate structure remains poorly understood. To make well-defined fragments of the GBC available for further studies and potential applications in novel conjugate vaccines, this Chapter describes the development of synthetic methodology to generate these fragments. As depicted in Fig. 1a, the GBC is built up from different substructures, and the target structures aimed at here representing the termini of the tetra-antennary structure. The boxed structure in Fig. 1a represents a tridecasaccharide, containing most components of the complete GBC and therefore

representing an attractive structure for immunological evaluation. It is built up from a pentasaccharide (Sub structure III) and an octasaccharide (Sub structure II), which are interconnected through a phosphate diester bridge. This Chapter describes the synthesis of conjugation-ready GBC-fragments **1** (the Sub III structure), **2** (the Sub II fragment) and **1** (the Sub II + Sub III oligomer). Because of the phosphate joints in the natural compound, a phosphate spacer was chosen to be coupled to the three different targets as shown in Fig. 1b.

Results and discussion

A retrosynthetic analysis towards the three targets is shown in Scheme 1. It was reasoned that the target tridecasaccharide **3** could be obtained from the protected tridecasaccharide **4** after a sequence of deprotection steps, including basic hydrolysis of the cyanoethyl, benzoyl groups and hydrogenation of the Bn, Nap and Cbz groups and transformation of the trichloroacetamide to the corresponding acetamide. Compound **4** could be constructed via a convergent [5 + 8] phosphate coupling strategy using pentasaccharide phosphoramidite **5** and the branched octasaccharide with a free galactosyl C-6-OH **6**. The key octasaccharide intermediate **6** was assembled by a [3 + 5] glycosylation strategy, which employed the trisaccharide **8** as donor and pentasaccharide **7** as acceptor. The latter pentasaccharide is also the precursor to the pentasaccharide phosphoramidite **5**. Both the tri- and pentasaccharides **7** and **8** were prepared via glycosylations using monosaccharide building blocks **A** to **F**.

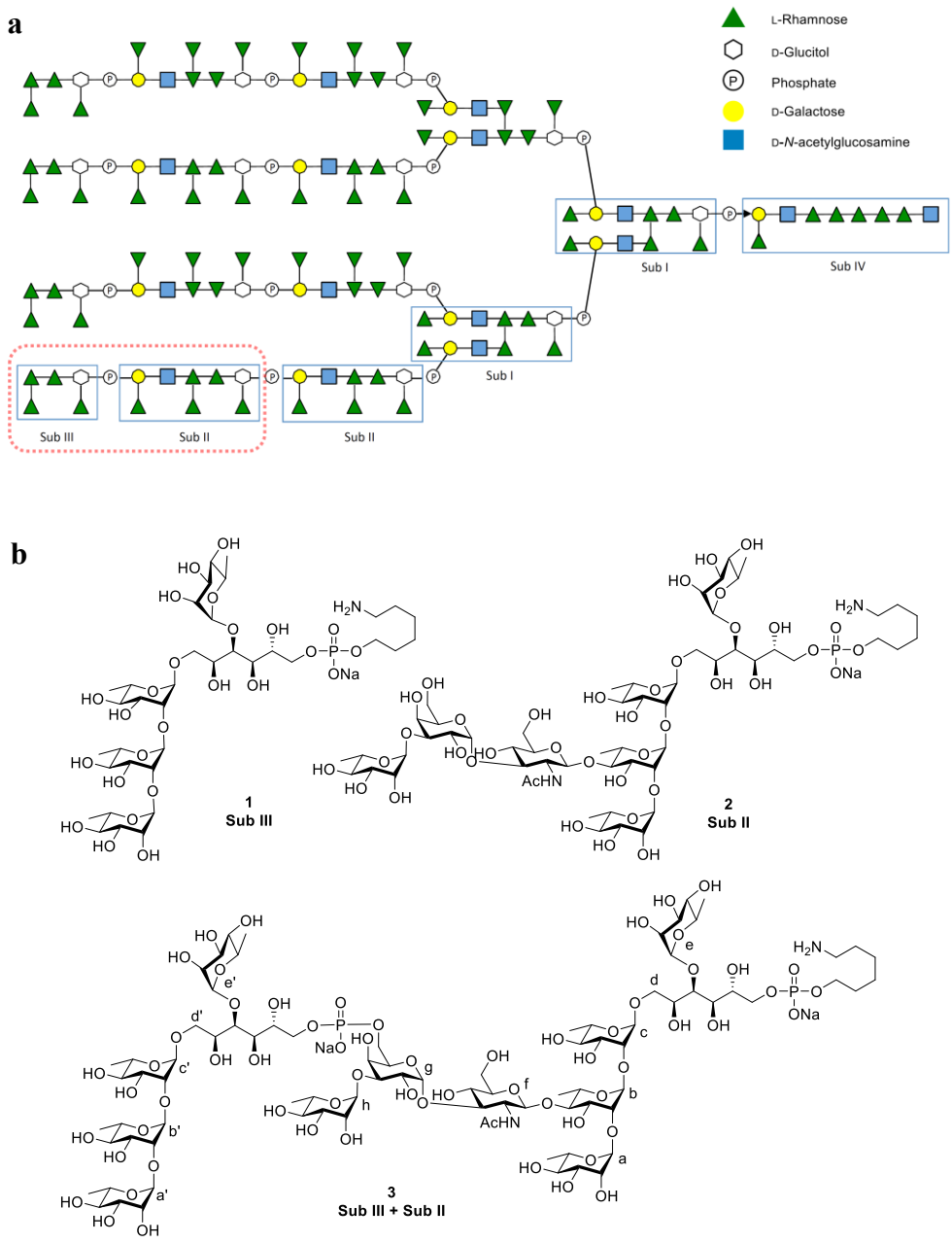
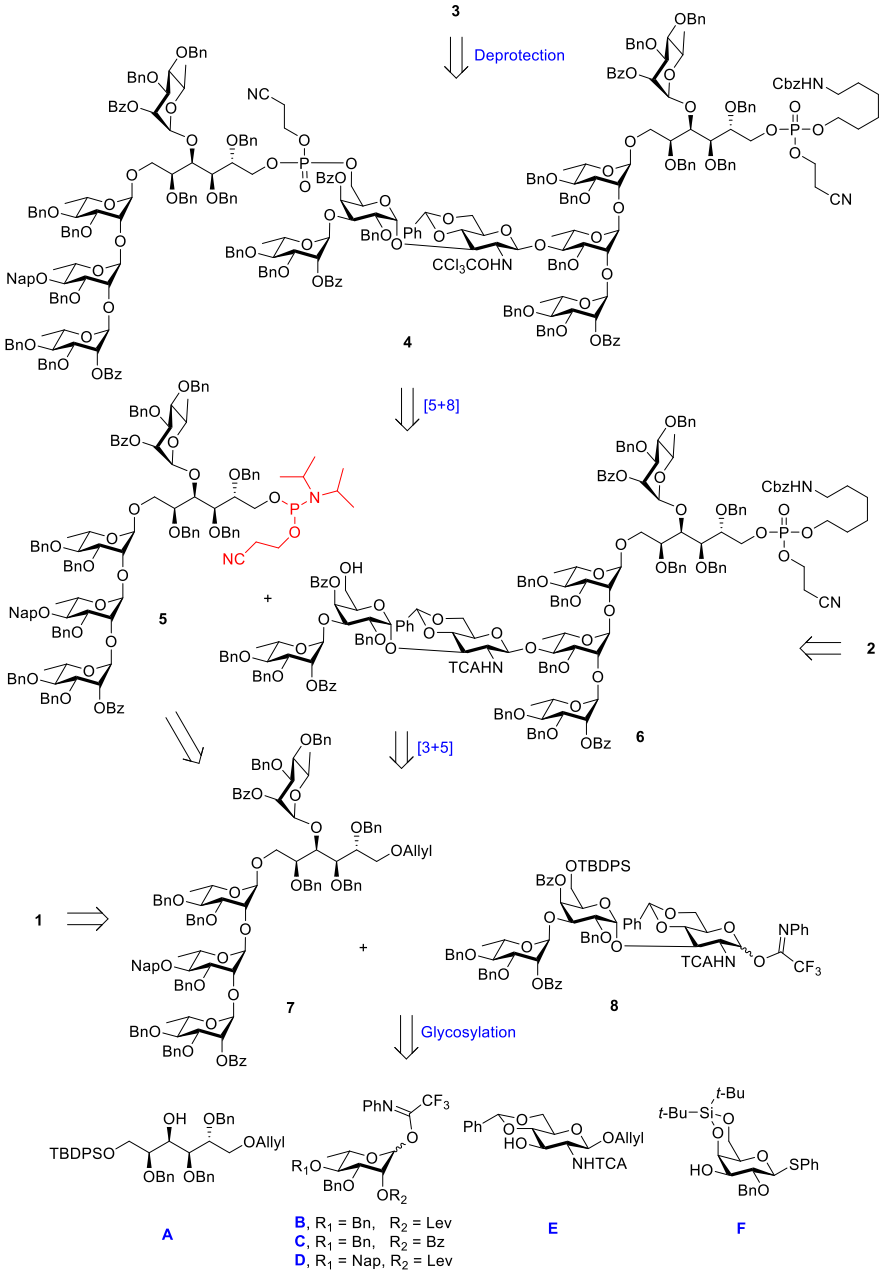
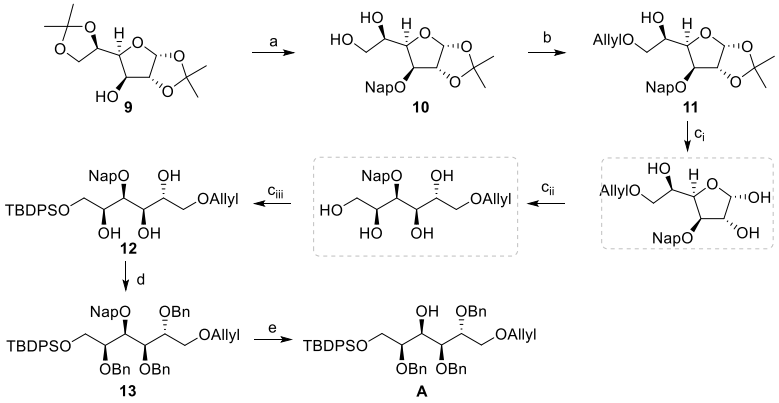


Figure 1. a) Structure of the GBC proposed by Jennings; b) Three conjugation-ready GBC fragments.



Scheme 1. Retrosynthetic analysis of the target oligosaccharides **1** – **3**.

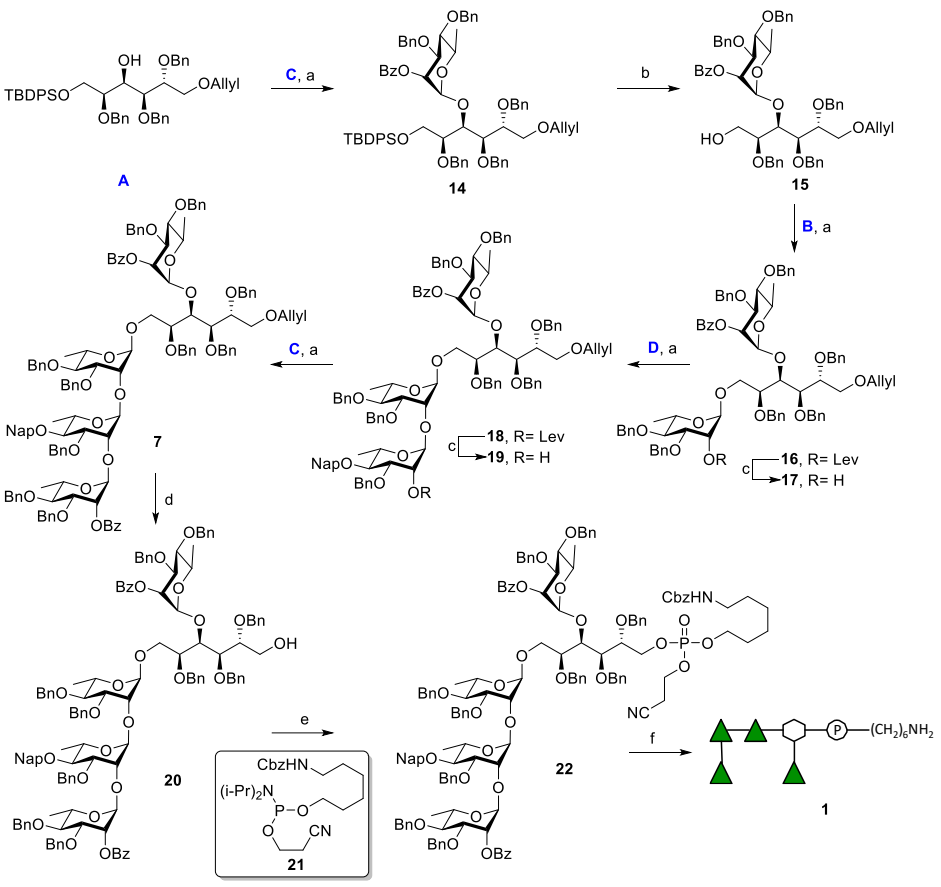
In the above described strategy, neighboring group participation is expected to control the anomeric selectivity in the glycosylations forming 1,2-*trans*-linkages. For the construction of the *cis*-galactosyl linkage, a silylidene group was to be used as stereochemistry controlling functionality.[19] Due to their high reactivity, convenient manipulation and facile purification, glycosyl *N*-phenyltrifluoroacetimidates were adopted as donors for all the glycosylation reactions. Of the listed building blocks (Scheme 1), rhamnosyl imidate donor **B**,[20] glucosamine acceptor **E**[21] and galactose acceptor **F**[12a] were prepared following reported procedures, while rhamnosyl imidate donors **C** and **D** were synthesized specifically for this study following adapted literature methods as described in the Experimental Section. A detailed description of glucitol acceptor **A** is shown in Scheme 2. 1,2-*O*-isopropylidene-3-*O*-napthylmethyl-α-D-glucofuranose **10**,[22] synthesized from diacetone-D-glucose **9**, was transformed into allyl-protected alcohol **11** in excellent yield *via* a borinic acid-catalyzed regioselective alkylation.[23] Subsequently, the ketal in **11** was removed in refluxing 80% acetic acid, which was followed by the sodium borohydride mediated reduction of the resulting hemiacetal and selective silylation using the bulky TBDPS group of the primary alcohol to afford triol **12** in 87% yield over three steps without purification of the intermediate products. Benzylation of the three hydroxyls was achieved in 94% yield. Detailed optimization of these benzylation conditions are showed in the Experimental Section, and several side products were identified, resulting from incomplete benzylation and silyl removal or migration. Finally, the D-glucitol building block **A** was obtained by removal of the Nap group in an oxidation with DDQ.



Scheme 2. Synthesis of the glucitol acceptor **A**.

Reagents and conditions: a) i, NapBr, NaH, DMF, 0 °C, 3 h; ii, 70% AcOH, rt, overnight, 92% (over 2 steps). b) 2-Aminoethyl diphenylborinate, KI, K_2CO_3, AllylBr, MeCN, 60 °C, 24 h, 91%. c) i, 80% AcOH, reflux, 2h; ii, $NaBH_4$, H_2O, EtOH-$CHCl_3$; iii, TBDPSCl, imidazole, DMF, 0 °C, 87% (over 3 steps). d) NaH, BnBr, TBAI, DMF, rt, 94%. e) DDQ, DCM/H_2O, 95%.

With all the six building blocks in hand, the assembly of the first target molecule **2** was undertaken as shown in Scheme 3. After an initial [3 + 2] model glycosylation showed that the stereochemistry of rhamnose-glucitol linkage was generated with poor selectivity,[24] the construction of the key pentasaccharide intermediate **7** was explored through a stepwise approach using monosaccharide building blocks. The first glycosylation between glucitol acceptor **A** and rhamnosyl donor **C** in the presence of TBSOTf as promotor gave disaccharide **14** in excellent yield. The selective deprotection of the TBDPS protecting group was performed utilizing TBAF in THF, and the subsequent glycosylation with donor building block **B** provided the trisaccharide **16** in 82% yield. Deprotection of the levulinoyl ester using $N_2H_4{\bullet}H_2O$ furnished trisaccharide acceptor **17** in 97% yield, which was glycosylated with building block **D** under the promotion of TBSOTf to furnish tetrasaccharide **18** in 71% yield. Selective removal of the levulinoyl group and subsequent glycosylation with building block **C** using the above-mentioned conditions provided the key intermediate pentasaccharide **7** in 87% yield. To complete the synthesis of target pentasaccharide **1**, de-allylation was performed using an isomerization reaction employing a catalytic amount of $Ir(COD)(Ph_2MeP)_2$, which was activated using H_2 in distilled THF. The resulting enol ether was cleaved by treatment with NIS and H_2O to provide the alcohol **20** in 90% yield.[25] Subsequently, the attachment of the spacer was achieved using phosphoramidite functionalized spacer **21** and dicyanoimidazole as an activator, followed by oxidation of the intermediate phosphite to the corresponding phosphate triester using CSO to give the fully protected pentasaccharide **22** in 90% yield over two steps. Finally, treatment of the pentasaccharide **22** with concentrated ammonia in dioxane led to removal of the cyanoethyl group, after which the compound was treated with NaOMe in MeOH/dioxane to remove the benzoyl esters. The subsequent palladium hydroxide mediated hydrogenation was performed in a mixture of water/*tert*-butanol under slightly acidic condition[26] at 1 atm for 3 days to give the target pentasaccharide **1** in 80% yield over the last 3 steps.

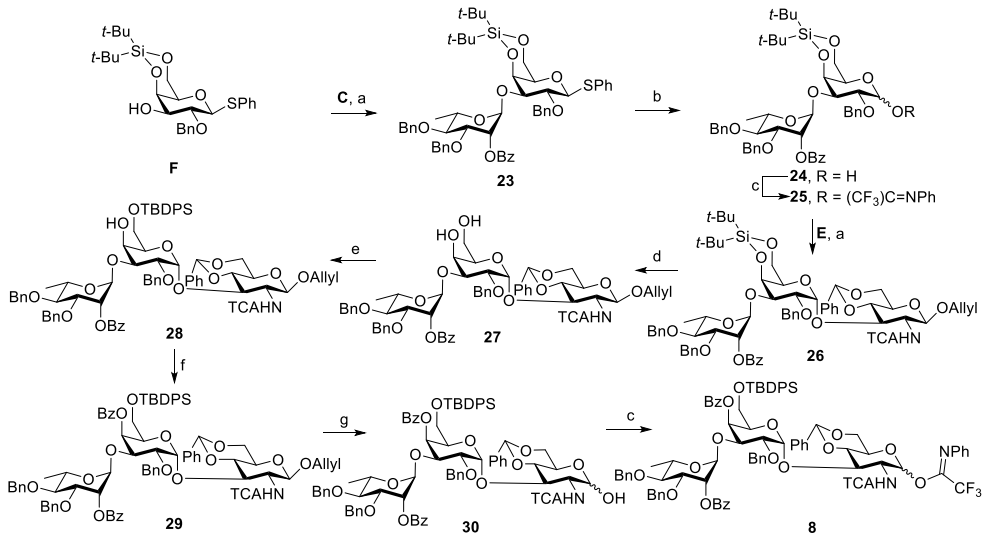


Scheme 3. Synthesis of the pentasaccharide **1**.

Reagents and conditions: a) TBSOTf, 4Å MS, DCM, 0 °C, **14**, 97%; **16**, 82%; **18**, 71%; **7**, 87%. b) TBAF, THF, 0 °C - RT, 93%. c) N_2H_4•H_2O, Py/AcOH, 0 °C - rt, **17**, 97%; **19**, 93%. d) $Ir(COD)(Ph_2MeP)_2$•PF_6, THF, H_2, 5s, then NIS and H_2O, 1h, 90%. e) **21**, DCI, MeCN, 3Å MS, 1h, then CSO, 15min, 90%. f) i, ammonium hydroxide, 1,4-dioxane; ii, NaOMe, MeOH/1,4-dioxane; iii, $Pd(OH)_2$/C, H_2, *t*-BuOH/H_2O, 3 days, 80%.

With the key pentasaccharide **7** in hand, and according to the retrosynthetic analysis, attention was turned to the trisaccharide donor **8** (Scheme 4). First, glycosylation of imidate donor **C** with acceptor **F** resulted in desired disaccharide **23** in 93% yield. Transformation of the thiophenyl donor into the corresponding imidate disaccharide donor gave **25** in excellent yield. Subsequently, the stereoselective formation of trisaccharide **26** was achieved through condensation **25** and acceptor **E** in 81% yield in the presence of catalytic amount of TBSOTf. To facilitate the phosphoramidite coupling to provide tridecasaccharide at a later stage, and prevent multiple protecting group manipulations on far-advanced intermediates, the

silylidene in **26** was removed using HF-Py in 87% yield, after which the primary C-6 alcohol of the galactoside moiety in **27** was selectively masked with a bulky TBDPS group to give **28**. The benzoylation of the remaining galactoside C-4 hydroxy was proved to be challenging, which can be attributed to the low reactivity of this alcohol. Several methods were tried, including the combination of BzCl and Et_3N. However, because of the acidic N-H of the glucosamine moiety, side-product was generated in which the amide was also benzoylated. The desired product **29** was finally obtained by stirring the substrate with BzCl in pyridine at RT for 3 days. Deprotection of the allyl group of the trisaccharide employing the iridium catalyst and subsequent NIS-mediated hydrolysis was followed by the installation of the imidate at the anomeric hydroxyl, to give the trisaccharide donor **8** in good yield.

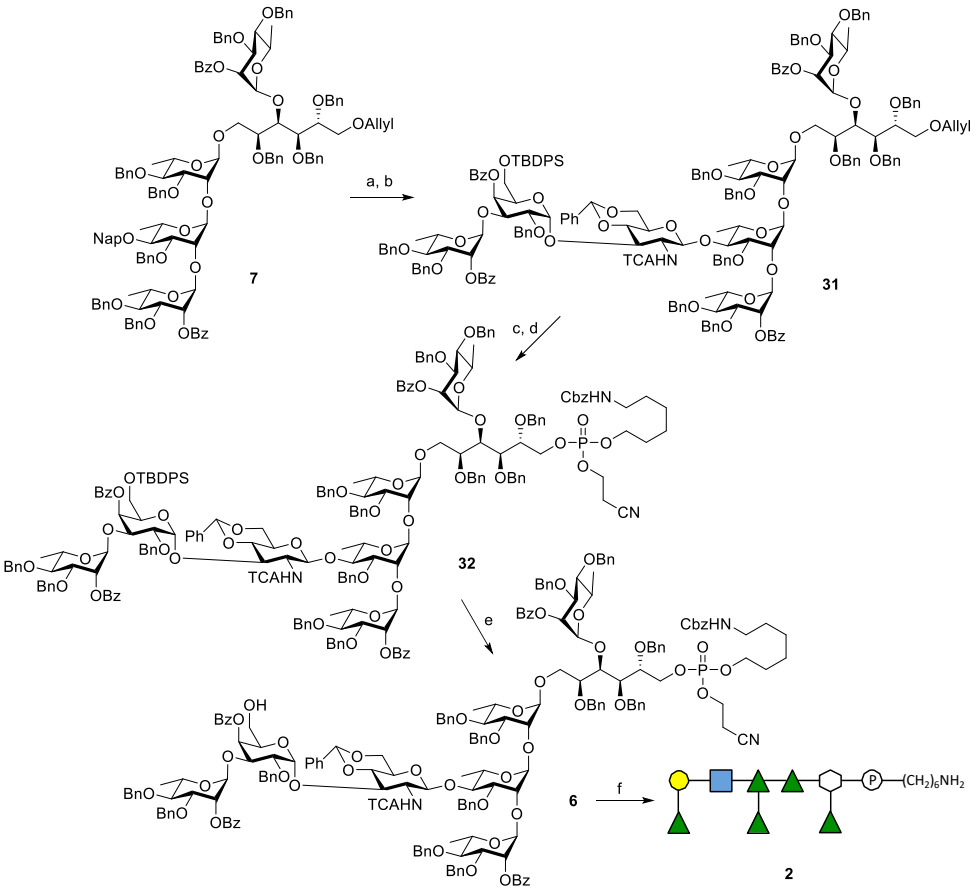


Scheme 4. Synthesis of the trisaccharide donor **8**.

