Synthesis and application of glycans unique to S. mansoni

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*Synthesis of fucosylated S. Mansoni LDN fragments**

Introduction

The *N*-acetylgalactosamine-β-(1-4)-*N*-acetylglucosamine disaccharide (GalNAc-β-(1-4)-GlcNAc, LacdiNAc or LDN), is a common backbone motif in Schistosoma glycans in all stages of its life cycle.[1] It is frequently fucosylated on either the C3-OH of the GlcNAc (LDN-F) or the C3-OH of the GalNAc (F-LDN) residue, but can also be fucosylated on both positions (F-LDN-F).[2], [3] Although the LDN-F motif is also present in humans and therefore not that useful as a biomarker, both F-LDN and F-LDN-F are unique to Schistosomes making them good candidates as biomarkers.[4], [5] F-LDN and F-LDN-F and difucosylated LDN fragments (F2)-LDN-(F2) are secreted in the urine of infected individuals. The monoclonal antibody 114-4D12 (See Chapter 2 and 3 for more detail) can then be used to detect these multi-fucosylated oligosaccharides in urine, which would allow for the development of an easy method to determine the level of infection, similar to that of the circulating cathodic antigen (CCA) dipstick test.[6]

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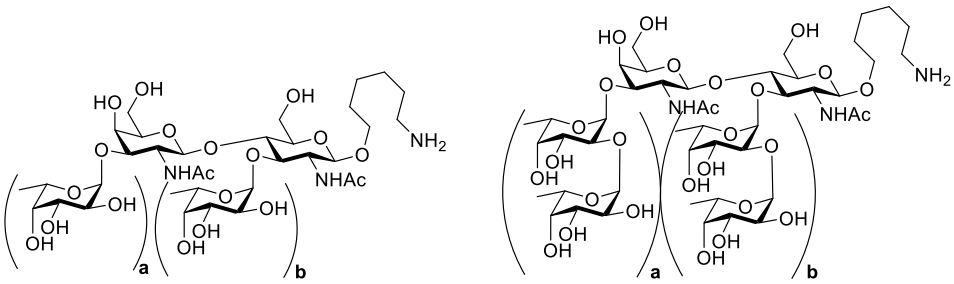


a = 1, **b** = 0: F-LDN
a = 0, **b** = 1: LDN-F
a = **b** = 1: F-LDN-F

a = 1, **b** = 0: F2-LDN
a = 0, **b** = 1: LDN-F2
a = **b** = 1: F2-LDN-F2

Figure 1: Fucosylated LDN fragments, left: mono-fucosylated LDN fragments, right: di-fucosylated LDN fragments.

Besides being potential biomarkers of schistosomiasis these fucosylated LDN fragments can be used as tools to probe biosynthesis enzymes. These fucosylated LDN fragments can be used to find both the enzymes that extend the α-fucosyl chains and the enzymes that hydrolyse the α-fucosyl chains, which are as of yet unknown.[7] The (F)-LDN-(F) fragments can be used to identify the former, while the (F2)-LDN-(F2) fragments can be used to identify the latter. This chapter describes a method to synthesize the fucosylated LDN fragments depicted in Figure 1.

Results and discussion

The synthetic route to the small set of fucosylated LDN fragments is retrosynthetically explained in Figure 2. The NHAc functionality in the target oligosaccharides is unsuitable for use in glycosylation reactions as the NHAc is known to form stable oxazolines and reduce the reactivity of the acceptor hydroxyl groups.[8]–[10] In order to avoid this the NHAc was masked as a trichloro acetamide (TCA) group. The amine of the linker was masked as an azide. Both the TCA and the azide can be converted into the NHAc and the amine, respectively, by a variety of methods enabling a flexible deprotection strategy at the end of the synthesis.[11]–[13] The LDN disaccharide backbone is decorated with two orthogonal protecting groups (R_1 and R_2) on the C3-O positions of both the GlcNAc and the GalNAc residues in order to install a mono- or di-fucosyl residue on this disaccharide selectively. The disaccharide can be synthesized from appropriately protected D-glucosamine and D-galactosamine building blocks. The galactosamine building block can also be synthesized from glucosamine, which is a significantly cheaper starting material. The NHTCA groups on these building blocks should induce the required β-selective linkages. Both these building blocks will be synthesized as thiophenyl glycosides, as thioglycosides can withstand a wide variety of protective group manipulations and can be used as glycosylating agents, or they can be transformed into other anomeric leaving

groups (such as imidates). The mono-fucosylated fragments will be synthesized by condensing the intrinsically α-selective fucosyl building block, whose preparation and use are described in Chapter 2, with the appropriate disaccharide. The di-fucosylated fragments will be synthesized using di-fucosyl building blocks, the synthesis of which is described in Chapter 3.