Reagents and conditions: a) TBSOTf, DCM, 0 °C, 1h, 4Å MS, **23**, 93%; **26**, 81%. b) NIS, TFA, DCM, 0 °C, 0.5h, 94%. c) *N*-phenyltrifluoroacetimidoyl chloride, Cs_2CO_3, acetone, overnight, **25**, 93%; **8**, 81%. d) HF•Py, Py, THF, 87%. e) TBDPSCl, DMF, imidazole, 94%. f) BzCl, Py, DMAP, 3 days, 95%. g) $Ir(COD)(Ph_2MeP)_2•PF_6$, THF, H_2, 5s, then NIS and H_2O, 90%. TCA, trichloroacetyl.

To assemble the octasaccharide **2**, pentasaccharide **7** was first transformed into an acceptor by the selective removal of the Nap group using DDQ in DCM-H_2O (Scheme 5). Next, the [3 + 5] glycosylation with trisaccharide donor **8** using TBSOTf as a promotor gave octasaccharide **31** in 75% yield. As described for the synthesis of **22**, octasaccharide **32** was produced after de-allylation, and reaction with the phosphoramidite spacer and subsequent in situ oxidation, to give the fully protected product in high yield. Deprotection of the octasaccharide started with the removal of the TBDPS group using HF-Py in 93% yield to

provide **6**, having a free galactosyl C-6-OH. No migration of the neighboring benzoate was observed under this condition. Next, the same sequence of reactions was performed for the deprotection of pentasaccharide, to generate target octasaccharide **2**. Thus, first the cyanoethyl group and benzoate esters were removed, after which the reduction of all benzyl ethers, the benzylidene acetal and the benzyl carbamate and the concomitant transformation of the trichloroacetamide into the corresponding acetamide delivered GBC-octasaccharide **2**.

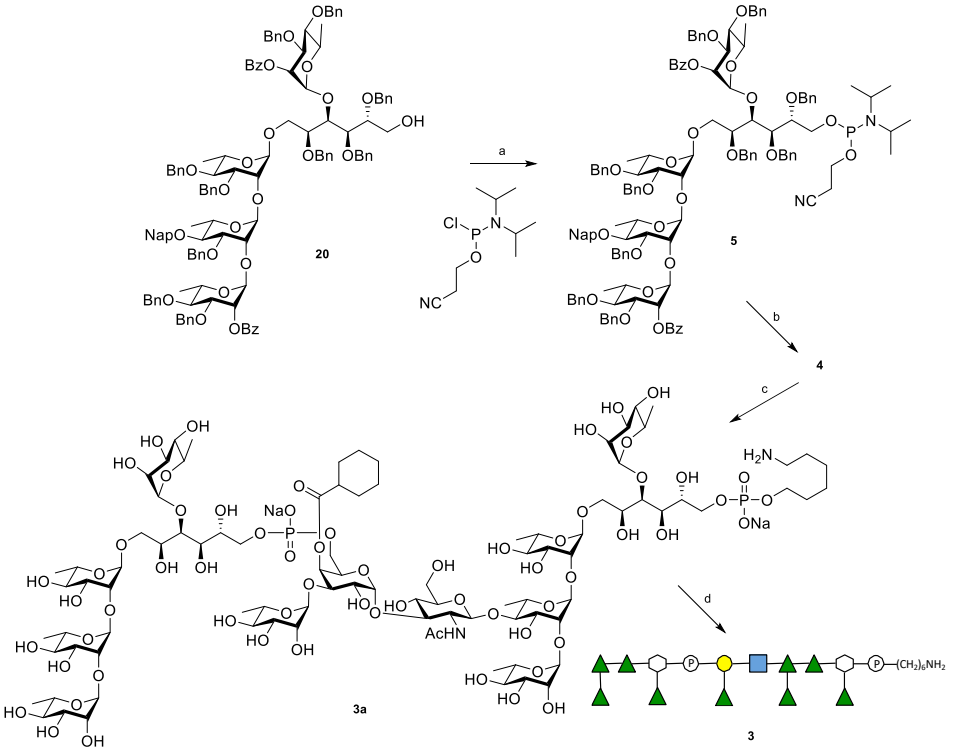


Scheme 5. The assembly of the octasaccharide **2**.

Reagents and conditions: a) DDQ, DCM/H_2O, 85%. b) **8**, TBSOTf, DCM, 4Å MS, 0 °C, 75%. c) $Ir(COD)(Ph_2MeP)_2$•PF_6, THF, H_2, then NIS and H_2O, 87%. d) **21**, DCI, ACN, 3Å MS, then, CSO, 92%. e) HF•Py, THF/Py, 93%. f) i, ammonium hydroxide, 1,4-dioxane; ii, NaOMe, MeOH/1,4-dioxane; iii, $Pd(OH)_2$/C, H_2, AcOH, *t*-BuOH/H_2O, 3 days, 70%

To be able to assemble the tridecasaccharide **3**, the pentasaccharide phosphoramidite **5** was synthesized from **20** using 2-cyanoethyl *N,N*-di-*iso*-propylchlorophosphoramidite and

DIPEA (Scheme 6). The key coupling of amidite **5** with octasaccharide **6** in the presence of DCI and in situ oxidation of the formed phosphite by CSO gave the fully protected tridecasaccharide **4** in 82% yield. When the global deprotection of this large oligosaccharide was performed using the procedures to generate **1** and **2**, undesired product **3a**, containing a cyclohexyl ester, was formed as the major product. This again underlines the low reactivity of the axial C-4 position of the galactose moiety. The cyclohexyl ester could be cleaved from **3a** by treatment with 1M NaOH for 24 hours, delivering the final compound **3**, after size exclusion chromatography.



Scheme 6. The assembly of the tridecasaccharide **3**.

Reagent and conditions: a) DIPEA, DCM, 3Å MS, 84%. b) **6**, DCI, ACN, 3Å MS, 2h, then, CSO, 15 min, 82%. c) i, ammonium hydroxide, 1,4-dioxane; ii, NaOMe, MeOH/1,4-diaxane; iii, $Pd(OH)_2/C$, H_2, AcOH, *t*-BuOH/H_2O, 3 days. d) 1M NaOH, H_2O, 52%.

The NMR data of compounds **1**, **2** and **3** closely matched the spectroscopic data reported for the isolated natural compounds, lacking the aminohexylphosphate spacer, as can be seen from Figure 2, Table 1 and 2.

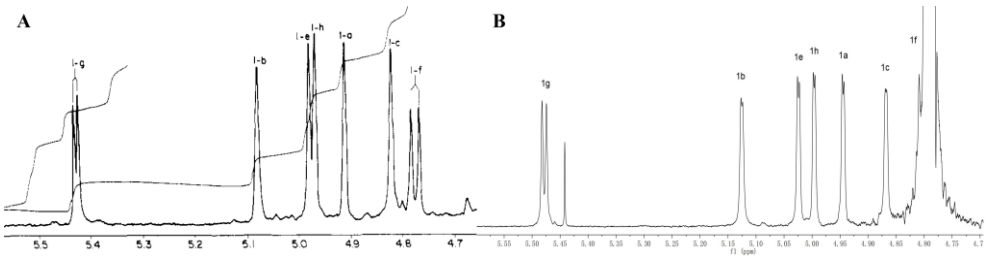


Figure 2. Partial ^{1}H NMR spectrum (anomeric proton region). A) isolated octasaccharide in D_2O. B) Synthesized target octasaccharide **2** in D_2O.

Table 1. ^{1}H NMR data (in D_2O) comparison of natural and synthetic fragments of GBC.

Anomeric Proton	Tridecasaccharide **3**		Octasaccharide **2**		Pentasaccharide **1**	
	Natural	Synthetic	Natural	Synthetic	Natural	Synthetic
1a	4.99	4.99	4.97	4.96		
1b	5.11	5.13	5.12	5.13		
1c	4.87	4.89	4.87	4.87		
1e	5.03	5.05	5.04	5.02		
1f	4.87	4.83	4.84	4.84		
1g	5.53	5.57	5.44	5.48		
1h	5.03	5.04	5.02	5.00		
1a’	4.98	4.97			4.97	4.99
1b’	5.12	5.14			5.10	5.14
1c’	4.89	4.90			4.87	4.90
1e’	5.03	5.02			5.03	5.05

Table 2. ^{13}C NMR data (in D_2O) comparison of natural and synthetic fragments of GBC.

Anomeric Carbon	Tridecasaccharide **3**		Octasaccharide **2**		Pentasaccharide **1**	
	Natural	Synthetic	Natural	Synthetic	Natural	Synthetic
1a	103.1	103.3	103.0	102.3		
1b	101.3	101.5	101.2	100.5		
1c	99.6	99.7	99.6	98.8		
1e	102.5	102.4	102.4	101.4		
1f	102.1	102.4	102.0	101.4		
1g	99.1	99.3	99.6	98.8		
1h	103.1	103.3	103.0	102.4		
1a’	103.0	103.2			102.9	102.3
1b’	101.7	101.8			101.6	100.9
1c’	99.6	99.7			99.6	98.8
1e’	102.1	102.3			102.4	101.4

Conclusion

The first chemical synthesis of fragments of the tetra-antennary group specific polysaccharide of GBS was achieved delivering the structures, equipped with a spacer for future conjugation purposes, in multi-milligrams quantities. The target structures represent the termini of the complex GBC and include branched oligosaccharides containing the pentasaccharide of GBC substructure III, the octasaccharide of substructure II and a tridecasaccharide, encompassing substructures II and III. A linear glycosylation strategy was used to construct the pentasaccharide **1**, a highly convergent [3 + 5] glycosylation approach delivered the octasaccharide **2** and a [5 + 8] strategy between a pentasaccharide phosphoramidite **5** and a branched octasaccharide with a free galactosyl C-6-OH **6** led to the challenging, complex tridecasaccharide target **3**. The spectroscopic data of the synthetic molecules matched well with those obtained for the isolated compounds. All the target fragments contain a free amino group at their downstream end for future regioselective modifications, such as conjugation with proteins, fluorophores or affinity tags, to provide compounds for various biological studies. Conjugation with a carrier protein such as CRM197, may deliver a conjugate vaccine that can be used to induce immunity against all GBS serotypes.

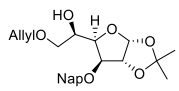
Experimental Section

General experimental procedures

All reagents were of commercial grade and used as received. All moisture sensitive reactions were performed under an argon atmosphere. DCM used in the glycosylation reactions was dried with flamed 4Å molecular sieves before being used. Reactions were monitored by TLC analysis with detection by UV (254 nm) and where applicable by spraying with 20% sulfuric acid in EtOH or with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ (10 g/L) in 10% sulfuric acid (aq.) followed by charring at ~150 °C. Flash column chromatography was performed on silica gel (40-63μm). ^1H and ^{13}C spectra were recorded on a Bruker AV 400 or Bruker AV 500 or Bruker AV 600 and Bruker AV 850 in $CDCl_3$ or D_2O. Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard (^1H NMR in $CDCl_3$) or the residual signal of the deuterated solvent. Coupling constants (*J*) are given in Hz. All ^{13}C spectra are proton decoupled. NMR peak assignments were made using COSY and HSQC experiments, where applicable Clean TOCSY, HMBC and GATED experiments were used to further elucidate the structure.

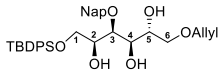
Experimental Procedures and Characterization Data of Products

6-Allyl-1,2-*O*-isopropylidene-3-*O*-(2-napthylmethyl)-α-D-glucofuranose (11)



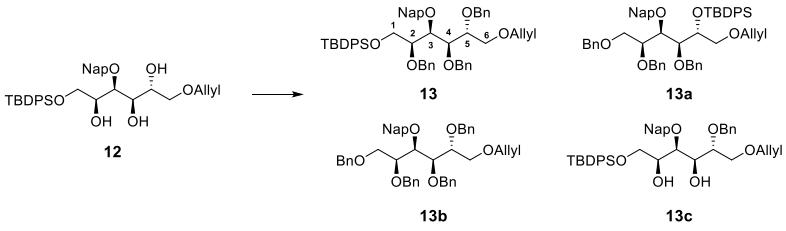
1,2-*O*-isopropylidene-3-*O*-(2-napthylmethyl)-α-D-glucofuranose[22] **10** (11.5 g, 32 mmol, 1 eq) was dissolved in CH_3CN (160 mL). 2-Aminoethyl diphenylborinate (2.1 g, 9.0 mmol, 0.28 eq), potassium iodide (7.4 g, 44.8 mmol, 1.4 eq) and potassium carbonate (6.64 g, 48 mmol, 1.5 eq), and allyl bromide (7 mL, 80 mmol, 2.5 eq) were added. The reaction was stirred at 60 °C for 24 hours. After analysis by TLC showed complete consumption of the starting material, diluted with EtOAc and washed with water and brine. The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*, and the product purified by column chromatography (PE/EA 10:1 – 3/1) to yield compound **11** (11.6 g, 29 mmol, 91%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.87-7.74 (m, 4H, Nap), 7.54-7.40 (m, 3H, Nap), 5.95 (d, *J* = 4.0 Hz, 1H, H-1), 5.93-5.84 (m, 1H, $OCH_2C\mathit{H}CH_2$), 5.25 (dt, *J* = 17.2, 1.6 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 5.16 (dt, *J* = 10.0, 1.6 Hz, 1H, OCH2CHC*H*2), 4.85 (d, *J* = 11.6 Hz, 1H, C*H*H), 4.76 (d, *J* = 12 Hz, 1H, CH*H*), 4.64 (d, *J* = 4.0 Hz, 1H, H-2). 4.18-4.14 (m, 3H, H-3, H-5, H-4), 4.01 (dt, 2H, *J* = 5.6, 1.2 Hz, $OC\mathit{H}_2CHCH_2$), 3.70 (dd, *J* = 3.2, 10 Hz, 1H, H-6), 3.55 (dd, *J* = 10, 6.0 Hz, 1H, H-6), 2.74 (d, *J* = 5.6 Hz, 1H, O*H*), 1.48 (s, 3H, CH_3), 1.31 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.86 (aromatic *C*), 134.56 ($OCH_2\mathit{C}HCH_2$), 133.28, 133.15 (aromatic *C*), 128.54, 128.02, 127.80, 126.83, 126.33, 126.18, 125.73 (aromatic *C*H), 117.37 ($OCH_2CH\mathit{C}H_2$), 111.85 (acetonide *C*), 105.26 (C-1), 82.44 (C-2), 82.00 (C-3), 79.96 (C-4), 72.54 (*C*H2), 72.41 ($O\mathit{C}H_2CHCH_2$), 72.00 (C-6), 68.02 (C-5), 26.87 ($\mathit{C}H_3$), 26.39 ($\mathit{C}H_3$). HR-MS: Calculated for $C_{23}H_{28}O_6$ $[M+Na]^+$: 423.1778, found: 423.1787. $[\alpha]^{20}_D$ = - 25.9° (c = 1, $CHCl_3$). TLC Rf = 0.40 (PE/EtOAc = 4/1, v/v).

6-Allyl-1-*O*-*tert*-butyldiphenylsilyl-3-*O*-(2-napthylmethyl)-D-glucitol (12)



Compound **11** (11.6 g, 29 mmol, 1 eq) was dissolved in acetic acid (116 mL) and water (30 mL). The reaction was refluxed at 120 °C for 2 hours. After analysis by TLC showed complete consumption of the starting material, co-evaporated with toluene to remove the solvent, diluted in EtOAc and washed with saturated aqueous sodium bicarbonate, water and brine. The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude was dissolved in ethanol (320 mL) and chloroform (160 mL). The reaction was cooled to 0 °C, sodium borohydride (6.6 g, 173.7 mmol, 6 eq) in water (160 mL) was added. It was slowly warmed to RT and stirred overnight. After analysis by TLC showed complete consumption of the starting material, quenched with acetic acid, and concentrated *in vacuo*. Diluted in EtOAc and washed with saturated aqueous sodium bicarbonate, water, and brine. The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was dissolved in DMF (58 mL) and cooled to 0 °C. *tert*-Butyl(chloro)diphenylsilane (TBDPSCl) (15 mL, 58 mmol, 2 eq) and imidazole (6 g, 88 mmol, 3 eq) were added at 0 °C. It was stirred at RT 4 hours and checked by TLC. After completed consumption of the starting material, diluted with EtOAc, and washed with water and brine. The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The compound was purified by flash chromatography (PE/EA 5:1 - 2:1) to yield compound **12** (15.16 g, 25.3 mmol, 87%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.79-7.71 (m, 4H, aromatic *H*), 7.65-7.62 (m, 4H, aromatic *H*), 7.46-7.30 (m, 9H, aromatic *H*), 5.92-5.82 (m, 1H, OCH_2CHCH_2), 5.24 (dt, *J* = 17.2, 1.6 Hz, 1H, OCH_2CHCH_2), 5.16 (dt, *J* = 10.4, 1.6 Hz, 1H, OCH_2CHCH_2), 4.89 (d, *J* = 11.4 Hz, 1H, CHH), 4.81 (d, *J* = 11.4 Hz, 1H, CHH), 4.09-4.06 (m, 1H, H-3), 4.00-3.97 (m, 3H, H-2, OCH_2CHCH_2), 3.85-3.67 (m, 5H, H-5, H-1, H-4, H-6), 3.56 (dd, *J* = 9.6, 6.0, Hz, 1H, H-6), 3.09-2.79 (m, 3H, 3 OH), 1.06 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.63 (aromatic CH), 135.52 (aromatic *C*), 134.42 (OCH_2CHCH_2), 133.24, 133.09, 133.07 (aromatic *C*), 129.91, 129.90, 128.29, 128.01, 127.86, 127.75, 126.99, 126.18, 126.06, 126.06 (aromatic CH), 117.48 (OCH_2CHCH_2), 76.75 (C-3), 74.98 (CH_2), 73.58 (C-2), 73.11 (C-4), 72.36 (OCH_2CHCH_2), 71.57 (C-6), 70.31 (C-5), 64.65 (C-1), 26.94 (3 CH_3), 19.26 ($C(CH_3)_3$). HR-MS: Calculated for $C_{36}H_{44}O_6Si$ $[M+Na]^+$: 623.2799, found : 623.2805. $[\alpha]^{20}_D$ = - 2.1° (c = 1, $CHCl_3$). TLC: Rf = 0.40 (PE/EtOAc = 7/3, v/v).

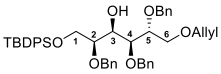
6-Allyl-2,4,5-tri-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-3-*O*-(2-naphthylmethyl)-D-glucitol (13)



Entry	Conditions	13	13a	13b	13c
1	DMF, NaH 6.0 eq, then BnBr 5.0 eq	51%	9%	19%	-
2	DMF, BnBr 4.0 eq, TBAI 0.3 eq, then NaH 4.0 eq	38% (>20:1)		9%	36%
3	DMF, BnBr 5.0 eq, TBAI 0.3 eq, then NaH 5.0 eq	52% (>20:1)		6%	41%
4	DMF, BnBr 10.0 eq, TBAI 3.0 eq, then NaH 6.0 eq	94% (>20:1)		trace	ND

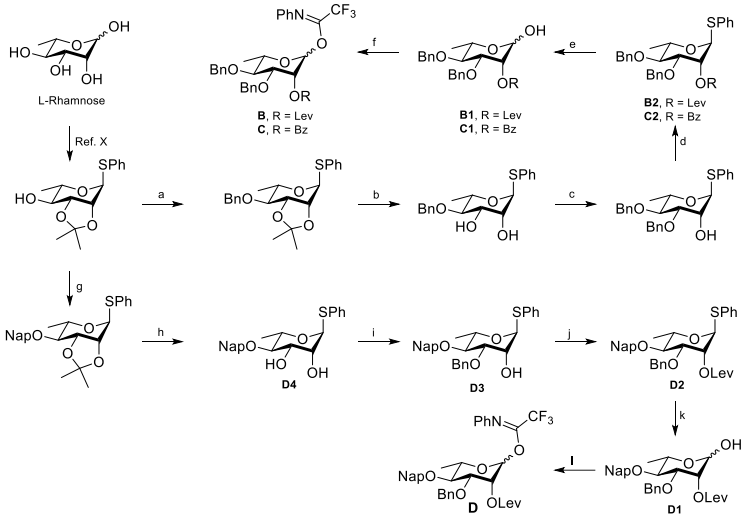
Triol **12** (1.62 g, 2.71 mmol, 1 eq) was dissolved in DMF (27 mL) and cooled to 0 °C. Benzyl bromide (3.2 mL, 27.1 mmol, 10 eq), tetrabutylammonium iodide (TBAI) (3 g, 8.12 mmol, 3 eq) were added. Then after sodium hydride (650 mg, 16.25 mmol, 6 eq) was added, the reaction was stirred at RT for 3 hours. After analysis by TLC showed complete consumption of the starting material, quenched by MeOH, extracted with Et_2O, and washed with water and brine. The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*, and the product purified by column chromatography (PE/EA 50:1 – 20/1) to yield compound **13** (2.22 g, 2.55 mmol, 94%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.79-7.75 (m, 1H, aromatic *H*), 7.71-7.60 (m, 7H, aromatic *H*), 7.44-7.30 (m, 8H, aromatic *H*), 7.26-7.19 (m, 16H, aromatic *H*), 5.93-5.83 (m, 1H, OCH_2CHCH_2), 5.25 (dt, *J* = 17.2, 2.0 Hz, 1H, OCH_2CHCH_2), 5.16 (dt, *J* = 10.4, 1.6 Hz, 1H, OCH_2CHCH_2), 4.82 (s, 2H, CH_2), 4.77 (d, *J* = 11.2 Hz, 1H, CH*H*), 4.66 (d, *J* = 12.0 Hz, 1H, C*H*H), 4.63 (d, *J* = 11.2 Hz, 1H, CH*H*), 4.58 (d, *J* = 11.6 Hz, 1H, CH*H*), 4.50 (d, *J* = 12.0 Hz, 1H, CH*H*), 4.38 (d, *J* = 12.0 Hz, 1H, CH*H*), 4.08-4.05 (m, 1H, H-5), 4.00-3.98 (m, 1H, H-2), 3.96-3.93 (m, 2H, OCH_2CHCH_2), 3.93-3.89 (m, 1H, H-1), 3.85-3.77 (m, 4H, H-6, H-4, H-1, H-3), 3.73-3.68 (m, 1H, H-6), 1.03 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.92, 138.89, 138.78, 136.31 (aromatic *C*), 135.80, 135.75 (aromatic *C*H), 135.00 (OCH_2CHCH_2), 133.49, 133.39, 133.34, 133.01 (aromatic *C*), 129.81, 129.76, 128.37, 128.33, 128.31, 128.11, 128.08, 128.00, 127.84, 127.80, 127.76, 127.57, 127.50, 127.46, 127.38, 126.89, 126.50, 125.97, 125.79 (aromatic *C*H), 116.86 (OCH_2CHCH_2), 80.42 (C-3), 79.63 (C-4), 79.50 (C-5), 78.95 (C-2), 75.06 (CH_2), 74.35 (CH_2), 73.07 (CH_2), 72.33 (OCH_2CHCH_2), 72.01 (CH_2), 70.05 (C-6), 63.63 (C-1), 26.99 (3 CH_3), 19.27 ($C(CH_3)_3$). HR-MS: Calculated for $C_{57}H_{62}O_6Si$ $[M+Na]^+$: 893.4208, found: 893.4217. $[\alpha]^{20}_D$ = - 1.4° (c = 1, $CHCl_3$). TLC: Rf = 0.50 (PE/EtOAc = 20/1, v/v).

6-Allyl-2,4,5-tri-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-D-glucitol (A)



Full protected **13** (2.37 g, 2.73 mmol, 1 eq) was dissolved in DCM (50 mL) and water (5 mL). After cooled to 0 °C, 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) (681 mg, 3 mmol, 1.1 eq) was added. The reaction was stirred at RT for 4 hours. After analysis by TLC showed complete consumption of the starting material, quenched by saturated aqueous sodium thiosulphate, extracted with DCM, and washed with water and brine. The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*, and the product purified by column chromatography (PE/EA 30:1 – 15/1) to yield building block **A** (1.9 g, 2.6 mmol, 95%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67-7.65 (m, 4H, aromatic *H*), 7.43-7.19 (m, 21H, aromatic *H*), 5.94-5.84 (m, 1H, OCH_2CHCH_2), 5.26 (dt, *J* = 17.2, 1.6 Hz, 1H, OCH_2CHCH_2), 5.16 (dt, *J* = 10.4, 1.6 Hz, 1H, OCH_2CHCH_2), 4.72-4.63 (m, 3H,), 4.54-4.47(m, 3H), 4.05 (bs, 1H, H-3), 3.97 (d, *J*

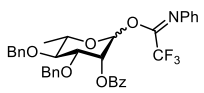
= 5.2 Hz, 2H, OC*H*$_2$CHCH$_2$),3.93-3.88 (m, 1H, H-1), 3.86-3.82 (m, 2H, H-5, H-4), 3.75-3.64 (m, 4H, H-6, H-1, H-2), 3.00 (s, 1H, O*H*), 1.04 (s, 9H, C(C*H*$_3$)$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.50, 138.21 (aromatic *C*), 135.73 (aromatic *C*H), 134.81 (OCH$_2$*C*HCH$_2$), 134.42, 133.24 (aromatic *C*), 129.77, 128.40, 128.38, 128.35, 128.05, 128.00, 127.80, 127.72, 127.67, 127.56 (aromatic *C*H), 117.01 (OCH$_2$CH*C*H$_2$), 80.43 (C-2), 79.44 (C-5), 77.80 (C-4), 73.61 (*C*H$_2$), 72.99 (*C*H$_2$), 72.58 (*C*H$_2$), 72.34 (O*C*H$_2$CHCH$_2$), 70.38 (C-3), 69.54 (C-6), 63.39 (C-1), 26.93 (3 *C*H$_3$), 19.24 (*C*(CH$_3$)$_3$). HR-MS: Calculated for $C_{46}H_{54}O_6Si$ [M+Na]$^+$: 753.3582, found: 753.3599. $[\alpha]^{20}_D$ = + 9.6° (c = 1, $CHCl_3$). TLC: Rf = 0.30 (PE/EtOAc = 10/1, v/v).



Scheme I. Synthesis of the rhamnoseyl donors **B**[20], **C**[27] and **D**[28]

Reagents ang conditions: a) BnBr, NaH, DMF, 4 h, 0 °C to rt, 96%. b) AcOH, 70 °C, 17 h, 95%. c) Bu_2SnO, toluene, 145 °C, 17 h, then BnBr, CsF, 120 °C, 17 h, 74%. d) Levulinic acid, EDCI, DMAP, DCM, 0 °C to rt, 19h, 96% (R = Lev); or BzCl, pyridine, DMAP, 0 °C to rt, 2h, 91% (R = Bz). e) NIS, TFA, DCM, 0 °C, 94% (R = Lev), 92% (R = Bz). f) $CF_3ClCNPh$, Cs_2CO_3, acetone, 0 °C - rt, 94% (R = Lev), quant. (R = Bz). g) NapBr, NaH, DMF, rt, 2 h. h) AcOH, 70 °C, overnight, 93% (over 2 steps). i) Bu_2SnO, toluene, 105 °C, 17h, then BnBr, DMF, rt, 5.5h, 72%. j) Levulinic acid, DIC, DMAP, DCM, 0 °C, 19h, 96%. k) NIS, TFA, DCM, 0 °C, 89%. l) $CF_3ClCNPh$, Cs_2CO_3, acetone, 0 °C - rt, 94%.

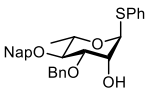
N-Phenyl-trifluoroacetimidate 2-*O*-benzoyl-3,4-di-*O*-benzyl-α/β-L-rhamnopyranoside (C)



Hemiacetal **C1** (11.8 g, 26.31 mmol, 1 eq) was dissolved in acetone (263 mL) and cooled to 0 °C. Cesium carbonate (9 g, 27.6 mmol, 1.05 eq) was added. After 15 min, *N*-phenyl trifluoroacetimidoyl chloride (6.6 g, 31.8 mmol, 1.2 eq) was added, and then it was allowed to stir for overnight at RT. After analysis by TLC showed complete consumption of the starting material, quenched by Et_3N, filtered and concentrated *in vacuo*, and the product purified by column chromatography (PE/EA 100:1 – 20/1) to yield building block **C** (15.9 g, 25.6 mmol, 97%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 (d, *J*

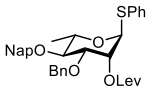
= 7.0 Hz, 2H, Bz), 7.61 – 7.51 (m, 1H, Bz), 7.51 – 7.40 (m, 2H, Bz), 7.39 – 7.18 (m, 12H), 7.13 – 7.01 (m, 1H), 6.88 – 6.78 (m, 2H), 6.31 (s, 1H, H-1), 5.75 (s, 1H, H-2), 4.93 (d, *J* = 10.8 Hz, 1H, CH_2), 4.82 (d, *J* = 11.2 Hz, 1H, CH_2), 4.67 – 4.61 (m, 2H, CH_2), 4.11 (dd, *J* = 9.4, 3.2 Hz, 1H, H-3), 4.05 – 3.91 (m, 1H, H-5), 3.64 (t, *J* = 9.5 Hz, 1H, H-4), 1.42 (d, *J* = 6.2 Hz, 3H, H-6). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.53 (Bz), 143.35, 142.83, 142.46, 142.11, 141.75, 138.11, 137.64, 133.53, 130.04, 129.59, 128.85, 128.59, 128.52, 128.49, 128.33, 127.99, 127.96, 124.53, 120.57, 120.32, 119.48, 117.47, 94.13 (C-1), 79.33 (C-4), 77.62 (C-3), 75.70 (*C*H_2), 72.12 (*C*H_2), 70.65 (C-5), 68.13 (C-2), 18.28 (C-6); HR-MS: Calculated for $C_{35}H_{32}F_3NO_6$ $[M+Na]^+$: 642.2074, found: 642.2070. TLC: Rf = 0.50 (PE/EtOAc = 20/1, v/v).

Phenyl 3-*O*-benzyl-4-*O*-(2-napthylmethyl)-1-thio-α-L-rhamnopyranoside (D3)



Phenyl 4-*O*-(2-napthylmethyl)-1-thio-α-L-rhamnopyranoside[28] **D4** (2.0 g, 5.04 mmol, 1 eq) was co-evaporated with anhydrous toluene three times under nitrogen and dissolved in anhydrous toluene (35 mL). Dibutyltin oxide (1.51 g, 1.2 eq) was added and the white suspension was heated to 145 °C. The reaction was stirred overnight after which the clear solution was cooled down. BnBr (785 µL, 1.3 eq) and CsF (1.53 g, 2 eq) were added and heated to 110 °C. After 6h, TLC showed complete consumption of the starting material, the reaction was diluted with EtOAc and washed with H_2O (2x), brine (2x). The organic phase was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The compound was purified by flash chromatography (PE/EA 8:1 - 5:1) to yield compound **D3** (1.8 g, 72%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 – 7.78 (m, 3H, Nap), 7.76 (s, 1H, Nap), 7.52 – 7.40 (m, 5H), 7.40 – 7.20 (m, 8H), 5.54 (s, 1H, H-1), 5.05 (d, *J* = 11.1 Hz, 1H, Nap), 4.82 (d, *J* = 11.1 Hz, 1H, Nap), 4.73 (s, 2H, Bn), 4.31 – 4.17 (m, 2H, H-2, H-5), 3.90 (dd, *J* = 9.0, 3.2 Hz, 1H, H-3), 3.59 (t, *J* = 9.3 Hz, 1H, H-4), 2.72 (s, 1H, H-2-OH), 1.33 (d, *J* = 6.2 Hz, 3H, H-6). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.72 (Bn), 135.86 (Nap), 135.86 (SPh), 134.23, 133.42, 131.52, 129.17, 128.77, 128.29, 128.25, 128.12, 128.05, 127.82, 127.48, 126.75, 126.23, 126.10, 126.05, 87.11 (C-1), 80.29 (C-4), 80.23 (C-3), 75.63 (Nap), 72.31 (Bn), 70.23 (C-2), 68.94 (C-5), 18.00 (C-6). HR-MS Calculated for $C_{30}H_{30}O_4S$ $[M+Na]^+$: 509.1757, found: 509.1769. $[\alpha]^{20}_D$ = - 213.9° (c = 1, $CHCl_3$). TLC Rf = 0.5 (PE/EtOAc = 4/1, v/v).

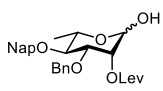
Phenyl 3-*O*-benzyl-2-*O*-levulinoyl-4-*O*-(2-napthylmethyl)-1-thio-α-L-rhamnopyranoside (D2)



The alcohol **D3** (1.8 g, 3.7 mmol, 1 eq) was co-evaporated with anhydrous toluene three times under nitrogen and dissolved in DCM (38 mL). Reduced to 0 °C, levulinic acid (1.2 g, 10.3 mmol, 2.8 eq), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) (1.2 g, 7.47 mmol, 2.0 eq) and 4-dimethylaminopyridine (DMAP) (46 mg, 0.38 mmol, 0.1 eq) were added. The reaction was stirred overnight and EDCI (1.2 g, 7.47 mmol, 2.0 eq) added, After TLC showed complete consumption of the starting material, the reaction was diluted with DCM and washed with H_2O (2x), brine. The organic phase was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The compound was purified by flash chromatography (PE/EA 9:1 - 4:1) to yield compound **D2** (2.15 g, 3.7 mmol, quantitive). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.94 – 7.84 (m, 3H), 7.82 (s, 1H), 7.59 – 7.46 (m, 5H), 7.46 – 7.30 (m, 8H), 5.73 – 5.65 (m, 1H), 5.49 (d, *J* = 1.7 Hz, 1H), 5.15 (d, *J* = 11.1 Hz, 1H), 4.87 (d, *J* = 11.1 Hz, 1H), 4.79 (d, *J* = 11.2 Hz, 1H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.39 – 4.26 (m, 1H),

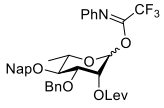
4.01 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.61 (t, *J* = 9.4 Hz, 1H), 2.89 – 2.65 (m, 4H), 2.20 (s, 3H), 1.43 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.29, 172.04, 137.81, 135.88, 133.92, 133.37, 133.07, 131.82, 129.17, 128.52, 128.28, 128.20, 128.00, 127.93, 127.78, 127.72, 126.76, 126.17, 126.13, 125.98, 86.06, 80.16, 78.35, 75.57, 71.77, 70.84, 69.10, 38.05, 29.90, 28.20, 18.05. HR-MS: Calculated for $C_{35}H_{36}O_6S$ $[M+Na]^+$: 607.2145, found: 607.2129. $[\alpha]^{20}_D$ = - 65.7° (c = 1, $CHCl_3$). TLC: Rf = 0.4 (PE/EtOAc = 4/1, v/v).

3-*O*-benzyl-2-*O*-levulinoyl-4-*O*-(2-napthylmethyl)-α/β-L-rhamnopyranoside (D1)



The compound **D2** (7.58 g, 15.58 mmol, 1 eq) was dissolved in DCM (160 mL) and reduced to 0 °C. NIS (5.3 g, 1.5 eq) and TFA (1.8 mL, 1.5 eq) were added and the solution stirred for 1 hour. After analysis by TLC showed complete consumption of the starting material, the reaction was quenched with triethyl amine and saturated aqueous sodium thiosulphate. The solution was diluted with DCM and washed with brine (3x). The organic phase was dried with $MgSO_4$, filtered, and concentrated in *vacuo*. The compound was purified by flash chromatography (PE/EA 4:1 - 1:1) to yield compound **D1** (7.52 g, 15.27 mmol, 98%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 – 7.75 (m, 3H, Nap), 7.74 (s, 1H, Nap), 7.52 – 7.38 (m, 3H, Nap), 7.37 – 7.21 (m, 5H, Bn), 5.43 – 5.36 (m, 1H, H-2), 5.16 – 5.10 (m, 1H, H-1), 5.06 (d, *J* = 11.1 Hz, 1H, CH_2), 4.82 – 4.66 (m, 2H, CH_2), 4.58 – 4.46 (m, 1H, CH_2), 4.08 – 3.95 (m, 2H, H-3, H-5), 3.53 – 3.36 (m, 1H, H-4), 2.97 – 2.56 (m, 4H, Lev), 2.15 (s, 3H, Lev), 1.32 (d, *J* = 6.2 Hz, 3H, H-6). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.63 (Lev), 172.19 (Lev), 138.05, 135.89, 133.28, 132.97, 128.36, 128.08, 128.07, 127.91, 127.69, 126.66, 126.08, 126.05, 125.86, 92.30 (C-1), 79.98 (C-4), 77.48 (C-3), 75.36, 71.60, 69.53 (C-2), 67.68 (C-5), 38.04 (Lev), 29.81 (Lev), 28.15 (Lev), 18.13 (C-6). HR-MS: Calculated for $C_{29}H_{32}O_7$ $[M+Na]^+$: 515.2040, found: 515.2047. TLC: Rf = 0.2 (PE/EtOAc = 2/1, v/v).

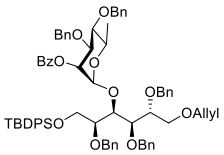
***N*-Phenyl-trifluoroacetimidate 3-*O*-benzyl-4-*O*-(2-napthylmethyl)-2-*O*-levulinoyl-α/β-L-rhamnopyranoside (D)**



Hemiacetal **D1** (720 mg, 1.46 mmol, 1.0 eq) was dissolved in Acetone (14 mL) and cooled to 0 °C. Cesium carbonate (476 mg, 1.5 mmol, 1.05 eq) was added. After 15 min, N-phenyl trifluoroacetimidoyl chloride (455 mg, 2.2 mmol, 1.5 eq) was added, and then it was allowed to stir for overnight at RT. After analysis by TLC showed complete consumption of the starting material, quenched by Et_3N, filtered and concentrated *in vacuo*, and the product purified by column chromatography (PE/EA 10:1 - 5/1) to yield building block **D** (915 mg, 1.38 mmol, 94%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 – 7.77 (m, 3H, Nap), 7.75 (d, *J* = 1.6 Hz, 1H, Nap), 7.53 – 7.40 (m, 3H, Nap), 7.40 – 7.26 (m, 7H), 7.16 – 7.06 (m, 1H), 6.86 – 6.76 (m, 2H), 6.15 (s, 1H, H-1), 5.49 (s, 1H, H-2), 5.08 (d, *J* = 11.0 Hz, 1H, CH_2), 4.88 – 4.70 (m, 2H, CH_2), 4.60 (d, *J* = 11.1 Hz, 1H, CH_2), 4.01 (dd, *J* = 9.4, 3.4 Hz, 1H, H-3), 3.97 – 3.84 (m, 1H, H-5), 3.54 (t, *J* = 9.5 Hz, 1H, H-4), 2.84 – 2.63 (m, 4H, Lev), 2.16 (s, 3H, Lev), 1.38 (d, *J* = 6.2 Hz, 3H, H-6). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.18 (Lev), 171.92 (Lev), 143.40, 137.73, 135.67, 133.41, 133.16, 128.87, 128.57, 128.40, 128.32, 128.05, 127.83, 126.97, 126.25, 126.21, 126.10, 124.55, 119.53, 94.15 (C-1), 79.30 (C-4), 77.50 (C-3), 75.76 (CH_2), 72.17 (CH_2), 70.57 (C-5), 67.90 (C-2), 38.07 (Lev), 29.93 (Lev), 28.13 (Lev), 18.20 (C-6). HR-MS: Calculated for $C_{37}H_{36}F_3NO_7$ $[M+Na]^+$:

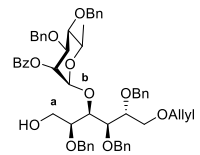
686.2336, found: 686.2377. TLC: Rf = 0.20 (PE/EtOAc = 9/1, v/v).

6-Allyl-3-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-2,4,5-tri-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-D-glucitol (14)



Donor **C** (6.63 g, 10.7 mmol, 2 eq) and acceptor **A** (3.91 g, 5.35 mmol, 1.0 eq) were co-evaporated with anhydrous toluene three times under nitrogen. Dry DCM (54 mL) and 4Å molecular sieves were added and the solution stirred for 20 minutes at RT. The reaction was then cooled to 0 °C and *tert* - butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (123 µL, 0.53 mmol, 0.1 eq) was added. The solution was stirred for 2 hours. After TLC showed complete consumption of the starting material, the reaction was quenched with saturated aqueous sodium bicarbonate and diluted with DCM. The solution was washed with water (2x) and brine. The aqueous layer was extracted with DCM (3x), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The compound was purified by flash chromatography (PE/EA 40:1 - 25:1) to yield compound **14** (6.0 g, 5.2 mmol, 97%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.08 – 7.99 (m, 2H, Bz), 7.67 – 7.59 (m, 4H), 7.59 – 7.53 (m, 1H, Bz), 7.44 (t, *J* = 7.8 Hz, 2H, Bz), 7.39 – 7.10 (m, 31H), 5.92 – 5.77 (m, 1H, OCH_2CHCH_2), 5.74 – 5.66 (m, 1H, H-2b), 5.27 – 5.17 (m, 2H, H-1b, OCH_2CHCH_2), 5.13 – 5.04 (m, 1H, OCH_2CHCH_2), 4.86 (d, *J* = 11.0 Hz, 1H, C*H*H), 4.75 – 4.49 (m, 7H, C*H*H), 4.46 (d, *J* = 11.5 Hz, 1H, C*H*H), 4.41 (d, *J* = 11.3 Hz, 1H, C*H*H), 4.26 – 4.17 (m, 1H, H-3a), 4.10 – 4.02 (m, 1H, H-5b), 4.02 – 3.86 (m, 5H, H-3b, OCH_2CHCH_2, 1a, 2a), 3.86 – 3.81 (m, 1H, H-5a), 3.81 – 3.74 (m, 2H, H-6a, 4a), 3.74 – 3.67 (m, 1H, H-1a), 3.67 – 3.60 (m, 1H, H-6a), 3.49 (t, *J* = 9.4 Hz, 1H, H-4b), 1.23 (d, *J* = 6.1 Hz, 3H, H-6b), 0.99 (s, 9H, TBDPS). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.48 (Bz), 139.00, 138.87, 138.62, 138.52, 138.31, 135.82, 135.15 (OCH2*C*HCH2), 133.46, 133.20, 133.06, 130.36, 130.04, 129.77, 129.75, 128.41, 128.31, 128.30, 128.28, 128.27, 128.18, 128.08, 127.81, 127.77, 127.67, 127.64, 127.56, 127.40, 127.38, 127.34, 116.55, 99.07 (C-1b), 80.46 (C-4a), 80.14 (C-4b), 79.74 (C-5a), 78.37 (C-2a), 78.27 (C-3b), 77.50 (C-3a), 75.22, 73.70, 72.79, 72.29, 72.25, 71.50, 70.23 (C-6a), 69.77 (C-2b), 68.48 (C-5b), 63.31 (C-1a), 26.95 (TBDPS), 19.26 (TBDPS), 18.29 (C-6b). HR-MS: Calculated for $C_{73}H_{80}O_{11}Si[M+Na]^+$: 1183.5362, found: 1183.5402. $[\alpha]^{20}_D$ = + 11.9 (c = 1, $CHCl_3$). TLC: Rf = 0.40 (PE/EtOAc = 20/1, v/v).

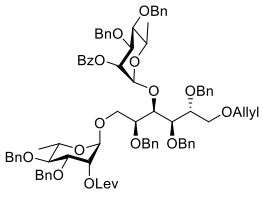
6-Allyl-3-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-2,4,5-tri-*O*-benzyl-D-glucitol (15)



Protected disaccharide **14** (6.14 g, 5.29 mmol, 1.0 eq) was dissolved in THF (110 mL) and cooled to 0 °C. Tetrabutylammonium fluoride hydrate (TBAF) (1.0 M in THF) (10 mL, 10 mmol, 2 eq) was added. The solution was stirred for overnight. After TLC showed complete consumption of the starting material, the reaction was quenched with saturated aqueous ammonium chloride and diluted with EtOAc. The solution was washed with water (2x) and brine. The aqueous layer was extracted with EtOAc (3x), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The compound was purified by flash chromatography (PE/EA 10:1 - 4:1) to yield compound **15** (4.5 g, 4.9 mmol, 93%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.06 (d, *J* = 7.2 Hz, 2H, Bz), 7.60 – 7.52 (m, 1H, Bz), 7.44 (t, *J* = 7.7 Hz, 2H, Bz), 7.39 – 7.13 (m, 25H, Bn), 5.94 – 5.79 (m, 1H, OCH_2CHCH_2), 5.72 – 5.60 (m, 1H, H-2b), 5.24 (dd, *J* = 17.2, 1.8 Hz, 1H,

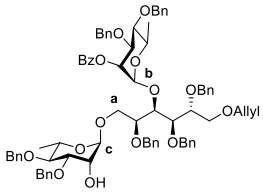
OCH_2CHCH_2), 5.18 – 5.07 (m, 2H, H-1b, OCH_2CHCH_2), 4.90 (d, *J* = 11.0 Hz, 1H, C*H*H), 4.79 – 4.65 (m, 4H, C*H*H), 4.65 – 4.56 (m, 3H, C*H*H), 4.56 – 4.45 (m, 2H, C*H*H), 4.11 (dd, *J* = 7.4, 3.3 Hz, 1H, H-3a), 4.08 – 3.72 (m, 9H), 3.72 – 3.64 (m, 2H, H-1a, 6a), 3.56 – 3.52 (m, 2H, H-1a, 4b) 1.27 (d, *J* = 6.2 Hz, 3H, H-6b). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.70 (Bz), 138.67, 138.64, 138.16, 138.13, 138.11, 134.90 (OCH2*C*HCH2), 133.18, 130.10, 129.97, 128.53, 128.42, 128.34, 128.32, 128.30, 128.08, 128.06, 128.03, 127.92, 127.81, 127.76, 127.72, 127.61, 127.53, 116.80 (OCH2CH*C*H2), 99.42 (C-1b), 80.07 (C-2a), 80.02 (C-4b), 79.28 (C-5a), 78.00 (C-4a), 77.96 (C-3b), 77.85 (C-3a), 75.25 (CH_2), 73.49 (Bn), 72.96 (CH_2), 72.46 (CH_2), 72.30 (O*C*H2CHCH2), 71.55 (CH_2), 69.88 (C-2b), 69.86 (C-6a), 68.58 (C-5b), 61.59 (C-1a), 18.22 (C-6b). HR-MS: Calculated for $C_{57}H_{62}O_{11}$ $[M+Na]^+$: 945.4184, found: 945.4222. $[\alpha]^{20}_D$ = + 3.3º (c = 1, $CHCl_3$). TLC: Rf = 0.25 (PE/EtOAc = 4/1, v/v).

6-Allyl-3-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-2,4,5-tri-*O*-benzyl-1-*O*-(2-*O*-levulinoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-D-glucitol (16)



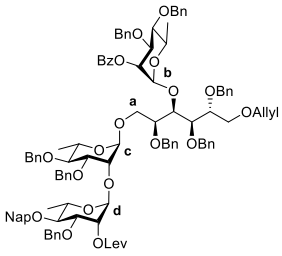
Donor **B** (5.36 g, 8.73 mmol, 1.8 eq) and acceptor **15** (4.38 g, 4.75 mmol, 1.0 eq) were co-evaporated with anhydrous toluene three times under nitrogen. Dry DCM (50 mL) and 4Å molecular sieves were added and the solution stirred for 20 minutes at RT. The reaction was then cooled to 0 ºC and *tert* - butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (110 µL, 0.47 mmol, 0.1 eq) was added. The solution was stirred for 2 hours. After TLC showed complete consumption of the starting material, the reaction was quenched with saturated aqueous sodium bicarbonate and diluted with DCM. The solution was washed with water (2x) and brine. The aqueous layer was extracted with DCM (3x), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The compound was purified by flash chromatography (PE/EA 7:1 - 5:1) to yield compound **16** (5.0 g, 3.71 mmol, 79%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.07 – 8.01 (m, 2H, Bz), 7.59 – 7.52 (m, 1H, Bz), 7.43 (t, *J* = 7.8 Hz, 2H, Bz), 7.36 – 7.10 (m, 35H), 5.93 – 5.77 (m, 1H, OCH_2CHCH_2), 5.67 – 5.59 (m, 1H, H-2b), 5.38 – 5.30 (m, 1H, H-2c), 5.22 (dd, *J* = 17.2, 1.7 Hz, 1H, OCH_2CHCH_2), 5.14 – 5.06 (m, 2H, H-1b, OCH_2CHCH_2), 4.88 (d, *J* = 11.1 Hz, 2H, CH_2), 4.77 – 4.52 (m, 12H, H-1c, CH_2), 4.49 (d, *J* = 11.4 Hz, 1H, CH_2), 4.38 (d, *J* = 11.2 Hz, 1H, CH_2), 4.06 – 3.96 (m, 3H, H-5b, 3a, 3b), 3.96 – 3.88 (m, 2H, OCH_2CHCH_2), 3.88 – 3.55 (m, 9H,), 3.50 (t, *J* = 9.4 Hz, 1H, H-4b), 3.35 (t, *J* = 9.4 Hz, 1H, H-4c), 2.73 – 2.58 (m, 4H, Lev), 2.12 (s, 3H, Lev), 1.26 – 1.18 (m, 6H, H-6b, 6c). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.37 (Lev), 171.90 (Lev), 165.63 (Bz), 138.84, 138.76, 138.41, 138.24, 138.22, 138.20, 135.03 (OCH_2CHCH_2), 133.12, 130.26, 130.03, 128.45, 128.42, 128.37, 128.34, 128.33, 128.19, 128.17, 128.12, 128.08, 127.91, 127.71, 127.67, 127.65, 127.62, 127.59, 127.49, 116.76 (OCH_2CHCH_2), 98.96 (C-1b), 97.64 (C-1c), 80.07 (C-4b), 80.02 (C-4c), 79.40, 78.44, 78.06, 77.97, 77.93, 77.44 (C-3a), 75.28, 75.22, 73.57, 73.45, 72.37, 72.31 (OCH_2CHCH_2), 71.57, 69.86 (C-2b), 69.78 (C-6a), 69.04 (C-2c), 68.61 (C-5b), 67.91 (C-5c), 67.52 (C-1a), 38.19 (Lev), 29.93 (Lev), 28.27 (Lev), 18.26, 18.14. HR-MS: Calculated for $C_{82}H_{90}O_{17}$ $[M+Na]^+$: 1369.6070, found: 1369.6078. $[\alpha]^{20}_D$ = - 2.6º (c = 1, $CHCl_3$). TLC: Rf = 0.25 (PE/EtOAc = 4/1, v/v).