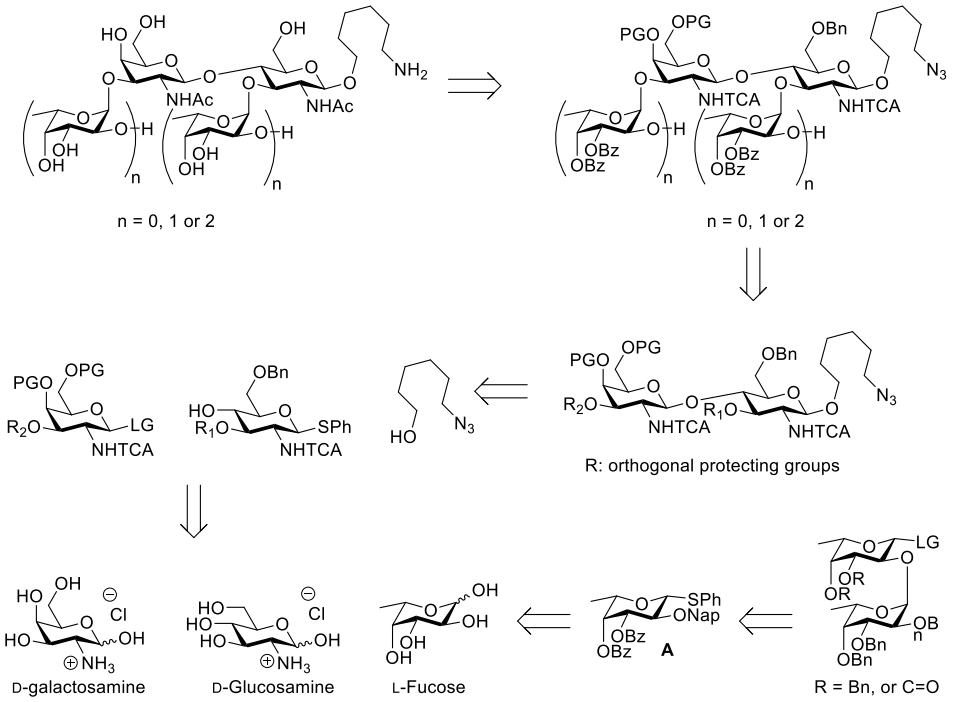


Figure 2: Retrosynthesis of fucosylated LDN fragments.

The synthesis of the glucosamine synthon is depicted in Scheme 1. Several different orthogonal protecting groups, naphthyl, benzoyl, levulinoyl and acetyl were explored at the C3-O position in order to optimize the backbone coupling. The naphthyl ether can be removed selectively using DDQ, the levulinoyl can be removed selectively using hydrazine and the acetyl and benzoyl esters can be removed by sodium methoxide. All final building blocks could be synthesized from known partially protected glucosamine **1**.

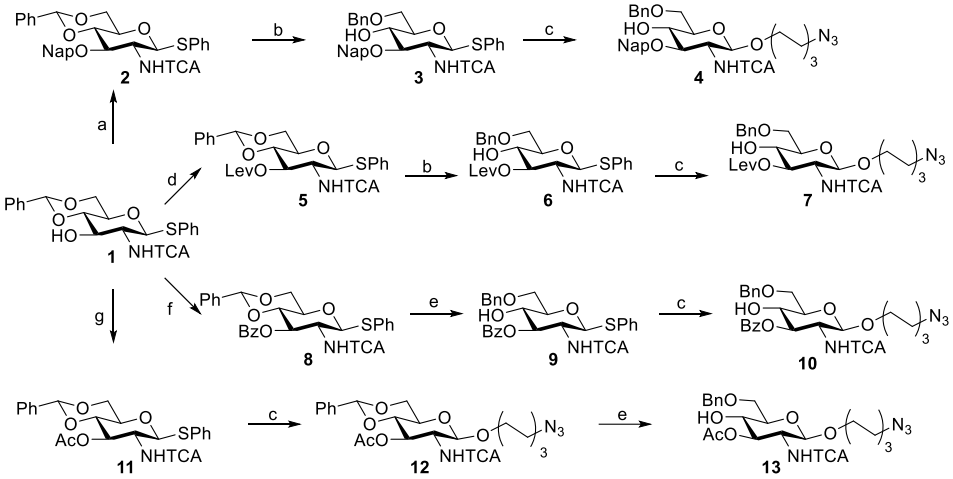
The naphthyl group was installed by treating **1** with an excess of three equivalents of sodium hydride and one equivalent of naphthyl bromide. This protocol reduced the unwanted alkylation of the amide, presumably due to formation of both the deprotonated amide and the C3-O alkoxide, the latter of is more nucleophilic, thus leading to the desired compound. The low solubility of compound **2** in DCM prevented