6-Allyl-3-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-2,4,5-tri-*O*-benzyl-1-*O*-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-D-glucitol (17)



Trimer **16** (1.53 g, 1.14 mmol, 1.0 eq) was dissolved in pyridine (9 mL) and acetic acid (2.5 mL). After cooled to 0 °C, hydrazine hydrate (N_2H_4 50-60 %) (138 µL, 2.8 mmol, 2.5 eq) was added slowly. After stirred 20 min at RT, checked by TLC complete consumption of the starting material, quenched by acetone. The solution was washed with water (2x) and brine. The aqueous layer was extracted with EtOAc (3x), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The compound was purified by flash chromatography (PE/EA 6:1 - 3:1) to yield compound **17** (1.38 g, 1.1 mmol, 97%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.09 – 8.01 (m, 2H, Bz), 7.58 – 7.49 (m, 1H, Bz), 7.42 (t, *J* = 7.8 Hz, 2H, Bz), 7.36 – 7.14 (m, 35H, Bn), 5.92 – 5.78 (m, 1H, OCH_2CHCH_2), 5.65 (dd, *J* = 3.2, 1.9 Hz, 1H, H-2b), 5.26 – 5.18 (m, 1H, OCH_2CHCH_2), 5.14 – 5.06 (m, 2H, H-1b, OCH_2CHCH_2), 4.93 – 4.83 (m, 2H, CH_2), 4.81 – 4.47 (m, 12H, CH_2, H-1c), 4.15 – 3.99 (m, 3H, H-3a, 3b, 5b), 3.99 – 3.95 (m, 1H, H-2c), 3.95 – 3.89 (m, 2H, OCH_2CHCH_2), 3.89 – 3.81 (m, 3H), 3.81 – 3.61 (m, 6H), 3.53 (t, *J* = 9.4 Hz, 1H, H-4b), 3.44 (t, *J* = 9.3 Hz, 1H, H-4c), 2.52 (s, 1H, 2c-OH), 1.32 – 1.19 (m, 6H, H-6b, 6c). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.72 (OBz), 138.79, 138.70, 138.65, 138.40, 138.14, 138.10, 138.02, 134.95 (OCH_2CHCH_2), 133.17, 130.08, 129.94, 128.48, 128.42, 128.39, 128.34, 128.31, 128.30, 128.27, 128.06, 128.05, 128.00, 127.89, 127.86, 127.84, 127.83, 127.63, 127.59, 127.58, 127.54, 127.41, 116.68 (OCH_2CHCH_2), 99.38 (C-1c), 98.88 (C-1b), 80.04 (C-4b), 79.93 (C-4c), 79.82 (C-3c), 79.35, 78.36, 77.96, 77.92, 77.44 (C-3a), 75.22, 75.18, 73.62, 73.08, 72.23, 72.22 (OCH_2CHCH_2), 71.85, 71.54, 69.91 (C-2b), 69.69 (C-6a), 68.55 (C-5b), 68.42 (C-2c), 67.65 (C-5c), 67.07 (C-1a), 18.23, 18.03. HR-MS: Calculated for $C_{77}H_{84}O_{15}$ $[M+Na]^+$: 1271.5702, found: 1271.5729. $[\alpha]^{20}_D$ = - 8.7 (c = 1, $CHCl_3$). TLC: Rf = 0.40 (Tol/EtOAc = 7/1, v/v).

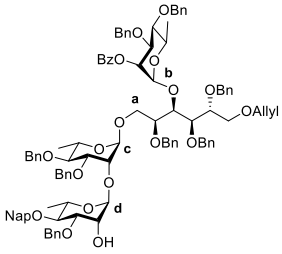
6-Allyl-3-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-2,4,5-tri-*O*-benzyl-1-*O*-(3,4-di-*O*-benzyl-2-*O*-(3-*O*-benzyl-2-*O*-levulinoyl-4-*O*-(2-napthylmethyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranosyl)-D-glucitol (18)



Donor **D** (5.05 g, 7.6 mmol, 2.2 eq) and acceptor **17** (4.28 g, 3.43 mmol, 1.0 eq) were co-evaporated with anhydrous toluene three times under nitrogen. Dry DCM (34 mL) and 4Å molecular sieves were added and the solution stirred for 20 minutes at RT. The reaction was then cooled to 0 °C and *tert* -butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (79 µL, 0.34 mmol, 0.1 eq) was added. The solution was stirred for 7 hours. After TLC showed complete consumption of the starting material, the reaction was quenched with saturated aqueous sodium bicarbonate and diluted with DCM. The solution was washed with water (2x) and brine. The aqueous layer was extracted with DCM (3x), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The compound was purified by flash chromatography (PE/EA 25:1 - 10:1) to yield compound **18** (4.23 g, 2.46 mmol, 71%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.08 – 7.99 (m, 2H, Bz), 7.85 – 7.75 (m, 3H, Nap), 7.73 (s, 1H, Nap), 7.57 – 7.50 (m, 1H, Bz), 7.48 – 7.09 (m, 45H), 5.90 – 5.78 (m, 1H, OCH_2CHCH_2), 5.67 (dd, *J* = 3.2, 1.9 Hz, 1H, H-2b), 5.54

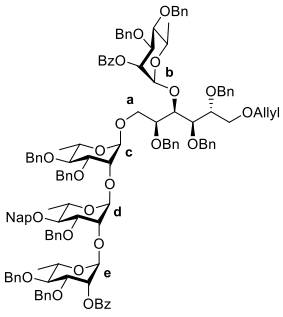
(dd, *J* = 3.3, 1.9 Hz, 1H, H-2d), 5.26 – 5.17 (m, 1H, OCH_2CHCH_2), 5.12 (d, *J* = 1.8 Hz, 1H, H-1b), 5.11 – 5.06 (m, 1H, OCH_2CHCH_2), 5.04 (d, *J* = 11.1 Hz, 1H, CH_2), 4.98 (d, *J* = 1.8 Hz, 1H, H-1d), 4.88 (d, *J* = 11.1 Hz, 2H, CH_2), 4.79 – 4.44 (m, 16H, CH_2, H-1c), 4.09 – 3.95 (m, 5H), 3.93 – 3.88 (m, 2H, OCH_2CHCH_2), 3.88 – 3.73 (m, 6H), 3.73 – 3.60 (m, 3H, H-1a, 5c, 6a), 3.56 (dd, *J* = 11.0, 3.0 Hz, 1H, H-1a), 3.51 (t, *J* = 9.4 Hz, 1H, H-4b), 3.46 – 3.33 (m, 2H, H-4d, 4c), 2.75 – 2.58 (m, 4H, Lev), 2.12 (s, 3H, Lev), 1.34 – 1.15 (m, 9H, 6b, 6c, 6d). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.26 (Lev), 171.80 (Lev), 165.53 (Bz), 138.86, 138.82, 138.70, 138.45, 138.36, 138.25, 138.18, 138.15, 136.05, 134.99, 133.38, 133.11, 133.05, 130.18, 129.99, 128.43, 128.40, 128.39, 128.32, 128.30, 128.26, 128.16, 128.12, 128.09, 128.07, 128.01, 127.97, 127.89, 127.75, 127.72, 127.68, 127.63, 127.60, 127.52, 127.44, 126.73, 126.20, 126.10, 125.91, 116.70 (OCH_2CHCH_2), 99.22 (C-1d), 99.00 (C-1b), 98.93 (C-1c), 80.08, 80.04, 79.60, 79.34, 78.49, 78.08, 78.04, 77.75, 77.44, 75.46, 75.27, 75.11, 74.77 (C-5d), 73.58, 73.33, 72.28, 72.25, 71.95, 71.68, 71.55, 69.77 (C-2b), 69.76 (C-6a), 69.23 (C-2d), 68.58, 68.26, 68.18, 67.15 (C-1a), 38.19 (Lev), 29.92 (Lev), 28.30 (Lev), 18.27, 18.16. HR-MS: Calculated for $C_{106}H_{114}O_{21}$ $[M+Na]^+$: 1745.7745, found: 1745.7706. $[\alpha]^{20}_D$ = - 0.6 (c = 1, $CHCl_3$). TLC: Rf = 0.30 (PE/EtOAc = 4/1, v/v).

6-Allyl-3-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-2,4,5-tri-*O*-benzyl-1-*O*-(3,4-di-*O*-benzyl-2-*O*-(3-*O*-benzyl-4-*O*-(2-napthylmethyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranosyl)-D-glucitol (19)



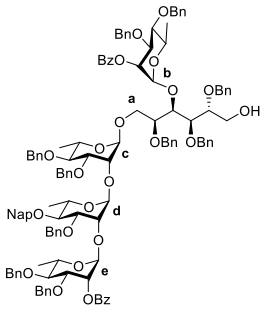
Tetramer **18** (1.22 g, 0.71 mmol, 1.0 eq) was dissolved in pyridine (6 mL) and acetic acid (1.5 mL). After cooled to 0 °C, hydrazine hydrate (N_2H_4 50-60 %) (70 µL, 1.4 mmol, 2.0 eq) was added slowly. After stirred 20 min at RT, checked by TLC complete consumption of the starting material, quenched by acetone. The solution was washed with water (2x) and brine. The aqueous layer was extracted with EtOAc (3x), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The compound was purified by flash chromatography (PE/EA 5:1 - 3:1) to yield compound **19** (1.07 g, 0.66 mmol, 93%). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.04 (d, J = 7.7 Hz, 2H, Bz), 7.86 – 7.76 (m, 3H, Nap), 7.75 (s, 1H, Nap), 7.53 (t, J = 7.4 Hz, 1H, Bz), 7.49 – 7.08 (m, 45H), 5.90 – 5.76 (m, 1H, OCH_2CHCH_2), 5.67 (s, 1H, H-2b), 5.21 (d, J = 17.3 Hz, 1H, OCH_2CHCH_2), 5.15 – 5.04 (m, 3H, OCH_2CHCH_2, H-1b, 1d), 5.01 (d, J = 11.1 Hz, 1H, CH_2), 4.92 – 4.81 (m, 2H), 4.81 – 4.41 (m, 16H, CH_2, H-1c), 4.13 (s, 1H, H-2d), 4.09 – 3.95 (m, 4H), 3.95 – 3.73 (m, 9H), 3.73 – 3.60 (m, 3H), 3.56 (dd, J = 11.1, 3.0 Hz, 1H, H-1a), 3.50 (t, J = 9.4 Hz, 2H, H-4b, 4d), 3.36 (t, J = 9.4 Hz, 1H, H-4c), 2.44 (s, 1H, 2d-OH), 1.33 – 1.14 (m, 9H, H-6b, 6c, 6d). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.55 (Bz), 138.90, 138.83, 138.72, 138.38, 138.35, 138.19, 138.17, 138.14, 136.03, 135.00, 133.40, 133.12, 133.08, 130.19, 130.01, 128.62, 128.46, 128.45, 128.43, 128.41, 128.34, 128.32, 128.20, 128.18, 128.11, 128.09, 128.04, 128.01, 127.90, 127.85, 127.83, 127.77, 127.70, 127.65, 127.61, 127.54, 127.45, 126.67, 126.14, 126.12, 125.95, 116.73 (OCH2CHCH2), 100.82 (C-1d), 99.08 (C-1c), 99.06 (C-1b), 80.34, 80.26, 80.06, 79.69, 79.65, 79.35, 78.55, 78.09, 78.06, 77.49 (C-1a), 75.49, 75.29, 75.10, 74.77 (C-5d), 73.59, 73.37, 72.30, 72.26, 72.21, 72.14, 71.57, 69.78 (C-2b), 69.76 (C-6a), 68.85 (C-2d), 68.60 (C-2c), 68.18 (C-5c), 68.01 (C-5b), 67.20 (C-1a), 18.28, 18.21, 18.08. HR-MS: Calculated for $C_{101}H_{108}O_{19}$ $[M+Na]^+$: 1647.7377, found: 1647.7346. $[\alpha]^{20}_D$ = - 4.5 (c = 1, $CHCl_3$).TLC: Rf = 0.30 (PE/EtOAc = 4/1, v/v).

6-Allyl-3-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-2,4,5-tri-*O*-benzyl-1-*O*-(3,4-di-*O*-benzyl-2-*O*-(2-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-3-*O*-benzyl-4-*O*-(2-napthylmethyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranosyl)-D-glucitol (7)



Donor **C** (1.3 g, 2.1 mmol, 3.0 eq) and acceptor **19** (1.14 g, 0.7 mmol, 1.0 eq) were co-evaporated with anhydrous toluene three times under nitrogen. Dry DCM (7 mL) and 4Å molecular sieves were added and the solution stirred for 20 minutes at RT. The reaction was then cooled to 0 °C and TBSOTf (19 µL, 0.07 mmol, 0.1 eq) was added. The solution was stirred for 2 hours. After TLC showed complete consumption of the starting material, the reaction was quenched with saturated aqueous $NaHCO_3$ and diluted with DCM. The solution was washed with water (2x), brine and extracted with DCM (3x), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The compound was purified by flash chromatography (PE/EA 10:1 - 5:1) to yield compound **7** (1.25 g, 0.61 mmol, 87%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.13 (d, *J* = 8.0 Hz, 2H, Bz), 8.06 (d, *J* = 7.7 Hz, 2H, Bz), 7.86 – 7.76 (m, 4H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.53 – 7.05 (m, 57H), 7.01 (t, *J* = 7.5 Hz, 1H), 5.92 – 5.75 (m, 2H), 5.74 – 5.64 (m, 1H), 5.29 – 5.00 (m, 6H), 4.98 – 4.37 (m, 24H), 4.21 – 4.14 (m, 1H, H-4d), 4.14 – 4.08 (m, 1H), 4.08 – 3.99 (m, 4H), 3.99 – 3.88 (m, 4H), 3.88 – 3.73 (m, 7H), 3.73 – 3.61 (m, 3H), 3.61 – 3.46 (m, 4H), 3.40 – 3.30 (m, 1H), 1.35 – 1.15 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.61, 165.50, 138.84, 138.80, 138.70, 138.55, 138.49, 138.34, 138.23, 138.20, 138.16, 138.13, 136.10, 134.98, 133.40, 133.18, 133.08, 133.03, 130.26, 130.16, 130.01, 129.97, 128.47, 128.44, 128.40, 128.38, 128.36, 128.31, 128.28, 128.19, 128.17, 128.15, 128.12, 128.06, 127.97, 127.94, 127.91, 127.88, 127.84, 127.75, 127.71, 127.63, 127.59, 127.57, 127.49, 127.43, 126.82, 126.27, 126.05, 125.86, 116.67, 100.43, 99.25, 99.07, 99.01, 80.31, 80.26, 80.02, 79.44, 79.34, 78.54, 78.06, 77.94, 77.45, 75.45, 75.37, 75.24, 75.22, 75.09, 74.53, 73.56, 73.40, 72.29, 72.22, 72.05, 71.62, 71.54, 69.80, 69.74, 69.55, 68.55, 68.53, 68.39, 68.22, 67.15, 18.25, 18.23, 18.17. HR-MS Calculated for $C_{128}H_{134}O_{24}$ $[M+H]^+$: 2055.9338, found: 2055.9336. $[\alpha]^{20}_D$ = + 0.6 (c = 1, $CHCl_3$). TLC Rf = 0.50 (PE/EtOAc = 4/1, v/v).

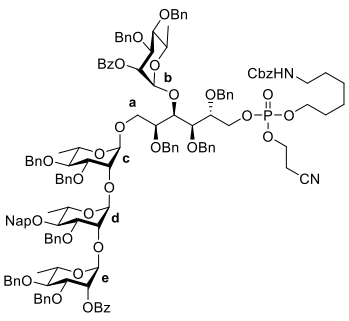
3-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-2,4,5-tri-*O*-benzyl-1-*O*-(3,4-di-*O*-benzyl-2-*O*-(2-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-3-*O*-benzyl-4-*O*-(2-napthylmethyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranosyl)-D-glucitol (20)



Allyl protected **7** (637 mg, 0.31 mmol, 1.0 eq) was dissolved in freshly distilled THF (6 ml). The mixture was degassed and placed under an argon atmosphere. (1,5-Cyclooctadiene) (pyridine)-(tricyclohexylphosphine)-iridium(I) hexafluorophosphate ($Ir(COD)(Ph_2MeP)_2 \cdot PF_6$) (17 mg, 0.02 mmol, 0.05 eq) was added and the reaction mixture was purged with H_2 for 5 seconds. The reaction mixture was stirred for 1 hour under an argon atmosphere. After analysis by TLC showed complete consumption of the starting material, diluted with THF (2 ml) and NIS (105 mg, 0.47 mmol, 1.5 eq), and water were added, and the solution stirred for 1 hours at room temperature. EtOAc was added and the organic layer was washed two times with saturated

aqueous sodium thiosulphate and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (PE/EA 5:1 - 3:1) yielded **20** (563 mg, 0.28 mmol, 90%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.16 – 8.10 (m, 2H), 8.10 – 8.03 (m, 2H), 7.84 – 7.75 (m, 4H), 7.61 – 7.35 (m, 11H), 7.35 – 7.08 (m, 47H), 7.01 (t, *J* = 7.4 Hz, 1H), 5.84 – 5.76 (m, 1H), 5.74 – 5.67 (m, 1H), 5.19 – 5.09 (m, 3H), 5.06 (d, *J* = 11.1 Hz, 1H), 4.95 – 4.84 (m, 3H), 4.84 – 4.78 (m, 2H), 4.78 – 4.48 (m, 18H), 4.38 (d, *J* = 11.7 Hz, 1H), 4.20 – 3.99 (m, 7H), 3.99 – 3.88 (m, 2H), 3.87 – 3.77 (m, 6H), 3.77 – 3.62 (m, 5H), 3.60 – 3.47 (m, 4H), 3.36 (t, *J* = 9.4 Hz, 1H), 1.33 – 1.17 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.60, 165.55, 138.70, 138.56, 138.52, 138.45, 138.24, 138.19, 138.14, 138.10, 137.97, 136.04, 133.39, 133.17, 133.11, 133.03, 130.25, 130.14, 129.98, 129.95, 128.49, 128.46, 128.44, 128.41, 128.37, 128.35, 128.32, 128.31, 128.24, 128.20, 128.17, 128.15, 128.12, 128.07, 128.04, 127.93, 127.87, 127.82, 127.78, 127.76, 127.70, 127.69, 127.65, 127.64, 127.60, 127.55, 126.84, 126.27, 126.05, 125.86, 100.48 (C-1d), 99.24 (C-1b, 1e), 99.12 (C-1c), 80.32, 80.25, 80.23, 79.99, 79.66, 79.34, 79.11, 78.57, 77.90, 77.81, 77.38, 75.44, 75.37, 75.27, 75.24, 74.42, 73.89, 73.43, 72.19, 71.88, 71.84, 71.60, 71.56, 69.79 (C-2b), 69.56 (C-2e), 68.57, 68.53, 68.39, 68.16, 66.77 (C-1a), 60.39 (C-6a), 18.29, 18.22, 18.18. HR-MS: Calculated for $C_{125}H_{130}O_{24}$ $[M+H]^+$: 2015.9025, found: 2015.9010. $[\alpha]^{20}_D$ = + 3.8 (c = 1, $CHCl_3$). TLC: Rf = 0.40 (PE/EtOAc = 3/1, v/v).

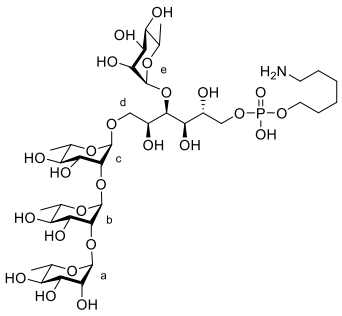
3-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-2,4,5-tri-*O*-benzyl-1-*O*-(3,4-di-*O*-benzyl-2-*O*-(2-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-3-*O*-benzyl-4-*O*-(2-napthylmethyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranosyl)-D-glucitol-*N*-benzyloxycarbonyl-6-aminohexanol-cyanoethyl phosphonate (22)



Alcohol **20** (238 mg, 0.12 mmol, 1.0 eq) was co-evaporated with dry acetonitrile 3 times. Dissolved in dry acetonitrile (4 ml), 4,5-dicyanoimidazole (DCI, 0.25M in acetonitrile) (0.94 mL, 0.24 mmol, 2.0 eq) and 3Å molecular sieves were added. The mixture was stirred for 15 mins under argon atmosphere. Benzyl 6-([*N*,*N*-diisopropylamino]-2-cyanoethyl-phosphite)-hexyl-1-carbamate (0.16M in acetonitrile) (1.5 mL, 0.24 mmol, 2.0 eq) was added. The reaction mixture was stirred for 1 hour. After analysis by TLC showed complete consumption of the starting material, (10-Camphorsulfonyl)-oxaziridine (CSO, 0.5M in acetonitrile) (0.71 mL, 0.36 mmol, 3.0 eq) was added. Stirred another 15 mins and diluted with EtOAc. The solution was washed with saturated aqueous sodium bicarbonate and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (DCM/Acetone 100:1 - 30:1) yielded **22** (252 mg, 0.11 mmol, 90%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.17 – 8.10 (m, 2H), 8.10 – 8.03 (m, 2H), 7.84 – 7.75 (m, 4H), 7.60 – 7.53 (m, 1H), 7.53 – 7.44 (m, 4H), 7.44 – 7.08 (m, 58H), 7.07 – 6.98 (m, 1H), 5.87 – 5.77 (m, 1H, H-2e), 5.70 – 5.60 (m, 1H, H-2b), 5.21 – 5.14 (m, 2H, H-1d, 1e), 5.14 – 5.02 (m, 4H, H-1b, CH_2), 4.95 – 4.84 (m, 4H, CH_2), 4.84 – 4.40 (m, 22H, H-1c, 6a, CH_2), 4.33 – 4.21 (m, 1H, H-6a), 4.21 – 4.15 (m, 1H, H-2d), 4.15 – 4.08 (m, 1H, H-3e), 4.08 – 3.77 (m, 16H), 3.77 – 3.48 (m, 6H, H-1a, 5c, 4b, 4d, 4e), 3.38 (t, *J* = 9.3 Hz, 1H, H-4c), 3.14 – 3.01 (m, 2H, CH_2NHCbz), 2.36 – 2.05 (m, 2H, OCH$_2$CH_2CN), 1.64 – 1.44 (m, 2H), 1.44 – 1.09 (m, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.51, 165.43, 156.35,

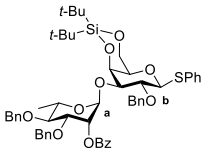
138.65, 138.44, 138.42, 138.40, 138.36, 138.09, 138.07, 137.96, 137.91, 137.87, 137.86, 137.81, 137.75, 137.73, 136.71, 135.96, 133.30, 133.10, 132.94, 130.15, 129.95, 129.89, 129.86, 128.45, 128.40, 128.38, 128.35, 128.32, 128.28, 128.25, 128.22, 128.16, 128.13, 128.10, 128.08, 128.06, 128.04, 128.00, 127.97, 127.95, 127.90, 127.83, 127.81, 127.76, 127.73, 127.70, 127.65, 127.61, 127.60, 127.55, 127.52, 127.49, 126.78, 126.21, 125.98, 125.79, 116.62, 116.56 (OCH_2CH_2CN), 100.36 (C-1d), 99.12 (C-1e), 98.97 (C-1c), 98.93, 98.89 (C-1b), 80.21, 80.17, 80.14, 79.88, 79.27, 79.07, 78.57, 78.52, 78.46, 78.41, 78.12, 78.06, 77.89, 77.82, 77.09, 77.01, 76.86, 75.34, 75.28, 75.11, 75.04 (C-2d), 74.41, 74.36, 73.71, 73.42, 73.37, 72.16, 72.12, 72.06, 71.89, 71.53, 71.50, 71.48, 69.64, 69.61, 69.45, 68.63, 68.47, 68.32 (C-5d), 68.18 (C-5c), 68.14, 68.12, 68.09, 66.80 (C-1a), 66.44 (Cbz), 66.34 (C-6a), 61.62, 61.58, 40.77 (CH_2Cbz), 29.97, 29.94, 29.91, 29.89, 29.65, 29.63, 29.25, 26.00, 24.89, 24.87, 19.21, 19.15, 19.09, 19.04, 18.19, 18.16, 18.14, 18.10. ^{31}P NMR (202 MHz, $CDCl_3$) δ -0.22, -0.66. HR-MS: Calculated for $C_{142}H_{153}N_2O_{29}P$ $[M+H]^+$: 2382.0369, found: 2382.0347. TLC: Rf = 0.50 (DCM/Acetone = 20/1, v/v).

3-*O*-(α-L-rhamnosyl)-1-*O*-(2-*O*-(2-*O*-(α-L-rhamnosyl)-α-L-rhamnosyl)-α-L-rhamnosyl)-D-glucitol-6-aminohexanol phosphate (1)



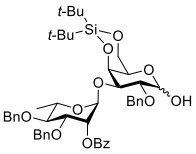
Full protected compound **22** (51.3 mg, 21.5 µmol, 1.0 eq) was dissolved in dioxane (6 mL) and ammonia solution (35%) (3 mL). The mixture was stirred at RT for overnight. After analysis by TLC showed complete consumption of the starting material, co-evaporated with toluene to remove the solvent. The crude was dissolved in methanol (2 mL) and dioxane (1 mL). Sodium methoxide (25 wt. % in methanol) (0.1 mL, 0.44 mmol, 20 eq) was added. The reaction was stirred overnight. After analysis by TLC showed complete consumption of the starting material, quenched with acetic acid and then quenched the excess acid using ammonia solution. Co-evaporated with toluene to remove all the solvent *in vacuo*. The mixture was purified by flash size exclusion (LH-20 column) (DCM/MeOH 1:1). The compound was dissolved in *tert*-butanol (7 mL), water (4 mL) and 4 drops acetic acid. After $Pd(OH)_2$/C (51 mg) was added, the reaction was stirred for 3 days under a H_2 atmosphere, filtered and concentrated *in vacuo*. The compound was purified by gel filtration (HW-40, 0.15M, NH_4OAc in H_2O) with a Shimadzu RID-10A refractive index detector, transformed into its sodium salt by passing a short Dowex Na^+ column and lyophilized to yield compound **2** (16.6 mg, 17.2 µmol, 80%). ^{1}H NMR (500 MHz, Deuterium Oxide) δ 5.141 (d, *J* = 1.8 Hz, 1H), 5.052 (d, *J* = 1.8 Hz, 1H), 4.987 (d, *J* = 1.8 Hz, 1H), 4.902 (d, *J* = 1.7 Hz, 1H), 4.167 – 4.067 (m, 5H), 4.067 – 3.970 (m, 3H), 3.957 – 3.635 (m, 15H), 3.515 – 3.440 (m, 4H), 3.027 – 2.982 (m, 2H), 1.745 – 1.609 (m, 4H), 1.492 – 1.382 (m, 4H), 1.358 – 1.237 (m, 12H). ^{13}C NMR (126 MHz, D_2O) δ 102.26, 101.44, 100.89, 98.84, 72.22, 72.16, 72.06, 71.96, 70.60, 70.48, 70.22, 70.13, 70.10, 70.00, 69.94, 69.87, 69.46, 69.35, 69.32, 69.21, 69.11, 68.85, 66.87, 66.83, 66.21, 66.17, 39.49, 29.53, 29.48, 26.75, 25.17, 24.47, 16.81, 16.77, 16.75, 16.69. ^{31}P NMR (202 MHz, D_2O) δ 1.96. HR-MS: Calculated for $C_{36}H_{68}NO_{25}P$ $[M+Na]^+$: 968.3710, found : 968.3719.

Phenyl 2-*O*-benzyl-4,6-*O*-di-*tert*-butylsilylidene-3-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-1-thio-β-D-galactopyranoside (23)



Donor **C** (4.6 g, 7.5 mmol, 1.4 eq) and acceptor **F** (2.7 g, 5.37 mmol, 1.0 eq) were co-evaporated with anhydrous toluene three times under nitrogen. Dry DCM (54 mL) and 4Å molecular sieves were added and the solution stirred for 20 minutes at RT. The reaction was then cooled to 0 °C and *tert* - butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (123 µL, 0.54 mmol, 0.1 eq) was added. The solution was stirred for 1 hour. After TLC showed complete consumption of the starting material, the reaction was quenched with saturated aqueous sodium bicarbonate and diluted with DCM. The solution was washed with water (2x) and brine. The aqueous layer was extracted with DCM (3x), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by flash chromatography (PE/EA 20:1 - 10:1) to yield compound disaccharide **23** (4.65 g, 4.99 mmol, 93%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.09 – 8.07 (m, 2H, Bz), 7.58 – 7.48 (m, 5H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.36 – 7.14 (m, 16H), 5.77 – 5.70 (m, 1H, H-2a), 5.15 (d, *J* = 1.8 Hz, 1H, H-1a), 4.95 (t, *J* = 11.2 Hz, 2H, C*H*$_2$), 4.81 (d, *J* = 10.0 Hz, 1H, C*H*$_2$), 4.74 (d, *J* = 11.5 Hz, 1H, C*H*$_2$), 4.70 – 4.62 (m, 2H, H-1b, C*H*$_2$), 4.56 (d, *J* = 11.5 Hz, 1H, C*H*$_2$), 4.43 (d, *J* = 3.1 Hz, 1H, H-4b), 4.24 – 4.08 (m, 4H, H-6b, 5a, 3a), 3.84 (t, *J* = 9.5 Hz, 1H, H-2b), 3.64 – 3.52 (m, 2H, H-3b, 4a), 3.30 (s, 1H, H-5b), 1.35 (d, *J* = 6.2 Hz, 3H, H-6a), 1.16 (s, 9H), 1.07 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.54 (Bz), 138.97, 138.02, 137.76, 134.83, 133.19, 132.08, 130.10, 129.95, 128.91, 128.88, 128.84, 128.51, 128.46, 128.40, 128.32, 128.20, 128.15, 128.00, 127.65, 127.45, 127.41, 127.37, 100.29 (C-1a), 88.95 (C-1b), 82.93 (C-3b), 80.03 (C-4a), 77.76 (C-3a), 77.03 (C-2b), 76.17 (*C*H$_2$), 74.73 (*C*H$_2$), 73.16 (C-4b), 71.76 (*C*H$_2$), 69.77 (C-2a), 68.52 (C-5a), 67.22 (C-6b), 27.94, 27.53, 23.52, 20.87, 18.49 (C-6a). HR-MS: Calculated for $C_{54}H_{64}O_{10}SSi$ $[M+Na]^+$: 955.3882, found: 955.3882. $[\alpha]^{20}_D$ = + 37.3 (c = 1, $CHCl_3$). TLC: Rf = 0.30 (PE/EA = 9/1, v/v).

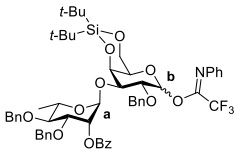
2-*O*-benzyl-4,6-*O*-di-*tert*-butylsilylidene-3-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-α/β-D-galactopyranoside (24)



Compound **23** (2.74 g, 2.94 mmol, 1.0 eq) was dissolved in DCM (30 mL) and reduced to 0 °C. NIS (727 mg, 3.23 mmol, 1.1 eq) and TFA (0.25 mL, 3.23 mmol, 1.1 eq) were added and the solution was stirred for 1 hour. After analysis by TLC showed complete consumption of the starting material, the reaction was quenched with triethyl amine and saturated aqueous sodium thiosulphate. The solution was diluted with DCM and washed with brine (3x). The organic phase was dried with MgSO4, filtered and concentrated in vacuo. The compound was purified by flash chromatography (PE/EA 10:1 - 4:1) to yield compound **24** (2.37 g, 2.82 mmol, 94%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 – 8.04 (m, 2H), 7.62 – 7.54 (m, 1H), 7.51 – 7.41 (m, 2H), 7.41 – 7.13 (m, 15H), 5.76 – 5.64 (m, 1H), 5.14-5.15 (m, 2H), 5.01 – 4.90 (m, 1H), 4.82 – 4.48 (m, 4H), 4.43 (d, *J* = 2.0 Hz, 1H), 4.25 – 4.16 (m, 1H), 4.16 – 4.00 (m, 2H), 3.96 – 3.81 (m, 2H), 3.61 – 3.48 (m, 1H), 3.42 – 3.31 (m, 1H), 3.11 (d, *J* = 2.0 Hz, 1H), 1.37 – 1.29 (m, 3H), 1.10 – 0.93 (m, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.78, 138.98, 138.11, 137.70, 133.26, 130.14, 130.02, 128.70, 128.67, 128.61, 128.52, 128.36, 128.33, 128.26, 128.23, 128.16, 128.12, 127.66, 127.52, 127.44, 127.43, 100.19, 91.92, 80.16, 77.78, 77.70, 74.80, 74.37, 73.75, 73.67, 71.66, 71.62, 69.78, 68.44, 67.47, 67.23,

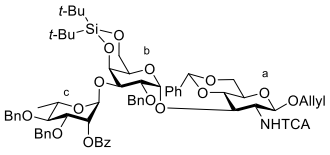
27.56, 27.54, 23.53, 20.84, 18.50. HR-MS: Calculated for $C_{48}H_{60}O_{11}Si$ $[M+K]^+$: 879.3536, found: 879.3521. TLC: Rf = 0.50 (PE/EA = 2/1, v/v).

N-Phenyl-trifluoroacetimidate 2-*O*-benzyl-4,6-*O*-di-*tert*-butylsilylidene-3-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-α/β-D-galactopyranoside (25)



Hemiacetal **24** (3.5 g, 4.16 mmol, 1.0 eq) was dissolved in Acetone (42 mL) and cooled to 0 ℃. Cesium carbonate (1.5 g, 4.6 mmol, 1.1 eq) was added. After 15 min, N-phenyl trifluoroacetimidoyl chloride (1.2 g, 5.78 mmol, 1.3 eq) was added, and then it was allowed to stir for overnight at RT. After analysis by TLC showed complete consumption of the starting material, quenched by Et_3N, filtered and concentrated *in vacuo*, and the product purified by column chromatography (PE/EA 40:1 – 10/1) to yield compound **25** (4.0 g, 3.95 mmol, 95%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.13 – 8.00 (m, 2H, Bz), 7.61 – 7.49 (m, 1H), 7.48 – 7.41 (m, 2H), 7.41 – 7.10 (m, 18H), 7.09 – 7.00 (m, 1H), 6.75 (d, *J* = 7.7 Hz, 2H), 6.41 (s, 1H, H-1b), 5.75 – 5.63 (m, 1H, H-2a), 5.18 (d, *J* = 2.0 Hz, 1H, H-1a), 4.93 (d, *J* = 11.5 Hz, 1H, C*H*$_2$), 4.80 – 4.59 (m, 4H, C*H*$_2$), 4.58 – 4.45 (m, 2H, H-4b, C*H*$_2$), 4.28 – 4.12 (m, 2H, H-6b), 4.12 – 4.00 (m, 3H, H-2b, 3a, 5a), 3.96 (dd, *J* = 10.0, 3.0 Hz, 1H, H-3b), 3.81 (s, 1H, H-5b), 3.57 (t, *J* = 9.3 Hz, 1H, H-4a), 1.34 (d, *J* = 6.3 Hz, 3H, H-5a), 1.04 (s, 9H), 0.98 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.78 (Bz), 143.97, 139.21, 138.35, 137.84, 133.16, 130.57, 130.09, 128.85, 128.69, 128.53, 128.39, 128.28, 128.19, 128.12, 127.68, 127.65, 127.44, 124.35, 119.70, 100.22 (C-1a), 94.89 (C-1b), 80.39 (C-4a), 78.00 (C-3a), 77.11 (C-3b), 74.86 , 73.71, 73.47 (C-2b, 4b), 71.79, 70.24 (C-5b), 69.93 (C-2a), 68.72 (C-5a), 66.92 (C-6b), 27.67, 27.55, 23.56, 20.94, 18.55 (C-6a). HR-MS: Calculated for $C_{56}H_{64}F_3NO_{11}Si$ $[M-[O(C=NPh)CF_3]+OH+Na]^+$: 863.3797, found: 863.3813. TLC: Rf = 0.80 (PE/EA = 4/1, v/v).

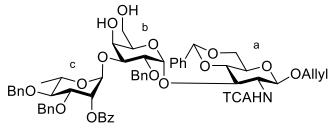
Allyl 4,6-*O*-benzylidene-3-*O*-(2-*O*-benzyl-4,6-*O*-di-tert-butylsilylidene-3-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-α-D-galactopyranosyl)-2-trichloroacetamido-2-deoxy-β-D-glucopyranoside (26)



Donor **25** (4.84 g, 4.79 mmol, 1.5 eq) and acceptor **E** (1.45 g, 3.2 mmol, 1.0 eq) were co-evaporated with anhydrous toluene three times under nitrogen. Dry DCM (32 mL) and 4Å molecular sieves were added and the solution stirred for 20 minutes at RT. The reaction was then cooled to 0 ℃ and *tert* - butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (84 μL, 0.32 mmol, 0.1 eq) was added. The solution was stirred for 1.5 hours. After TLC showed complete consumption of the starting material, the reaction was quenched with saturated aqueous sodium bicarbonate and diluted with DCM. The solution was washed with water (2x) and brine. The aqueous layer was extracted with DCM (3x), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by flash chromatography (PE/EA 10:1 - 5:1) to yield compound **26** (3.30 g, 2.59 mmol, 81%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 – 8.03 (m, 2H, Bz), 7.63 – 7.55 (m, 1H, Bz), 7.47 (t, *J* = 7.6 Hz, 2H, Bz), 7.42 – 7.22 (m, 12H), 7.22 – 7.16 (m, 3H), 7.16 – 7.03 (m, 5H), 7.00 (d, *J* = 7.5 Hz, 1H，N*H*TCA), 5.92 – 5.77 (m, 1H, OCH_2CHCH_2), 5.72 – 5.65 (m, 1H, H-2c), 5.54 (d, *J* = 3.5 Hz, 1H, H-1b), 5.47 (s, 1H, PhC*H*), 5.32 – 5.22 (m, 1H, OCH_2CHCH_2), 5.22 – 5.15 (m, 1H, OCH_2CHCH_2), 5.12 (s, 1H, H-1c), 5.07 (d, *J* =

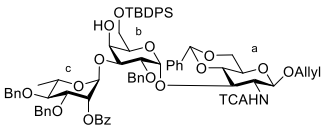
8.3 Hz, 1H, H-1a), 4.92 (d, *J* = 11.4 Hz, 1H, Bn), 4.73 (d, *J* = 11.5 Hz, 1H, Bn), 4.68 – 4.58 (m, 2H, Bn), 4.56 – 4.47 (m, 3H, Bn), 4.39 – 4.27 (m, 3H, H-5a, OCH_2CHCH$_2$), 4.15 – 3.95 (m, 5H, OCH_2CHCH$_2$, H-5c, H-3c), 3.94 – 3.70 (m, 4H, H-2b, H-4a), 3.64 (s, 1H), 3.59 – 3.47 (m, 3H, H-2a, H-4c), 1.29 (d, *J* = 6.3 Hz, 3H, H-6c), 0.99 (s, 9H, *t*-Bu), 0.89 (s, 9H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.69 (Bz), 161.69 (TCA), 139.00, 138.13, 137.61, 136.96, 133.31 (OCH$_2$*C*HCH$_2$), 133.22, 130.18, 130.02, 129.41, 128.52, 128.48, 128.35, 128.25, 128.21, 128.13, 127.86, 127.63, 127.53, 127.42, 126.31, 118.52 (OCH$_2$CH*C*H$_2$), 101.63 (Ph*C*H), 100.12 (C-1c), 98.62 (C-1a), 96.48 (C-1b), 92.50 (TCA), 82.75 (C-4a), 80.11 (C-4c), 77.82 (C-3c), 77.11, 74.79 (Bn), 73.77 (C-5a), 72.60 (C-2b), 72.54 (Bn), 71.71 (C-3a), 71.51 (Bn), 70.92 (O*C*H$_2$CHCH$_2$), 69.54, 68.83, 68.37 (C-2c), 67.67 (C-5c), 67.26, 65.94, 58.35 (C-2a), 27.56 (*t*-Bu), 27.38 (*t*-Bu), 23.55 (*t*-Bu), 20.77 (*t*-Bu), 18.48 (C-6c). HR-MS calculated for $C_{66}H_{78}Cl_3NO_{16}Si$ $[M+Na]^+$: 1296.4048, found: 1296.4050. $[\alpha]^{20}_D$ = + 43° (c = 1, $CHCl_3$). TLC: Rf = 0.3 (PE/EtOAc = 4/1, v/v).

Allyl 4,6-*O*-benzylidene-3-*O*-(2-*O*-benzyl-3-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-α-D-galactopyranosyl)-2-trichloroacetamido-2-deoxy-β-D-glucopyranoside (27)



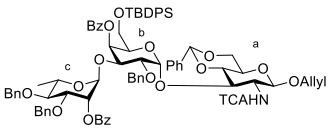
Compound **26** (222 mg, 0.174 mmol, 1.0 eq) was dissolved in THF (1 mL) and pyridine (1mL), then cooled to 0 °C and hydrogen fluoride (HF)/pyridine (70%) (0.1 mL) was added dropwise. The solution was stirred for overnight. After TLC showed complete consumption of the starting material, the reaction was quenched with saturated aqueous sodium bicarbonate slowly and diluted with EtOAc. The solution was washed with water (2x) and brine. The aqueous layer was extracted with EtOAc (3x), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by flash chromatography (DCM/Acetone 20:1 - 7:1) to yield compound **27** (172 mg, 0.152 mmol, 87%). ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.48 (d, *J* = 9.4 Hz, 1H, NHTCA), 8.16 – 8.08 (m, 2H, Bz), 7.70 – 7.62 (m, 1H, Bz), 7.59 – 7.48 (m, 4H, Bz), 7.45 – 7.37 (m, 3H), 7.37 – 7.12 (m, 15H), 5.96 – 5.78 (m, 3H, OCH$_2$C*H*CH$_2$, H-1b, H-2c), 5.74 (s, 1H, PhC*H*), 5.36 (d, *J* = 1.8 Hz, 1H, H-1c), 5.29 (dq, *J* = 17.2, 1.8 Hz, 1H, OCH$_2$CHC*H*$_2$), 5.12 (dq, *J* = 10.6, 1.5 Hz, 1H, OCH$_2$CHC*H*$_2$), 4.96 – 4.78 (m, 3H, H-1a, Bn), 4.67 (dd, *J* = 11.6, 9.7 Hz, 2H, Bn), 4.59 – 4.43 (m, 3H, Bn, H-3a), 4.37 – 4.27 (m, 3H, OCH_2CHCH$_2$, H-6a), 4.25 – 4.04 (m, 6H, H-3c, H-2a), 4.04 – 3.71 (m, 7H, H-4a, H-5c, H-5a, H-6a, H-2b), 3.67 – 3.52 (m, 2H), 3.23 (s, 1H), 1.34 (d, *J* = 6.2 Hz, 3H, H-6c). ^{13}C NMR (101 MHz, Acetone) δ 165.96, 162.65, 139.64, 139.34, 139.24, 138.50, 134.87, 134.02, 130.93, 130.36, 129.77, 129.35, 128.98, 128.96, 128.87, 128.79, 128.76, 128.44, 128.34, 128.20, 128.12, 128.05, 127.10, 116.92 (OCH$_2$CH*C*H$_2$), 102.12 (Ph*C*H), 101.43 (C-1c), 99.80 (C-1a), 96.24 (C-1b), 93.60 (TCA), 83.98 (C-4a), 80.97, 79.16, 75.87, 75.65, 75.02, 72.81 (C-3a), 72.05, 71.46, 71.00, 70.59 (O*C*H$_2$CHCH$_2$), 70.47, 70.13 (C-2c), 69.08, 68.64 (C-5c), 66.47, 62.62, 57.37 (C-2a), 18.44 (C-6c). HR-MS: Calculated for $C_{58}H_{62}Cl_3NO_{16}$ $[M+NH_4]^+$: 1151.3472, found: 1151.3491. $[\alpha]^{20}_D$ = + 21.5° (c = 1, $CHCl_3$). TLC: Rf = 0.3 (DCM/Acetone = 10/1, v/v).

Allyl 4,6-*O*-benzylidene-3-*O*-(2-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-3-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-α-D-galactopyranosyl)-2-trichloroacetamido-2-deoxy-β-D-glucopyranoside (28)



Compound **27** (170 mg, 0.15 mmol, 1.0 eq) was dissolved in DMF (2 mL), then cooled to 0 °C and *tert*-butyl(chloro)diphenylsilane (TBDPSCl) (41.3 mg, 0.15 mmol, 1.0 eq) and imidazole (13 mg, 0.18 mmol, 1.2 eq) were added. The solution was stirred for overnight. After TLC showed complete consumption of the starting material, the reaction was diluted with EtOAc. The solution was washed with water (2x) and brine. The aqueous layer was extracted with EtOAc (3x), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by flash chromatography (PE/EA 10:1 - 3:1) to yield compound **28** (193 mg, 0.14 mmol, 94%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 – 8.02 (m, 2H, Bz), 7.71 – 7.63 (m, 4H), 7.61 – 7.54 (m, 1H, Bz), 7.50 – 7.43 (m, 2H, Bz), 7.43 – 7.07 (m, 26H), 6.85 (d, *J* = 8.2 Hz, 1H, NHTCA), 5.89 – 5.76 (m, 1H, OCH_2CHCH_2), 5.73 (dd, *J* = 3.3, 1.9 Hz, 1H, H-2c), 5.68 (d, *J* = 3.8 Hz, 1H, H-1b), 5.40 (s, 1H, PhC*H*), 5.30 – 5.21 (m, 2H, H-1c, OCH_2CHCH_2), 5.17 (dq, *J* = 10.4, 1.3 Hz, 1H, OCH_2CHCH_2), 4.90 (d, *J* = 10.9 Hz, 1H, Bn), 4.86 – 4.74 (m, 2H, H-1a, Bn), 4.62 (d, *J* = 10.9 Hz, 1H, Bn), 4.57 – 4.40 (m, 4H, Bn), 4.37 – 4.25 (m, 2H, H-6a, Bn), 4.08 – 3.95 (m, 4H, H-4a, OCH_2CHCH_2), 3.95 – 3.67 (m, 8H, H-6a, H-5c, H-2a), 3.58 – 3.42 (m, 2H), 2.51 (s, 1H), 1.32 (d, *J* = 6.2 Hz, 3H, H-6c), 1.07 (s, 9H, TBDPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.57 (Bz), 161.75 (TCA), 138.44, 138.12, 137.90, 136.86, 135.86 (Bz), 135.78 (OCH_2CHCH_2), 133.29, 133.23, 132.99, 132.78, 130.06, 130.01, 129.98, 129.44, 128.53, 128.50, 128.47, 128.45, 128.38, 128.17, 128.12, 127.93, 127.81, 127.77, 127.70, 126.23, 118.29 (OCH_2CHCH_2), 101.69 (PhCH), 99.66 (C-1c), 99.30 (C-1a), 95.81 (C-1b), 92.41 (TCA), 82.84, 80.06, 78.03, 75.61, 75.50, 74.74, 72.23, 71.73, 71.62, 70.66 (OCH_2CHCH_2), 70.08, 69.83, 69.18, 68.81, 68.47, 65.89, 63.95, 57.54 (C-2a), 27.14 (TBDPS), 19.32 (TBDPS), 18.28 (C-6c). HR-MS: Calculated for $C_{74}H_{80}Cl_3NO_{16}Si$ $[M+NH_4]^+$: 1391.4647, found: 1391.4677. $[\alpha]^{20}_D$ = + 28.8° (c = 1, $CHCl_3$). TLC: Rf = 0.3 (PE/EA = 4/1, v/v).