the introduction of the 6-azidohexan-1-ol using NIS/TMSOTf as the activator couple at this stage. Therefore, the benzylidene ring was opened prior to glycosylation. Several ring opening protocols were tested, including TfOH and TES in DCM at -78˚C, TFA with TES in DCM and iodine with TES in acetonitrile.[14]–[16] Although both the TfOH and TFA methods did result in the desired product, the yields were low. The solubility of compound **2** proved to be a severe limitation for these methods as the reactions had to be very dilute in order to dissolve it. However, when $BF_3{\cdot}OEt_2$ was used as the Lewis acid together with twelve equivalents of TES, the suspension of **2** immediately turned into a clear yellow solution, allowing it to react.[17] Compound **3** could be obtained in a yield of 61% and the location of the benzyl ether was verified after acetylation of the remaining alcohol and subsequent NMR analysis. Compound **3** was much more soluble in DCM than its precursor and the 6-azidohexan-1-ol linker could be installed selectively in a β-fashion using NIS/TMSOTf as the activator couple to give acceptor **4** with a C3-O naphthyl group in 64% yield.

En route to the corresponding levulinoyl ester protected acceptor **7**, compound **1** was subjected to a Steglich esterification using levulinic acid, DIC and DMAP. The same benzylidene ring opening methods as described above were screened and, like before, the use of $BF_3{\cdot}OEt_2$ as the lewis acid gave **6** in the highest yield (~60%).[17] Reduction of the ketone functionality in the levulinoyl ester, proved to be a major side reaction in these Lewis acid catalyzed reductive reactions. The 6-azidohexan-1-ol linker was introduced selectively in a β-fashion using NIS/TMSOTf as the activator couple resulting in acceptor **7** in 55% yield. A drawback in the synthesis of the levulinoyl protected compounds **5**, **6** and **7** was the similar polarity of these compounds, which hindered purification.

The synthesis of the C3-O benzoyl protected acceptor **10**, started by benzoylation of **1** using benzoyl chloride and DMAP in pyridine, which gave **8** in 81% yield. The benzylidene ketal in **8** was opened regioselectively and this time the TFA and TES couple gave the highest yield of **9** (69%).[15] The 6-azidohexan-1-ol linker could be installed using NIS/TMSOTf as the activator couple in 73% yield. Reversing the order of the ring-opening reaction and condensation reactions, led to a lower overall yield. The C3-O acetyl bearing acceptor **13** was synthesized by first acetylating the free alcohol in **1** using Ac_2O in pyridine and DCM, followed by introduction of the 6-azidohexan-1-ol linker using NIS/TMSOTf as the activator couple. The benzylidene acetal in to so-formed glucosamine (**12**) was opened regioselectively using the TFA/TES method.[15] Unlike the syntheses of the naphthyl, levulinoyl and benzoyl bearing acceptors the efficiency of the acetyl bearing acceptor was highest when the linker was installed prior to the reductive opening of the benzylidene ring.