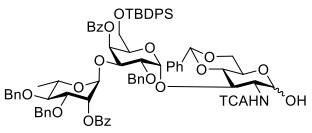
Allyl 4,6-*O*-benzylidene-3-*O*-(4-*O*-benzoyl-2-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-3-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-α-D-galactopyranosyl)-2-trichloroacetamido-2-deoxy-β-D-glucopyranoside (29)



Compound **28** (2.47 g, 1.8 mmol, 1.0 eq) was dissolved in pyridine (18 mL), then cooled to 0 °C and 4-dimethylaminopyridine (DMAP) (110 mg, 0.9 mmol, 0.5 eq) were added, benzoyl chloride (BzCl) (630 µL, 5.4 mmol, 3 eq) was added dropwise. The solution was stirred for 3 days at RT. After TLC showed complete consumption of the starting material, the reaction was quenched by MeOH and diluted with EtOAc. The solution was washed with water (2x) and brine. The aqueous layer was extracted with EtOAc (3x), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by flash chromatography (PE/EA 10:1 - 5:1) to yield compound **29** (2.53 g, 1.71 mmol, 95%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 – 7.97 (m, 2H, Bz-2c), 7.86 – 7.77 (m, 2H, Bz-4b), 7.71 – 7.62 (m, 2H), 7.58 – 7.47 (m, 4H), 7.47 – 7.04 (m, 30H), 6.89 (d, *J* = 8.7 Hz, 1H, NHTCA), 5.91 – 5.72 (m, 2H, OCH_2CHCH_2, H-1b), 5.61 (d, *J* = 3.9 Hz, 1H, H-4b), 5.52 – 5.42 (m, 2H, H-2c, PhC*H*), 5.33 – 5.21 (m, 2H, OCH_2CHCH_2, H-1c), 5.21 – 5.12 (m, 1H, OCH_2CHCH_2), 4.83 (d, *J* = 11.6 Hz, 1H,

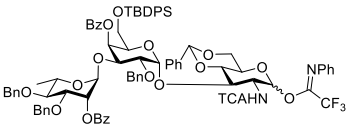
Bn), 4.70 (d, *J* = 8.3 Hz, 1H, H-1a), 4.66 – 4.24 (m, 9H, Bn, H-3a, H-3b, H-6a, OC*H*$_2$CHCH$_2$), 4.17 (d, *J* = 11.3 Hz, 1H, H-4a), 4.12 – 3.90 (m, 3H, H-5c, H-2a, OC*H*$_2$CHCH$_2$), 3.90 – 3.68 (m, 6H, H-2b, H-3c, H-6b, H-6a), 3.59 – 3.37 (m, 2H, H-4c, H-5a), 1.33 (d, *J* = 6.2 Hz, 3H, H-6c), 1.06 (s, 9H, TBDPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.59 (Bz), 165.51 (Bz), 161.68 (TCA), 138.89, 138.15, 137.55, 136.95, 135.75, 135.53, 133.17 (OCH$_2$*C*HCH$_2$), 133.05, 132.99, 132.96, 132.73, 130.00, 129.91, 129.86, 129.81, 129.73, 129.41, 128.49, 128.36, 128.33, 128.31, 128.14, 128.11, 127.85, 127.78, 127.72, 127.67, 127.34, 127.32, 126.32, 118.11 (OCH$_2$CH*C*H$_2$), 101.84 (Ph*C*H), 99.71 (C-1a), 98.84 (C-1c), 95.40 (C-1b), 92.42 (TCA), 82.92, 79.35 (C-4c), 77.74, 75.38 (C-2b), 73.86 (Bn), 71.72, 71.65, 71.60, 71.46, 70.97 (C-4b), 70.35 (O*C*H$_2$CHCH$_2$), 70.17, 69.58 (C-2c), 68.72 (C-6a), 68.46 (C-5c), 65.87 (C-5a), 62.71 (C-6b), 56.95 (C-2a), 27.11 (TBDPS), 19.22 (TBDPS), 18.21 (C-6c). HR-MS: Calculated for $C_{81}H_{84}Cl_3NO_{17}Si$ $[M+NH_4]^+$: 1493.4912, found: 1493.4919. $[\alpha]^{20}_D$ = + 27.3° (c = 1, $CHCl_3$). TLC: Rf = 0.3 (PE/EA = 4/1, v/v).

4,6-*O*-benzylidene-3-*O*-(4-*O*-benzoyl-2-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-3-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-α-D-galactopyranosyl)-2-trichloroacetamido-2-deoxy-α/β-D-glucopyranoside (30)



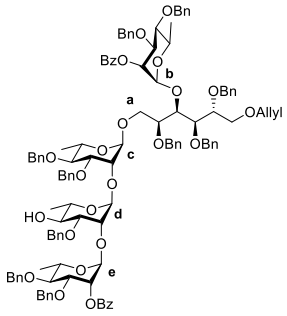
Allyl protected **29** (346 mg, 0.23 mmol, 1 eq) was dissolved in freshly distilled THF (3 ml). The mixture was degassed and placed under an argon atmosphere. (1,5-Cyclooctadiene)(pyridine)-(tricyclohexylphosphine)-iridium(I) hexafluorophosphate (Ir(COD)(Ph$_2$MeP)$_2$·PF$_6$) (10 mg, 0.01 mmol, 0.05 eq) was added and the reaction mixture was purged with H_2 for 5 seconds. The reaction mixture was stirred for 1 hour under an argon atmosphere. After analysis by TLC showed complete consumption of the starting material, diluted with THF (2 ml) and *N*-iodosuccinimide (NIS) (77.6 mg, 0.35 mmol, 1.5 eq), and water were added and the solution stirred for 2 hours at room temperature. EtOAc was added and the organic layer was washed two times with saturated aqueous sodium thiosulphate and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Column chromatography yielded **30** (300 mg, 0.21 mmol, 90%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 – 7.95 (m, 2H), 7.77 – 7.71 (m, 2H), 7.69 – 7.59 (m, 2H), 7.56 – 7.21 (m, 24H), 7.21 – 7.02 (m, 16H), 5.80 (d, *J* = 3.5 Hz, 1H), 5.60 – 5.51 (m, 1H), 5.50 – 5.40 (m, 2H), 5.26 (s, 1H), 5.15 (t, *J* = 3.7 Hz, 1H), 4.80 (d, *J* = 11.6 Hz, 1H), 4.65 – 4.52 (m, 2H), 4.48 – 3.91 (m, 12H), 3.88 – 3.57 (m, 6H), 3.49 (t, *J* = 9.4 Hz, 1H), 1.34 (d, *J* = 6.1 Hz, 3H), 1.04 (s, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.71, 165.64, 161.80, 138.91, 138.16, 137.53, 137.13, 135.87, 135.79, 135.58, 133.13, 132.99, 130.02, 129.92, 129.82, 129.67, 129.55, 128.60, 128.45, 128.41, 128.37, 128.35, 128.22, 128.19, 128.17, 127.93, 127.89, 127.84, 127.79, 127.65, 127.41, 127.38, 126.50, 126.42, 102.14, 98.76, 95.68, 92.36, 91.74, 83.60, 79.47, 77.76, 77.36, 74.96, 73.79, 71.61, 71.21, 71.12, 71.09, 70.37, 70.19, 69.59, 69.04, 68.43, 62.87, 62.27, 54.44, 27.04, 19.18, 18.25. HR-MS: Calculated for $C_{78}H_{80}Cl_3NO_{17}Si$ $[M+H]^+$: 1436.4334, found: 1436.4340. TLC: Rf = 0.15 (PE/EA = 7/3, v/v).

_N_-Phenyl-trifluoroacetimidate 4,6-_O_-benzylidene-3-_O_-(4-_O_-benzoyl-2-_O_-benzyl-6-_O_-_tert_-butyldiphenylsilyl-3-_O_-(2-_O_-benzoyl-3,4-di-_O_-benzyl-α-L-rhamnopyranosyl)-α-D-galactopyranosyl)-2-trichloroacetamido-2-deoxy-α/β-D-glucopyranoside (8)



Hemiacetal **30** (282 mg, 0.2 mmol, 1 eq) was dissolved in acetone (3 mL) and cooled to 0 ℃. Cesium carbonate (66 mg, 0.2 mmol, 1.0 eq) was added. After 15 min, N-phenyl trifluoroacetimidoyl chloride (62 mg, 0.3 mmol, 1.5 eq) was added, and then the reaction was allowed to stir for overnight at RT. After analysis by TLC showed complete consumption of the starting material, quenched by Et_3N, filtered and concentrated *in vacuo*, and the product purified by column chromatography (PE/EA 10:1 – 4/1) to yield compound **8** (289 mg, 0.18 mmol, 91%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10 – 7.91 (m, 3H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.72 – 7.60 (m, 2H), 7.60 – 7.00 (m, 38H), 6.95 – 6.71 (m, 2H), 5.79 (d, *J* = 3.6 Hz, 1H), 5.70 (t, *J* = 4.0 Hz, 1H), 5.61 – 5.36 (m, 2H), 5.36 – 5.17 (m, 1H), 4.98 – 4.75 (m, 1H), 4.75 – 3.44 (m, 18H), 1.48 – 1.31 (m, 3H), 1.15 – 0.95 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.55, 165.41, 161.93, 142.73, 139.01, 138.27, 137.48, 136.79, 136.69, 135.88, 135.80, 135.68, 135.63, 133.69, 133.08, 132.97, 132.92, 132.63, 130.49, 130.12, 130.05, 129.92, 129.85, 129.79, 129.68, 129.60, 128.98, 128.64, 128.50, 128.39, 128.21, 128.17, 128.04, 127.97, 127.90, 127.86, 127.78, 127.73, 127.66, 127.56, 127.39, 126.45, 126.33, 124.97, 119.26, 105.88, 102.32, 98.92, 96.23, 91.98, 82.61, 79.43, 79.32, 77.79, 77.68, 77.48, 77.16, 76.84, 75.70, 75.04, 73.87, 73.59, 72.18, 71.84, 71.67, 71.61, 70.95, 70.78, 70.61, 70.49, 70.34, 69.93, 69.68, 69.44, 68.58, 68.48, 68.22, 64.65, 63.37, 62.12, 61.41, 53.61, 27.03, 19.08, 18.21. HR-MS: Calculated for $C_{86}H_{84}Cl_3F_3N_2O_{17}Si$ $[M+H]^+$: 1607.4630, found: 1607.4565. TLC: Rf = 0.5 (PE/EA = 4/1, v/v).

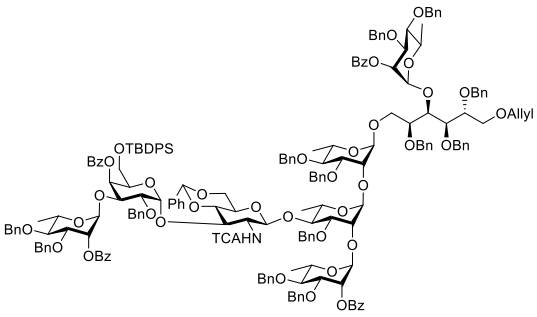
6-Allyl-3-_O_-(2-_O_-benzoyl-3,4-di-_O_-benzyl-α-L-rhamnopyranosyl)-2,4,5-tri-_O_-benzyl-1-_O_-(3,4-di-_O_-benzyl-2-_O_-(2-_O_-(2-_O_-benzoyl-3,4-di-_O_-benzyl-α-L-rhamnopyranosyl)-3-_O_-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranosyl)-D-glucitol



Full protected **7** (903 mg, 0.44 mmol, 1 eq) was dissolved in DCM (5 mL) and water (0.5 mL). After cooled to 0 ℃, 2,3-Dichloro-5,6-dicyano-p-benzoquinone (DDQ) (110 mg, 0.48 mmol, 1.1 eq) was added. The reaction was stirred at RT for 4 hours. After analysis by TLC showed complete consumption of the starting material, quenched by saturated aqueous sodium thiosulphate, extracted with DCM and washed with water and brine. The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*, and the product purified by column chromatography (PE/EA 6:1 – 4/1) to yield title compound (716 mg, 0.37 mmol, 85%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.14 – 8.09 (m, 2H, Bz), 8.09 – 8.04 (m, 2H, Bz), 7.61 – 7.53 (m, 1H), 7.52 – 7.42 (m, 3H), 7.42 – 7.06 (m, 51H), 7.05 – 6.96 (m, 1H), 5.92 – 5.78 (m, 1H, OCH_2CHCH_2), 5.75 – 5.64 (m, 2H, H-2e, 2b), 5.27 – 5.17 (m, 2H, H-1d, OCH_2CHCH_2), 5.14 (d, *J* = 1.9 Hz, 1H, H-1b), 5.10 (dd, *J* = 10.5, 1.6 Hz, 1H, OCH_2CHCH_2), 5.00 (d, *J* = 1.9 Hz, 1H, H-1e), 4.94 – 4.85 (m, 3H, CH_2), 4.84 – 4.65 (m, 6H, H-1c, CH_2), 4.65 – 4.54 (m, 10H, CH_2), 4.54 – 4.43 (m, 2H, CH_2), 4.16 – 3.98 (m,

6H), 3.98 – 3.58 (m, 15H), 3.58 – 3.47 (m, 2H), 3.38 (t, *J* = 9.4 Hz, 1H), 2.43 (s, 1H), 1.33 – 1.22 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.51 (Bz), 138.75, 138.63, 138.49, 138.30, 138.16, 138.09, 137.91, 134.92 ($OCH_2\mathit{C}HCH_2$), 133.13, 133.05, 130.15, 130.09, 129.91, 128.55, 128.41, 128.36, 128.34, 128.32, 128.29, 128.26, 128.24, 128.22, 128.16, 128.12, 128.09, 128.07, 128.04, 128.01, 127.90, 127.84, 127.80, 127.74, 127.63, 127.58, 127.56, 127.54, 127.53, 127.48, 127.38, 116.61 ($OCH_2CH\mathit{C}H_2$), 100.52 (C-1d), 99.32 (C-1e), 98.97 (C-1b, 1c), 80.27, 80.07, 79.96, 79.38, 79.30, 78.89, 78.47, 78.00, 77.93, 77.43, 77.36, 75.35, 75.18, 74.99, 74.66, 74.63, 73.50, 73.33, 72.24, 72.16, 72.04, 71.80, 71.74, 71.60, 71.49, 69.74 (C-2b), 69.72 (C-6a), 69.52 (C-2e), 68.94, 68.52, 68.37, 68.16, 67.07 (C-1a), 18.20, 18.18, 18.15, 17.89. HR-MS: Calculated for $C_{117}H_{126}O_{24}$ $[M+H]^+$: 1915.8712, found: 1915.8734. $[\alpha]^{20}_D$ = + 0.5º (c = 1, $CHCl_3$). TLC: Rf = 0.30 (PE/EA = 4/1, v/v).

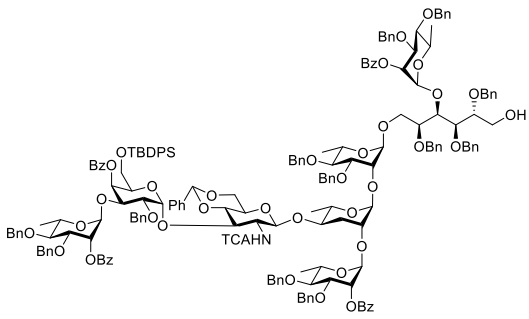
The synthesis of the octamer 31



Donor **8** (758 mg, 0.472 mmol, 2.0 eq) and acceptor **7d** (452 mg, 0.236 mmol, 1.0 eq) were co-evaporated with anhydrous toluene three times under nitrogen. Dry DCM (5 mL) and 4Å molecular sieves were added and the solution stirred for 20 minutes at RT. The reaction was then cooled to 0 ℃ and *tert* - butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (6 µL, 0.023 mmol, 0.1 eq) was added. The solution was stirred for 4 hours. After TLC showed complete consumption of the starting material, the reaction was quenched with saturated aqueous sodium bicarbonate and diluted with DCM. The solution was washed with water (2x) and brine. The aqueous layer was extracted with DCM (3x), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by flash chromatography (PE/EA 10:1 - 4:1) to yield compound **31** (590 mg, 0.177 mmol, 75%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.13 – 8.08 (m, 2H), 8.07 – 8.03 (m, 2H), 8.03 – 7.98 (m, 2H), 7.83 – 7.77 (m, 2H), 7.62 – 7.55 (m, 3H), 7.55 – 7.04 (m, 86H), 7.04 – 6.94 (m, 3H), 6.69 (d, *J* = 8.9 Hz, 1H), 5.91 – 5.79 (m, 1H), 5.76 – 5.63 (m, 4H), 5.52 – 5.41 (m, 2H), 5.32 – 5.04 (m, 6H), 4.94 – 4.82 (m, 4H), 4.82 – 4.33 (m, 25H), 4.26 – 4.15 (m, 3H), 4.10 – 4.00 (m, 4H), 4.00 – 3.61 (m, 24H), 3.60 – 3.44 (m, 5H), 3.29 (t, *J* = 9.3 Hz, 1H), 1.37 (d, *J* = 6.2 Hz, 3H), 1.31 – 1.18 (m, 12H), 0.99 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.58, 165.55, 165.50, 165.37, 161.55, 139.13, 138.87, 138.83, 138.73, 138.37, 138.34, 138.32, 138.28, 138.26, 138.18, 138.15, 138.07, 137.70, 137.16, 135.85, 135.81, 135.65, 135.60, 135.02, 133.25, 133.07, 133.02, 132.99, 132.83, 132.81, 130.29, 130.20, 130.18, 129.97, 129.94, 129.87, 129.65, 129.56, 129.42, 128.74, 128.63, 128.51, 128.42, 128.40, 128.39, 128.36, 128.35, 128.32, 128.28, 128.27, 128.17, 128.14, 128.07, 127.98, 127.95, 127.90, 127.87, 127.85, 127.84, 127.78, 127.69, 127.65, 127.63, 127.61, 127.57, 127.50, 127.44, 127.38, 127.34, 127.30, 126.48, 126.32, 116.63, 101.96, 100.22, 99.97, 99.01, 98.96, 98.81, 95.64, 92.64, 83.14, 80.66, 80.14, 80.06, 79.50, 79.43, 79.32, 78.57, 78.16, 78.07, 77.94, 77.78, 77.46, 77.36, 75.55, 75.39, 75.28, 75.23, 75.11, 73.65, 73.37, 72.95, 72.32, 72.22, 72.01, 71.94, 71.67, 71.61, 71.56, 71.54, 71.02, 70.82, 69.95, 69.90, 69.78, 69.48, 68.85, 68.55, 68.48, 68.35, 68.10, 67.62, 67.15, 65.57, 61.97, 57.44, 27.06, 19.11, 18.35, 18.26, 18.21, 18.18,

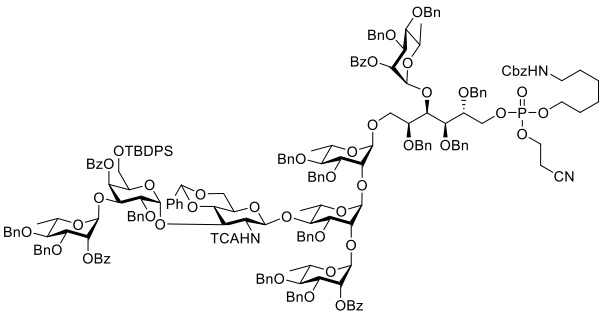
18.05. HR-MS: Calculated for $C_{195}H_{204}Cl_3NO_{40}Si$ $[M+H]^+$: 3333.2867, found: 3333.2771. $[\alpha]^{20}_D$ = + 28.6° (c = 1, $CHCl_3$). TLC: Rf = 0.30 (PE/EtOAc = 4/1, v/v).

The octasaccharide 31a



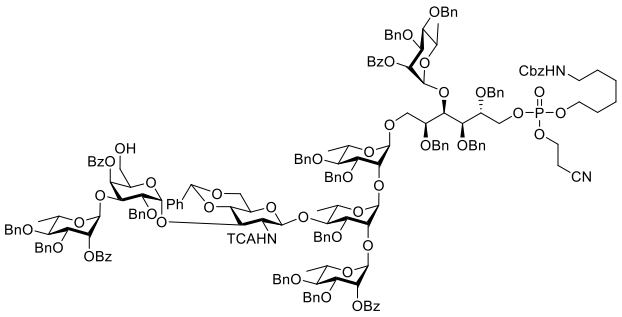
Allyl protected **31** (418 mg, 0.125 mmol, 1.0 eq) was dissolved in freshly distilled THF (4 ml). The mixture was degassed and placed under an argon atmosphere. (1,5-Cyclooctadiene) (pyridine)-(tricyclohexylphosphine)-iridium(I) hexafluorophosphate ($Ir(COD)(Ph_2MeP)_2{\cdot}PF_6$) (10 mg, 0.01 mmol, 0.1 eq) was added and the reaction mixture was purged with H_2 for 5 seconds. The reaction mixture was stirred for 1 hour under an argon atmosphere. After analysis by TLC showed complete consumption of the starting material, diluted with THF (2 ml) and *N*-iodosuccinimide (NIS) (42 mg, 0.19 mmol, 1.5 eq), and water were added, and the solution stirred for 2 hours at room temperature. EtOAc was added and the organic layer was washed two times with saturated aqueous sodium thiosulphate and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (PE/EA 5:1 - 3:1) yielded **31a** (359 mg, 0.11 mmol, 87%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.13 – 8.05 (m, 4H), 8.04 – 7.98 (m, 2H), 7.84 – 7.77 (m, 2H), 7.62 – 7.55 (m, 3H), 7.55 – 7.03 (m, 86H), 7.03 – 6.94 (m, 3H), 6.71 (d, *J* = 9.0 Hz, 1H, N*H*TCA), 5.80 – 5.62 (m, 4H, H-1), 5.52 – 5.39 (m, 2H, PhC*H*), 5.28 (d, *J* = 1.7 Hz, 1H, H-1), 5.18 – 5.05 (m, 3H, H-1), 4.94 – 4.82 (m, 4H), 4.82 – 4.27 (m, 25H), 4.25 – 3.60 (m, 29H), 3.58 – 3.41 (m, 5H), 3.29 (t, *J* = 9.3 Hz, 1H), 2.32 (s, 1H), 1.37 (d, *J* = 6.1 Hz, 3H, H-6), 1.32 – 1.19 (m, 12H, H-6), 0.99 (s, 9H, *t*-Bu). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.57, 165.54, 165.35, 161.57, 139.11, 138.70, 138.59, 138.32, 138.29, 138.27, 138.23, 138.17, 138.12, 138.04, 137.97, 137.66, 137.13, 135.83, 135.63, 133.25, 133.11, 132.99, 132.83, 132.78, 130.25, 130.18, 130.16, 130.14, 129.96, 129.93, 129.86, 129.65, 129.56, 129.42, 129.08, 128.73, 128.63, 128.51, 128.46, 128.42, 128.39, 128.35, 128.34, 128.30, 128.28, 128.19, 128.16, 128.13, 128.12, 128.05, 127.99, 127.92, 127.89, 127.86, 127.84, 127.80, 127.78, 127.75, 127.71, 127.68, 127.65, 127.49, 127.47, 127.34, 127.30, 126.47, 125.36, 101.95, 100.18, 99.99, 99.30, 98.99, 98.80, 95.64, 92.60, 83.11, 80.66, 80.12, 80.03, 79.70, 79.47, 79.21, 78.65, 77.92, 77.90, 77.77, 77.36, 75.57, 75.34, 75.29, 74.89, 73.97, 73.65, 73.43, 72.93, 71.91, 71.76, 71.65, 71.60, 71.58, 71.52, 71.00, 70.78, 69.94, 69.81, 69.75, 69.45, 68.83, 68.53, 68.47, 68.33, 68.02, 67.61, 66.79, 65.56, 61.95, 60.40, 57.37, 29.75, 27.05, 19.10, 18.37, 18.30, 18.20, 18.15, 18.04. HR-MS: Calculated for $C_{185}H_{194}Cl_3NO_{39}Si$ $[M+H]^+$: 3293.2554, found: 3293.2729. $[\alpha]^{20}_D$ = + 26.8° (c = 1, $CHCl_3$). TLC: Rf = 0.25 (PE/EtOAc = 3/1, v/v).

The octasaccharide 32



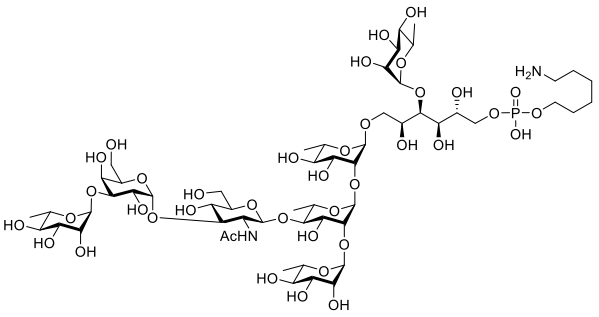
Alcohol **31a** (365 mg, 0.11 mmol, 1.0 eq) was co-evaporated with dry acetonitrile 3 times. Dissolved in dry acetonitrile (4 ml), 4,5-dicyanoimidazole (DCI, 0.25M in acetonitrile) (0.89 mL, 0.22 mmol, 2.0 eq) and 3Å molecular sieves were added. The mixture was stirred for 15 mins under argon atmosphere. Benzyl 6-([*N, N*-diisopropylamino]-2-cyanoethyl-phosphite)-hexyl-1-carbamate (0.16M in acetonitrile) (1.4 mL, 0.22 mmol, 2.0 eq) was added. The reaction mixture was stirred for 1 hour. After analysis by TLC showed complete consumption of the starting material, (10-Camphorsulfonyl)-oxaziridine (CSO, 0.5M in acetonitrile) (0.67 mL, 0.33 mmol, 3.0 eq) was added. Stirred another 15 mins and diluted with EtOAc. The solution was washed with saturated aqueous sodium bicarbonate and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (DCM/Acetone 100:1 - 10:1) yielded **32** (374 mg, 0.10 mmol, 92%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.14 – 7.98 (m, 6H, Bz), 7.81 (d, *J* = 7.6 Hz, 2H, Bz), 7.63 – 7.54 (m, 3H), 7.54 – 7.04 (m, 91H), 7.04 – 6.95 (m, 3H), 6.73 (d, *J* = 9.1 Hz, 1H), 5.82 – 5.63 (m, 4H), 5.54 – 5.41 (m, 2H), 5.28 (s, 1H), 5.19 – 5.02 (m, 5H), 4.92 – 4.34 (m, 30H), 4.33 – 4.11 (m, 5H), 4.09 – 3.44 (m, 32H), 3.31 (t, *J* = 9.3 Hz, 1H), 3.16 – 2.99 (m, 2H), 2.40 – 2.03 (m, 2H), 1.66 – 1.47 (m, 2H), 1.45 – 1.33 (m, 5H), 1.33 – 1.10 (m, 16H), 1.00 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.52, 165.47, 165.44, 165.30, 161.50, 156.37, 139.03, 138.68, 138.46, 138.43, 138.25, 138.23, 138.21, 138.11, 137.97, 137.93, 137.89, 137.87, 137.82, 137.75, 137.73, 137.57, 137.06, 136.72, 135.77, 135.56, 133.20, 133.12, 132.96, 132.91, 132.78, 132.70, 130.17, 130.08, 130.05, 129.98, 129.89, 129.85, 129.78, 129.59, 129.50, 129.37, 128.67, 128.49, 128.45, 128.41, 128.38, 128.32, 128.28, 128.20, 128.18, 128.15, 128.12, 128.10, 128.07, 128.04, 128.00, 127.93, 127.83, 127.81, 127.79, 127.76, 127.72, 127.68, 127.64, 127.60, 127.58, 127.53, 127.48, 127.43, 127.28, 127.24, 126.40, 116.73, 116.64, 101.89, 100.11, 99.94, 98.90, 98.85, 98.71, 95.56, 92.55, 83.04, 80.56, 80.03, 79.92, 79.39, 79.17, 78.66, 78.60, 78.53, 78.48, 78.16, 78.09, 77.92, 77.83, 77.68, 77.36, 77.00, 75.49, 75.36, 75.32, 75.25, 75.18, 74.94, 73.85, 73.56, 73.46, 73.39, 72.85, 72.22, 72.11, 71.86, 71.59, 71.57, 71.51, 71.44, 71.42, 70.92, 70.70, 69.86, 69.69, 69.66, 69.63, 69.35, 68.75, 68.62, 68.40, 68.28, 68.16, 68.12, 68.05, 67.57, 66.91, 66.47, 65.50, 61.88, 61.66, 61.62, 57.27, 40.80, 30.00, 29.98, 29.95, 29.92, 29.69, 26.99, 26.04, 24.93, 24.90, 19.25, 19.19, 19.16, 19.10, 19.03, 18.30, 18.21, 18.14, 18.11, 18.00. ^{31}P NMR (202 MHz, $CDCl_3$) δ -0.33, -0.80. MALDI-TOF: Calculated for $C_{209}H_{223}Cl_3N_3O_{45}PSi$ $[M+Na]^+$: 3681.372, found: 3680.636. TLC: Rf = 0.50 (DCM/Acetone = 20/1, v/v).

The octasacchride 6



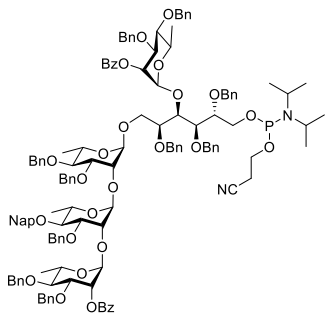
Compound **32** (355 mg, 0.097 mmol, 1.0 eq) was dissolved in THF (1 mL) and pyridine (1mL), then cooled to 0 °C and hydrogen fluoride (HF)/pyridine (70%) (0.1 mL) was added dropwise. The solution was stirred for 6 h. After TLC showed complete consumption of the starting material, the reaction was quenched with saturated aqueous sodium bicarbonate slowly and diluted with EtOAc. The solution was washed with water (2x) and brine. The aqueous layer was extracted with EtOAc (3x), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by flash chromatography (DCM/Acetone 40:1 - 10:1) to yield compound **6** (308 mg, 0.09 mmol, 93%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.12 – 7.99 (m, 6H), 7.86 – 7.78 (m, 2H), 7.62 – 7.55 (m, 1H), 7.55 – 7.49 (m, 3H), 7.49 – 7.14 (m, 66H), 7.14 – 7.02 (m, 10H), 7.00 – 6.94 (m, 1H), 6.91 (d, *J* = 9.0 Hz, 1H), 5.70 (d, *J* = 3.5 Hz, 1H, H-1), 5.68 – 5.62 (m, 2H), 5.60 – 5.54 (m, 1H), 5.50 (s, 1H), 5.40 (d, *J* = 3.2 Hz, 1H), 5.27 (d, *J* = 1.8 Hz, 1H, H-1), 5.21 (s, 2H, H-1), 5.14 – 5.02 (m, 3H, H-1), 4.92 – 4.80 (m, 5H), 4.81 – 4.35 (m, 24H, H-1), 4.34 – 4.23 (m, 2H), 4.23 – 4.11 (m, 2H), 4.11 – 3.38 (m, 33H), 3.33 (t, *J* = 9.3 Hz, 1H), 3.16 – 3.00 (m, 2H, C*H*$_2$NHCbz), 2.48 – 2.37 (m, 1H), 2.37 – 2.06 (m, 2H, OCH$_2$*CH*$_2$CN), 1.65 – 1.45 (m, 2H), 1.45 – 1.33 (m, 2H), 1.33 – 1.09 (m, 19H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.84, 165.57, 165.45, 161.93, 156.38, 138.67, 138.64, 138.46, 138.44, 138.24, 138.16, 138.06, 137.99, 137.98, 137.96, 137.93, 137.89, 137.87, 137.81, 137.73, 137.34, 137.04, 136.72, 133.40, 133.23, 133.12, 133.05, 129.98, 129.90, 129.88, 129.86, 129.47, 129.30, 128.73, 128.66, 128.49, 128.45, 128.42, 128.39, 128.34, 128.31, 128.29, 128.27, 128.22, 128.18, 128.15, 128.12, 128.10, 128.04, 128.00, 127.96, 127.85, 127.83, 127.80, 127.77, 127.71, 127.68, 127.64, 127.62, 127.57, 127.54, 127.36, 127.32, 127.11, 126.50, 116.73, 116.64, 102.19, 100.35, 100.04, 99.04, 98.88, 98.83, 98.79, 95.94, 92.41, 83.00, 80.44, 80.04, 79.93, 79.43, 79.23, 78.64, 78.58, 78.51, 78.46, 78.16, 78.07, 77.92, 77.85, 77.72, 77.69, 77.36, 76.97, 75.50, 75.36, 75.32, 75.12, 74.96, 74.89, 74.47, 74.26, 74.08, 73.85, 73.42, 72.21, 72.00, 71.98, 71.73, 71.58, 71.42, 71.39, 71.09, 70.81, 69.68, 69.64, 69.57, 69.45, 69.43, 69.27, 68.81, 68.63, 68.54, 68.38, 68.18, 68.13, 68.06, 67.47, 66.97, 66.91, 66.49, 66.34, 65.71, 61.67, 61.63, 60.86, 57.17, 40.81, 30.01, 29.98, 29.95, 29.93, 29.69, 26.06, 26.04, 24.93, 24.91, 19.26, 19.20, 19.16, 19.11, 18.28, 18.21, 18.12, 18.11, 17.99. ^{31}P NMR (202 MHz, $CDCl_3$) δ -0.37, -0.85. HR-MS: Calculated for $C_{193}H_{205}Cl_3N_3O_{45}P$ $[M+NH_4]^+$: 3421.2721, found: 3421.2795. TLC: Rf = 0.3 (DCM/Acetone = 20/1, v/v).

The Octasaccharide 2



Full protected octamer **6** (64.5 mg, 18.8 µmol, 1.0 eq) was dissolved in dioxane (6 mL) and ammonia solution (35%) (3 mL). The mixture was stirred at RT for overnight. After analysis by TLC showed complete consumption of the starting material, co-evaporated with toluene to remove the solvent. The crude was dissolved in methanol (3 mL) and dioxane (2 mL). Sodium methoxide (25 wt. % in methanol) (0.1 mL, 0.44 mmol, 23 eq) was added. The reaction was stirred overnight. After analysis by TLC showed complete consumption of the starting material, quenched with acetic acid and then quenched the excess acid using ammonia solution. Co-evaporated with toluene to remove all the solvent *in vacuo*. The mixture was purified by flash size exclusion (LH-20) (DCM/MeOH 1:1). The compound was dissolved in *tert*-butanol (7 mL), water (3 mL) and 4 drops acetic acid. After $Pd(OH)_2/C$ (60 mg) was added, the reaction was stirred for 3 days under a H_2 atmosphere, filtered and concentrated *in vacuo*. The compound was purified by gel filtration (HW-40, 0.15M, NH_4OAc in H_2O) with a Shimadzu RID-10A refractive index detector, transformed into its sodium salt by passing a short Dowex Na^+ column and lyophilized to yield compound **3** (19.2 mg, 13.2 µmol, 70%). ^{1}H NMR (500 MHz, Deuterium Oxide) δ 5.478 (d, *J* = 4.0 Hz, 1H), 5.125 (d, *J* = 1.8 Hz, 1H), 5.024 (d, *J* = 1.8 Hz, 1H), 4.996 (d, *J* = 1.7 Hz, 1H), 4.945 (d, *J* = 1.8 Hz, 1H), 4.868 (d, *J* = 1.7 Hz, 1H), 4.808 (d, *J* = 8.1 Hz, 1H), 4.148 – 3.944 (m, 11H), 3.940 – 3.858 (m, 6H), 3.858 – 3.674 (m, 19H), 3.674 – 3.596 (m, 2H), 3.491 – 3.377 (m, 5H), 2.977 – 2.900 (m, 2H), 2.061 (s, 3H), 1.639 (m, *J* = 6.9 Hz, 4H), 1.466 – 1.360 (m, 4H), 1.358 – 1.220 (m, 15H). ^{13}C NMR (126 MHz, D_2O) δ 174.45, 102.40, 102.32, 101.43, 101.40, 100.47, 98.81, 98.76, 80.06, 79.13, 78.70, 78.37, 77.83, 77.22, 75.44, 72.26, 72.05, 71.97, 71.02, 70.74, 70.60, 70.45, 70.22, 70.14, 70.12, 70.10, 70.02, 69.98, 69.46, 69.34, 69.24, 69.17, 69.11, 68.90, 68.84, 67.76, 67.65, 66.89, 66.24, 66.20, 60.51, 60.44, 54.42, 39.61, 29.56, 29.51, 27.32, 25.24, 24.52, 22.47, 17.21, 16.85, 16.74, 16.70, 16.68. ^{31}P NMR (202 MHz, D_2O) δ 1.96. HR-MS: Calculated for $C_{56}H_{101}N_2O_{39}P$ $[M+Na]^+$: 1457.5792, found : 1457.5803.

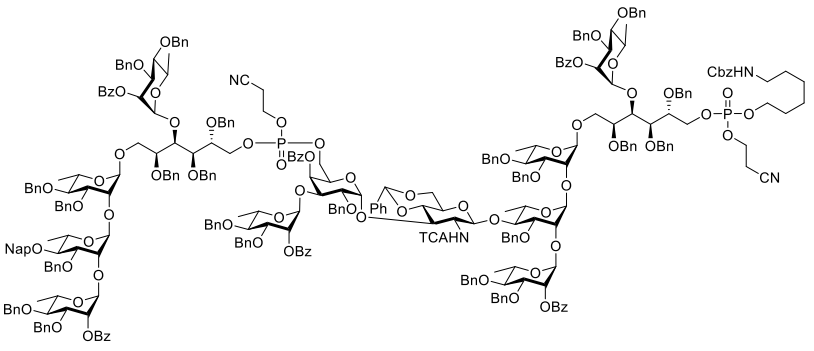
The pentasaccharide 5



Alcohol **20** (266 mg, 0.132 mmol, 1.0 eq) was co-evaporated with dry acetonitrile 3 times. Dissolved in dry DCM (5 ml), *N,N*-Diisopropylethylamine (DIPEA) (0.12 mL, 0.65 mmol, 5.0 eq) and 3Å molecular sieves were added. The mixture was stirred for 15 mins under argon atmosphere. 2-Cyanoethyl *N,N*-diisopropylchlorophosphoramidite (90 µL, 0.39 mmol, 3.0 eq) was added. The reaction mixture was stirred for 1.5 hours. After analysis by TLC showed complete consumption of the starting material, DCM 5 mL was added. The solution was washed with

saturated aqueous sodium bicarbonate and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (PE/EA 8/1 – 3/1) yielded **5** (239 mg, 0.108 mmol, 84%). ^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.15 – 8.07 (m, 2H), 8.07 – 7.99 (m, 2H), 7.88 – 7.78 (m, 4H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.61 – 7.51 (m, 3H), 7.51 – 7.40 (m, 5H), 7.39 – 7.03 (m, 50H), 5.77 – 5.69 (m, 1H), 5.68 – 5.60 (m, 1H), 5.18 – 5.08 (m, 3H), 5.00 (d, *J* = 11.4 Hz, 1H), 4.89 – 4.39 (m, 21H), 4.22 – 3.47 (m, 24H), 3.46 – 3.36 (m, 1H), 2.57 – 2.30 (m, 2H), 1.32 – 1.04 (m, 28H). ^{13}C NMR (126 MHz, CD_3CN) δ 166.24, 166.18, 139.95, 139.84, 139.81, 139.78, 139.52, 139.49, 139.46, 139.41, 139.14, 139.11, 137.44, 134.44, 134.34, 134.20, 133.86, 130.93, 130.87, 130.56, 130.51, 129.69, 129.60, 129.30, 129.25, 129.20, 129.18, 129.16, 129.14, 129.11, 129.05, 128.96, 128.93, 128.87, 128.85, 128.82, 128.80, 128.71, 128.68, 128.59, 128.55, 128.53, 128.49, 128.45, 128.40, 128.33, 128.29, 127.51, 127.37, 127.10, 126.90, 118.26, 101.04, 99.70, 99.58, 81.08, 80.98, 80.86, 80.79, 80.24, 80.17, 80.04, 79.98, 79.72, 79.54, 79.46, 78.84, 78.82, 78.45, 78.16, 77.94, 77.80, 75.85, 75.73, 75.69, 75.65, 75.62, 75.51, 75.40, 75.36, 74.27, 73.75, 72.53, 72.44, 72.40, 72.37, 72.16, 72.12, 72.02, 70.60, 70.56, 70.17, 69.45, 69.43, 69.29, 69.26, 68.92, 67.72, 62.99, 62.89, 62.77, 59.49, 59.34, 59.31, 59.16, 43.91, 43.82, 25.20, 25.13, 25.07, 24.96, 24.90, 24.85, 21.01, 20.95, 20.89, 18.76, 18.65. ^{31}P NMR (202 MHz, CD_3CN) δ 149.50, 149.21. HR-MS: Calculated for $C_{134}H_{147}N_2O_{25}P$ $[M+H]^+$: 2216.0103, found: 2216.0112. TLC: Rf = 0.40 (PE/EA = 4/1, v/v).

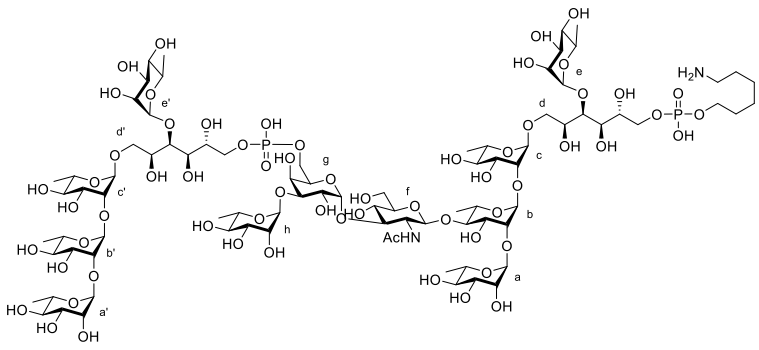
The Tridecasaccharide 4



Alcohol **6** (93 mg, 0.03 mmol, 1.0 eq) and phosphoramidite **5** (122 mg, 0.06 mmol, 2.0 eq) were co-evaporated with dry acetonitrile 3 times. Dissolved in dry acetonitrile (5 ml), and 3Å molecular sieves was added. After stirred 15 mins under argon atmosphere, 4,5-dicyanoimidazole (DCI, 0.25M in acetonitrile) (0.33 mL, 0.08 mmol, 3.0 eq) was added. The reaction mixture was stirred for 1 hour. After analysis by TLC showed complete consumption of the starting material, (10-Camphorsulfonyl)-oxaziridine (CSO, 0.5M in acetonitrile) (0.22 mL, 0.11 mmol, 4.0 eq) was added. Stirred another 15 mins and diluted with EtOAc. The solution was washed with saturated aqueous sodium bicarbonate and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (DCM/Acetone 60:1 - 10:1) yielded **4** (124 mg, 0.022 mmol, 82%). ^{1}H NMR (850 MHz, Chloroform-*d*) δ 8.29 – 8.14 (m, 1H), 8.12 (d, *J* = 7.8 Hz, 2H), 8.08 – 7.95 (m, 8H), 7.85 – 7.78 (m, 3H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.55 – 6.88 (m, 143H), 5.93 – 5.81 (m, 1H), 5.80 – 5.74 (m, 1H), 5.70 – 5.62 (m, 2H), 5.60 – 5.51 (m, 1H), 5.51 – 5.41 (m, 3H), 5.24 (d, *J* = 4.8 Hz, 1H), 5.21 – 5.01 (m, 8H), 5.01 – 4.92 (m, 2H), 4.92 – 4.17 (m, 57H), 4.17 – 3.36 (m, 54H), 3.35 – 3.28 (m, 1H), 3.24 (t, *J* = 9.3 Hz, 1H), 3.17 – 3.03 (m, 2H), 2.38 – 1.87 (m,

2H), 1.83 – 1.68 (m, 2H), 1.59 – 1.51 (m, 2H), 1.43 – 1.35 (m, 2H), 1.33 – 1.05 (m, 31H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 165.96, 165.93, 165.65, 165.64, 165.56, 165.54, 165.51, 165.48, 162.29, 162.26, 156.47, 139.05, 138.96, 138.95, 138.88, 138.84, 138.79, 138.77, 138.62, 138.59, 138.56, 138.51, 138.47, 138.42, 138.41, 138.32, 138.31, 138.27, 138.23, 138.22, 138.19, 138.17, 138.13, 138.10, 138.04, 138.02, 138.00, 137.98, 137.96, 137.94, 137.93, 137.89, 137.81, 137.66, 137.53, 137.49, 137.11, 136.80, 136.09, 136.07, 133.43, 133.42, 133.25, 133.21, 133.18, 133.07, 130.27, 130.12, 130.06, 130.03, 130.01, 129.99, 128.68, 128.62, 128.56, 128.53, 128.50, 128.48, 128.47, 128.44, 128.42, 128.41, 128.39, 128.37, 128.36, 128.35, 128.34, 128.32, 128.31, 128.30, 128.29, 128.27, 128.25, 128.24, 128.23, 128.21, 128.20, 128.19, 128.18, 128.15, 128.11, 128.10, 128.06, 128.00, 127.96, 127.92, 127.90, 127.89, 127.87, 127.85, 127.81, 127.79, 127.78, 127.76, 127.75, 127.74, 127.69, 127.66, 126.35, 116.88, 116.81, 116.77, 102.02, 101.85, 100.58, 100.46, 100.40, 100.30, 100.28, 99.29, 99.18, 99.01, 98.99, 98.93, 98.87, 98.81, 98.75, 95.91, 95.53, 92.81, 83.49, 80.83, 80.81, 80.37, 80.34, 80.31, 80.29, 80.27, 80.19, 80.06, 80.04, 79.90, 79.88, 79.53, 79.38, 79.31, 79.23, 79.20, 78.67, 78.25, 78.15, 78.14, 78.09, 78.07, 78.06, 77.97, 77.92, 77.31, 77.23, 77.16, 77.09, 77.06, 77.01, 76.83, 76.77, 76.04, 75.58, 75.52, 75.50, 75.48, 75.43, 75.41, 75.37, 75.36, 75.33, 75.32, 75.27, 75.22, 75.20, 74.82, 74.59, 74.46, 74.39, 74.33, 74.27, 74.04, 74.03, 73.76, 73.69, 73.60, 73.57, 73.52, 73.51, 73.33, 73.23, 73.21, 72.95, 72.51, 72.36, 72.24, 72.23, 72.04, 72.01, 71.97, 71.79, 71.78, 71.68, 71.67, 71.65, 71.58, 71.55, 71.53, 71.46, 71.44, 71.29, 71.17, 70.55, 70.52, 69.72, 69.69, 69.66, 69.59, 69.54, 69.40, 69.38, 69.36, 69.34, 69.03, 68.82, 68.80, 68.67, 68.66, 68.63, 68.61, 68.56, 68.54, 68.42, 68.41, 68.25, 68.23, 68.20, 68.18, 68.16, 68.14, 67.79, 67.16, 66.99, 66.91, 66.75, 66.64, 66.55, 66.52, 65.49, 65.35, 62.37, 62.35, 62.01, 61.98, 61.74, 61.73, 61.72, 61.71, 56.83, 56.74, 40.96, 40.95, 30.11, 30.09, 30.06, 29.83, 29.81, 26.21, 26.19, 25.06, 25.04, 19.35, 19.31, 19.26, 19.23, 19.01, 18.97, 18.77, 18.74, 18.39, 18.31, 18.29, 18.27, 18.25, 18.21, 18.19, 18.13. ^{31}P NMR (202 MHz, $CDCl_3$) δ -0.48, -0.96, -2.57, -3.73. MALDI-FTICR: Calculated for $C_{321}H_{337}Cl_3N_4O_{71}P_2$ $[M+Na]^+$: 5573.1316, found: 5572.9005. TLC: Rf = 0.30 (DCM/Acetone = 20/1, v/v).

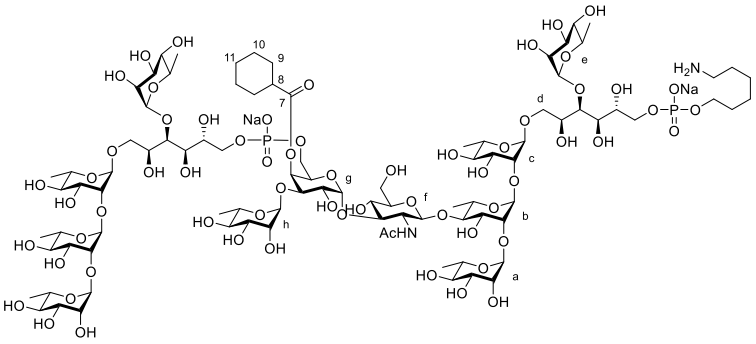
The Tridecasaccharide 3



Full protected tridecamer **4** (44 mg, 7.9 μmol, 1.0 eq) was dissolved in dioxane (5 mL) and ammonia solution (35%) (2 mL). The mixture was stirred at RT for overnight. After analysis by TLC showed complete consumption of the starting material, co-evaporated with toluene to remove the solvent. The crude was dissolved in methanol (3 mL) and dioxane (2 mL). Sodium methoxide (25 wt. % in methanol) (0.1 mL, 0.44 mmol, 56 eq) was added. The reaction was stirred overnight. After analysis by TLC showed complete consumption of the starting material, the mixture was quenched with acetic acid and then quenched the excess acid using ammonia

solution. Co-evaporated with toluene to remove all the solvent *in vacuo*. The mixture was purified by flash size exclusion (LH-20) (DCM/MeOH 1:1). The crude compound was dissolved in *tert*-butanol (7 mL), water (3 mL) and 2 drops acetic acid. After $Pd(OH)_2/C$ (60 mg) was added, the reaction was stirred for 3 days under a H_2 atmosphere, filtered and concentrated *in vacuo*. The crude was dissolved in sodium hydroxide (0.2 M, 2 mL), stirred overnight, quenched with acetic acid and then quenched the excess acid using ammonia solution. The compound was purified by gel filtration (HW-40, 0.15M, NH_4OAc in H_2O) with a Shimadzu RID-10A refractive index detector, transformed into its sodium salt by passing a short Dowex Na^+ column and lyophilized to yield compound **3a**, and the final compound **3** (9.4 mg, 4.1 µmol, 52%) was obtained after hydrolyzed by NaOH in water. ^{1}H NMR (850 MHz, Deuterium Oxide) δ 5.569 (d, *J* = 4.0 Hz, 1H, H-1g), 5.143 (d, *J* = 1.8 Hz, 1H, H-1b′), 5.133 (d, *J* = 1.8 Hz, 1H, H-1b), 5.052 (d, *J* = 1.8 Hz, 1H, H-1e), 5.044 (d, *J* = 1.8 Hz, 1H, H-1e′), 5.022 (d, *J* = 1.7 Hz, 1H, H-1h), 4.988 (d, *J* = 1.8 Hz, 1H, H-1a), 4.971 (d, *J* = 1.8 Hz, 1H, H-1a′), 4.903 (d, *J* = 1.7 Hz, 1H, H-1c′), 4.892 (d, *J* = 1.7 Hz, 1H, H-1c), 4.836 (dd, *J* = 7.2, 1.7 Hz, 1H, H-1f), 4.172 – 3.956 (m, 25H), 3.921 (m, *J* = 10.5, 7.3, 3.5 Hz, 8H), 3.887 – 3.703 (m, 28H), 3.705 – 3.638 (m, 3H), 3.522 – 3.424 (m, 10H), 2.995 – 2.933 (m, 2H), 2.117 (s, 3H), 1.703 – 1.632 (m, 4H), 1.478 – 1.391 (m, 4H), 1.375 – 1.248 (m, 27H). ^{13}C NMR (214 MHz, D_2O) δ 175.42 (Ac), 103.21 (C-1h, 1a′), 103.10 (C-1a), 102.31 (C-1f), 102.28 (C-1e), 102.20 (C-1e′), 101.72 (C-1b′), 101.37 (C-1b), 99.66 (C-1c′), 99.64 (C-1c), 99.21 (C-1g), 80.96, 79.60, 79.34, 79.32, 79.17, 79.03, 78.68, 78.50, 77.76, 76.28, 73.07, 73.01, 72.91, 72.84, 72.81, 71.85, 71.45, 71.44, 71.30, 71.27, 71.07, 71.06, 70.98, 70.96, 70.94, 70.92, 70.86, 70.83, 70.80, 70.77, 70.71, 70.30, 70.21, 70.19, 70.05, 70.02, 69.95, 69.66, 69.41, 68.60, 68.46, 67.88, 67.72, 67.06, 67.04, 64.93, 61.25, 55.25, 40.42, 30.38, 30.35, 28.02, 26.06, 25.35, 23.50, 18.08, 17.69, 17.68, 17.63, 17.62, 17.58, 17.53. ^{31}P NMR (202 MHz, D_2O) δ 1.95, 1.41. HR-MS: Calculated for $C_{86}H_{154}N_2O_{63}P_2$ $[M+H]^+$: 2285.8456, found : 2285.8435.

The tridecasaccharide 3a



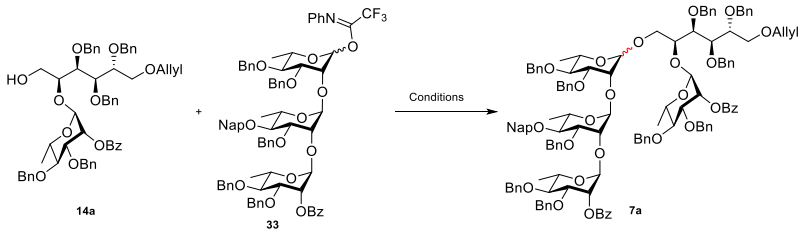
^{1}H NMR (850 MHz, Deuterium Oxide) δ 5.57 (d, *J* = 3.5 Hz, 1H, H-1g), 5.41 – 5.36 (m, 1H, H-4g), 5.11 – 5.06 (m, 2H), 5.02 – 4.98 (m, 2H), 4.97 (d, *J* = 1.8 Hz, 1H), 4.94 – 4.89 (m, 2H), 4.86 – 4.83 (m, 2H), 4.16 (t, *J* = 6.4 Hz, 1H, H-5g), 4.11 – 3.91 (m, 28H), 3.90 – 3.54 (m, 50H), 3.47 – 3.33 (m, 13H), 2.96 (t, *J* = 7.5 Hz, 2H), 2.54 – 2.47 (m, 1H, H-8), 2.07 (s, 3H, NHAc), 1.93 – 1.81 (m, 2H, Cyclohexyl), 1.77 – 1.51 (m, 7H), 1.50 – 1.35 (m, 6H), 1.36 – 1.16 (m, 30H). ^{13}C NMR (214 MHz, D_2O) δ 178.68, 175.51 (NHAc), 103.26, 103.14, 102.74, 102.40, 102.28, 102.27, 102.21, 101.75, 101.38, 99.68, 99.64, 99.39, 80.97, 79.65, 79.37, 79.34, 79.30, 79.20, 78.67, 78.62, 78.49, 76.27, 75.04, 73.08, 73.06, 73.05, 73.00, 72.90, 72.83, 72.80, 72.77, 71.84, 71.76, 71.46, 71.43, 71.34, 71.30, 71.27, 71.06, 71.05, 71.00, 70.98, 70.96, 70.94, 70.92, 70.91, 70.86, 70.84, 70.81,

70.77, 70.74, 70.70, 70.32, 70.31, 70.28, 70.21, 70.13, 70.08, 70.04, 69.98, 69.96, 69.94, 69.72, 69.69, 69.47, 69.32, 68.63, 67.82, 67.80, 67.74, 67.72, 67.04, 67.02, 64.58 (C-6g), 61.19, 55.22, 43.79 (C-8), 40.30 (CH_2NH_2), 30.36, 30.33, 29.87, 29.39, 27.47, 26.15, 26.01, 25.80, 25.61, 25.33, 23.54, 18.09, 17.72, 17.69, 17.66, 17.64, 17.61, 17.59, 17.55, 17.54. ^{31}P NMR (202 MHz, D_2O) δ 1.93, 1.05.

Appendix

Due to the misinterpretation of GBC structure from the reported literature[11a], pentasaccharide **1a**, an regioisomeic analogue of the pentasaccharide **1** isolated from GBC, was synthesized. The synthesis of compound **1** was achieved using the optimized strategy of **1a**, which was described below.

Table I. The model reaction of convergent **[3+2]** glycosylation

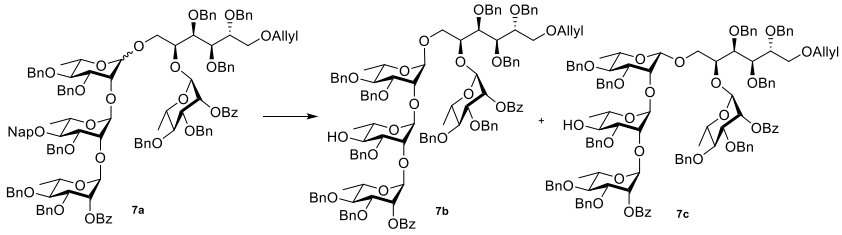


Entry	Reagents	solvent	Temp.	Yield	α/β
1	TBSOTf	DCM	0 ℃	55%	2.4 : 1
2	TBSOTf	DCM	-78 ℃	13%	1 : 2.1
3	TBSOTf, TMSI, Ph_3PO	DCM	RT	NR	-
4	TBSOTf	ACN	RT	65%	2.7 : 1
5	DMF, TfOH	DCM	-78 ℃ to 0 ℃	33%	1.9 : 1

For the reactions depicted in entry 1, 2 and 4, conditions were followed as described below. The reactions in 3 and 5, followed the published procedure.[29] Donor **33** (1.2 eq) and acceptor **14a** (1.0 eq) were co-evaporated with anhydrous toluene three times under nitrogen. Dry DCM or ACN (2 mL) and 4Å molecular sieves were added and the solution stirred for 20 minutes at RT. The reaction was then cooled to 0 ℃ or -78 ℃ and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) or another activator (0.1 eq) was added. The solution was stirred until TLC showed complete consumption of the starting material, the reaction was quenched with saturated aqueous sodium bicarbonate and diluted with DCM. The solution was washed with water (2x) and brine. The aqueous layer was extracted with DCM (3x), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The compound was purified by flash chromatography (PE/EA 6:1 - 3:1) to yield a α/β mixture compound **7a**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 (d, *J* = 7.7 Hz, 2H), 8.04 (d, *J* = 7.7 Hz, 2H), 7.86 – 7.72 (m, 4H), 7.65 – 7.40 (m, 10H), 7.40 – 7.06 (m, 54H), 6.99 (t, *J* = 7.5 Hz, 1H), 5.94 – 5.71 (m, 2H), 5.60 (s, 1H), 5.28 – 5.18 (m, 1H), 5.17 – 4.37 (m, 29H), 4.18 – 3.73 (m, 17H), 3.74 – 3.58 (m, 4H), 3.58 – 3.42 (m, 3H), 3.35 (t, *J* = 9.4 Hz, 1H), 1.38 – 1.14 (m, 19H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.65, 165.61, 138.81, 138.76, 138.58, 138.56, 138.51, 138.49, 138.43, 138.30, 138.24, 138.22,

136.12, 134.97, 133.45, 133.23, 133.18, 133.09, 130.31, 130.17, 130.06, 130.00, 128.58, 128.52, 128.49, 128.44, 128.41, 128.37, 128.33, 128.29, 128.21, 128.18, 128.11, 128.03, 127.96, 127.93, 127.84, 127.81, 127.76, 127.68, 127.65, 127.60, 127.57, 127.55, 127.49, 126.86, 126.31, 126.09, 125.90, 116.96, 100.45, 99.29, 99.12, 98.45, 80.33, 80.28, 79.97, 79.77, 79.17, 79.13, 78.67, 78.37, 78.13, 77.96, 77.73, 75.52, 75.43, 75.38, 75.31, 75.18, 74.92, 74.72, 74.16, 72.43, 72.34, 72.26, 72.16, 71.65, 71.61, 69.73, 69.60, 69.57, 68.60, 68.43, 68.38, 68.19, 66.57, 18.35, 18.28, 18.22, 18.19. HR-MS Calculated for $C_{128}H_{134}O_{24}$ $[M+H]^+$: 2055.9336, found: 2055.9309. $[\alpha]^{20}_D$ = - 1.8 (c = 1, $CHCl_3$) TLC: Rf = 0.20 (PE/EA = 9/1, v/v).

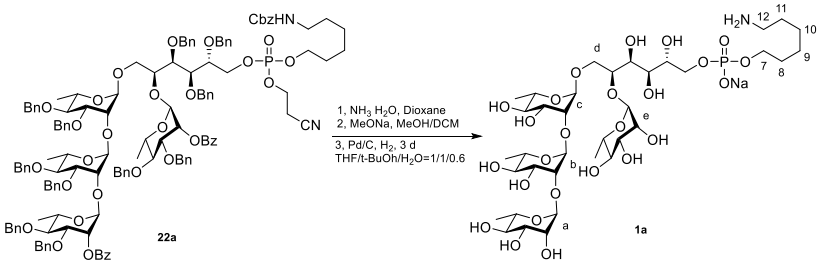
Scheme II. The Nap removal in pentasaccharide **7a** to give **7b** and **7c**



Fully protected **7a** (482 mg, 0.234 mmol, 1 eq) was dissolved in DCM (5 mL) and water (0.5 mL). After cooled to 0 ℃, 2,3-Dichloro-5,6-dicyano-p-benzoquinone (DDQ) (59 mg, 0.26 mmol, 1.1 eq) was added. The reaction was stirred at RT for 4 hours. After analysis by TLC showed complete consumption of the starting material, quenched by saturated aqueous sodium thiosulphate, extracted with DCM and washed with water and brine. The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*, and the product purified by column chromatography (PE/EA 6:1 – 3/1) to yield compound **7b** and **7c** (382 mg, 0.20 mmol, 85%). **α-isomer:** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.13 – 8.06 (m, 2H), 8.06 – 8.00 (m, 2H), 7.67 – 7.54 (m, 2H), 7.54 – 7.39 (m, 4H), 7.38 – 7.06 (m, 49H), 7.02 – 6.93 (m, 1H), 5.92 – 5.77 (m, 1H), 5.66 (t, *J* = 2.5 Hz, 1H), 5.60 (d, *J* = 2.8 Hz, 1H), 5.28 – 5.17 (m, 1H), 5.14 (d, *J* = 1.8 Hz, 1H), 5.12 – 5.05 (m, 1H), 5.00 (s, 1H), 4.96 – 4.72 (m, 6H), 4.71 – 4.37 (m, 16H), 4.10 – 3.74 (m, 14H), 3.74 – 3.45 (m, 9H), 3.35 (t, *J* = 9.4 Hz, 1H), 2.23 (s, 1H), 1.34 – 1.14 (m, 26H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.67, 165.64, 138.82, 138.81, 138.61, 138.52, 138.47, 138.30, 138.26, 138.22, 137.96, 135.01, 133.28, 133.21, 130.29, 130.21, 130.06, 130.03, 128.72, 128.55, 128.54, 128.50, 128.48, 128.46, 128.44, 128.41, 128.40, 128.38, 128.37, 128.34, 128.32, 128.30, 128.26, 128.22, 128.19, 128.10, 128.05, 127.98, 127.97, 127.93, 127.90, 127.79, 127.73, 127.72, 127.70, 127.69, 127.64, 127.58, 127.53, 116.98, 100.66, 99.43, 99.13, 98.51, 80.32, 80.19, 79.94, 79.80, 79.21, 78.92, 78.71, 78.41, 78.18, 78.03, 77.83, 75.52, 75.35, 75.15, 74.99, 74.95, 74.78, 74.16, 72.48, 72.38, 72.20, 71.88, 71.79, 71.75, 71.63, 69.76, 69.66, 69.63, 69.03, 68.49, 68.38, 68.23, 66.66, 18.36, 18.28, 18.21, 18.01. HR-MS: Calculated for $C_{117}H_{126}O_{24}$ $[M+H]^+$: 1915.8712, found: 1915.8657. $[\alpha]^{20}_D$ = - 2.7 (c = 1, $CHCl_3$). TLC: Rf = 0.20 (PE/EA = 4/1, v/v). **β-isomer**: ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.09 – 8.00 (m, 4H), 7.62 – 7.54 (m, 2H), 7.51 – 7.41 (m, 4H), 7.38 – 7.06 (m, 49H), 7.06 – 7.01 (m, 1H), 5.94 – 5.79 (m, 1H), 5.70 – 5.65 (m, 1H), 5.63 – 5.58 (m, 1H), 5.28 (d, *J* = 1.8 Hz, 1H), 5.23 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.10 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.05 (d, *J* = 1.9 Hz, 1H), 4.92 (d, *J* = 1.9 Hz, 1H), 4.90 – 4.81 (m, 3H), 4.80 – 4.70 (m, 4H), 4.70 – 4.39 (m, 14H), 4.19 – 4.00 (m, 8H), 4.00 – 3.81 (m, 8H), 3.75 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.71 – 3.63 (m, 1H),

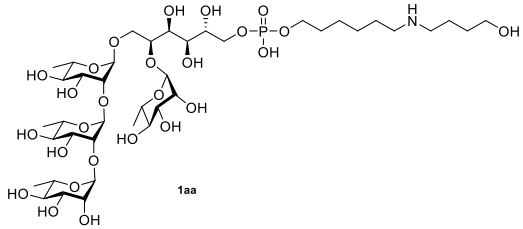
3.61 – 3.44 (m, 3H), 3.39 – 3.28 (m, 3H), 3.23 – 3.15 (m, 1H), 2.50 (s, 1H), 1.36 – 1.15 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.60, 165.56, 138.78, 138.70, 138.57, 138.52, 138.47, 138.43, 138.29, 138.24, 138.22, 137.92, 135.01, 133.19, 133.17, 130.35, 130.25, 130.05, 128.75, 128.53, 128.52, 128.51, 128.49, 128.48, 128.45, 128.42, 128.40, 128.37, 128.35, 128.26, 128.25, 128.21, 128.18, 128.13, 127.93, 127.91, 127.88, 127.81, 127.75, 127.72, 127.69, 127.65, 127.64, 127.61, 127.59, 117.01, 100.72, 99.29, 99.10, 82.66, 80.33, 80.22, 79.64, 79.51, 79.47, 79.41, 78.95, 78.39, 78.20, 75.53, 75.46, 75.32, 75.08, 74.97, 73.64, 72.38, 72.27, 72.23, 72.09, 71.95, 71.92, 71.73, 71.45, 70.03, 69.89, 69.81, 69.56, 68.80, 68.40, 68.24, 18.53, 18.17. HR-MS: Calculated for $C_{117}H_{126}O_{24}$ $[M+Na]^+$: 1937.8531, found: 1937.8519. TLC: Rf = 0.40 (PE/EA = 4/1, v/v);

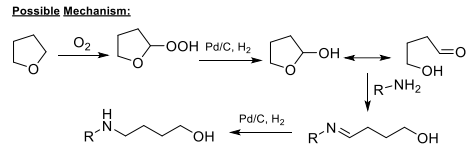
Scheme III. The optimization of the hydrogenation



Fully protected compound **22a** (10 mg, 4.3 μmol, 1.0 eq) was dissolved in dioxane (6 mL) and ammonia solution (35%) (3 mL). The mixture was stirred at RT for overnight. After analysis by TLC showed complete consumption of the starting material, co-evaporated with toluene to remove the solvent. The crude was dissolved in methanol (2 mL) and DCM (1 mL). Sodium methoxide (25 wt. % in methanol) (0.05 mL, 0.22 mmol, 50 eq) was added. The reaction was stirred overnight. After analysis by TLC showed complete consumption of the starting material, quenched with acetic acid and then quenched the excess acid using ammonia solution. Co-evaporated with toluene to remove all the solvent *in vacuo*. The mixture was purified by flash size exclusion (LH-20 column) (DCM/MeOH 1:1). The compound was dissolved in *tert*-butanol (2 mL), THF (2 mL), water (1.6 mL) and 4 drops acetic acid. After Pd/C (51 mg) was added, the reaction was stirred for 3 days under a H_2 atmosphere, filtered and concentrated *in vacuo*. The compound was firstly purified by gel filtration (HW-40, 0.15M, NH_4OAc in H_2O) with a Shimadzu RID-10A refractive index detector, transformed into its sodium salt by passing a short Dowex Na^+ column and then purified by HPLC (C30 column) to yield compound **1a** and **1aa**. ^{1}H NMR (400 MHz, Deuterium Oxide) δ 5.10 (d, *J* = 1.8 Hz, 1H, H-1b), 4.99 (d, *J* = 1.8 Hz, 1H, H-1e), 4.96 (d, *J* = 1.8 Hz, 1H, H-1a), 4.89 (d, *J* = 1.7 Hz, 1H, H-1c), 4.13 – 4.03 (m, 4H), 4.03 – 4.00 (m, 1H), 4.00 – 3.93 (m, 3H), 3.93 – 3.81 (m, 7H), 3.81 – 3.62 (m, 7H), 3.51 – 3.38 (m, 4H), 3.00 – 2.92 (m, 2H, H-12), 1.71 – 1.59 (m, 4H), 1.46 – 1.36 (m, 4H), 1.35 – 1.22 (m, 12H). ^{13}C NMR (151 MHz, D_2O) δ 103.14 (C-1a), 102.37 (C-1e), 101.84 (C-1b), 99.88 (C-1c), 80.31, 79.21, 79.03, 73.08, 73.01, 72.92, 72.91, 71.11, 71.07, 70.94, 70.75, 70.72, 70.67, 70.43, 70.24, 70.11, 70.05, 69.93, 69.76, 68.13 (C-1d), 67.76 (d, *J* = 5.5 Hz, C-6d), 67.07 (d, *J* = 5.7 Hz, C-7), 67.03, 40.32 (C-12), 30.38, 30.34, 27.50, 26.04, 25.34, 17.73, 17.70, 17.66, 17.57. HR-MS: Calculated for $C_{36}H_{68}NO_{25}P$ $[M+Na]^+$: 968.3710, found : 968.3723. ^{31}P NMR (202 MHz, D_2O) δ 1.82.

Pentasaccharide 1aa





^{1}H NMR (500 MHz, Deuterium Oxide) δ 5.15 – 5.12 (m, 1H), 5.02 (d, *J* = 1.8 Hz, 1H), 5.01 – 4.99 (m, 1H), 4.94 – 4.91 (m, 1H), 4.14 – 4.07 (m, 5H), 4.07 – 4.04 (m, 1H), 4.03 – 3.97 (m, 4H), 3.96 – 3.86 (m, 8H), 3.81 (dt, *J* = 9.8, 3.4 Hz, 2H), 3.79 – 3.67 (m, 6H), 3.65 (t, *J* = 6.3 Hz, 2H), 3.53 – 3.44 (m, 4H), 3.11 – 3.04 (m, 4H), 1.80 – 1.60 (m, 8H), 1.49 – 1.40 (m, 4H), 1.37 – 1.27 (m, 12H). ^{13}C NMR (151 MHz, D_2O) δ 103.19, 102.42, 101.90, 99.96, 80.35, 79.26, 79.10, 73.17, 73.10, 73.00, 71.19, 71.03, 70.84, 70.54, 70.30, 70.17, 70.12, 69.99, 69.85, 69.49, 68.20, 67.84 (d, *J* = 5.1 Hz), 67.11 (d, *J* = 5.7 Hz), 61.85, 48.45, 48.29, 30.43, 29.36, 26.38, 26.24, 25.43, 23.33, 21.04, 17.80, 17.78, 17.74, 17.64. ^{31}P NMR (202 MHz, D_2O) δ 1.95. HR-MS: Calculated for $C_{40}H_{76}NO_{26}P$ $[M+H]^+$: 1018.4466, found : 1018.4489.

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[24] Before the linear strategy was explored, a [3 + 2] model glycosylation between a rhamnosyl trisaccharide donor and a rhamnosylated glucitol disaccharide acceptor was performed. Unfortunately, the α:β ratio of this convergent glycosylation was poor (α:β = 2.4:1 at 0 °C; 1.2:1 at -78 °C, see Table I in the appendix of experimental part).

[25] Customarily, this type of enol ethers is cleaved by the combination of I_2 and $NaHCO_3$, however, these conditions proved unsuitable for this pentasaccharide, and the corresponding (*Z*) and (*E*) enol ethers were isolated. Fot the use of I_2 and $NaHCO_3$, see for example: D. van der Es, N. A. Groenia, D. Laverde, H. S. Overkleeft, J. Huebner, G. A. van der Marel and J. D. C. Codée, *Biorg. Med. Chem.* **2016**, *24*, 3893-3907.

[26] when THF was used in solution for the hydrogenation step to synthesize a pentasaccharide analogue, an unimaginable side product was speculated, the THF ring was opened and conjugated with the free amine of the spacer, and its structure was confirmed by HRMS and NMR data, and a possible mechanism was proposed in Scheme III of the appendix in experimental part. Additionally, when the THF was replaced by dioxane, the similar side-product was detected by LC-MS. In the end, water/tert-butanol system was selected as the optimum solvent for the hydrogenation step.

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