*Scheme 1: Synthesis of glucosamine acceptors **4, 7, 10** and **13.***



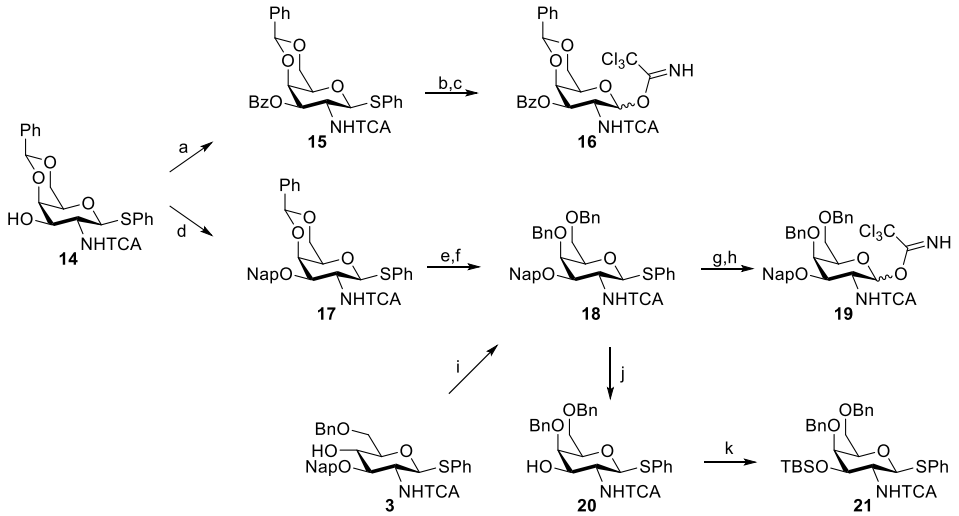
Reagents and conditions: **a**: NaH, Nap-Br, DMF, -20˚C to RT, 84%, **b**: $BF_3{\cdot}OEt_2$, TES, DCM, 0˚C, **3** 61%, **6** 60% **c**: 6-azidohexan-1-ol, NIS, TMSOTf (cat.), DCM, -20˚C to 0˚C, **4** 64%, **7** 55%, **10** 73%, **12** 59%, **d**: Lev-OH, DIC, DMAP, 0˚C to RT, 99%, **e**: TFA, TES, DCM, **9** 69%, **13** 96%, **f**: Bz-Cl, DMAP, DCM, pyr., 81%, **g**: Ac_2O, pyr., DCM, 95%.

In order to arrive at the backbone disaccharide a variety of galactosamine donors was synthesized from known partially protected galactosamine **14** (Scheme 2). Initially, the benzylidene protected donors were explored, but the benzylidene on these donors, however, reduced the reactivity of the donor and therefore the acetal was replaced by two benzyl ethers. Similar to the glucosamine synthon a variety of orthogonal groups were probed for protection of the galactosamine synthon as well. The C3-OH of these synthons were protected with either a naphthyl, benzoyl or tert-butyldimethylsilyl (TBDMS) group.

Benzoylation of the C3-OH in **14** using benzoyl chloride in conjunction with a catalytic amount of DMAP in a mixture of pyridine and DCM resulted in thioglycoside **15**. This thioglycoside donor was turned into imidate donor **16** by hydrolysis of the thiophenyl group with NBS in acetone followed by imidoylation of the formed hemi-acetal.[18] In order to increase the reactivity of the donor it was decided to exchange the benzylidene ring for two benzyl groups.[19] The naphthyl ether at the C3-OH was introduced by treatment of **14** with three equivalents of sodium hydride, followed by addition of naphthyl bromide, which gave compound **17** as in 85% yield. Any attempts to selectively open the benzylidene ring resulted in failure due to the low solubility of **17**. Therefore, the benzylidene was removed using *p*-TsOH in a mixture of dichloroethane and methanol at 50˚C to provide the diol in 80% yield. The subsequent benzylation using benzyl bromide with five equivalents of sodium hydride in DMF also required an elevated temperature of 50˚C , which resulted in donor **18** in 84% yield.

An alternative route to obtain donor **18** starting from the much cheaper glucosamine was investigated as well. The C4-OH of previously synthesized compound **3** was inverted in two steps. First the C4-OH was triflated by treating **3** with triflic anhydride in a mixture of DCM and pyridine.[20] Second the formed triflate was substituted using benzyl alcohol and triethylamine. To this end the mixture was heated to 50˚C and left for 18 hours. Although this method did lead to compound **18**, the yield (40%) was not competitive enough to make this a viable route. The thiophenyl group in fully protected naphthyl donor **18** was hydrolysed using NBS in aqueous acetone. The formed hemiacetal was treated with trichloroacetonitrile and a catalytic amount of DBU in dry DCM, which gave imidate donor **19** in 78% yield over two steps. In order to further increase the reactivity of the donor, the naphthyl group was exchanged for a TBDMS group. The selective removal of the naphthyl ether using DDQ in a mixture of DCM and methanol afforded compound **20** in a 85% yield.[21] The C3-OH of **20** was silylated by treating it with TBDMS-Cl and DMAP in DMF.[22] As the reaction proceeded slowly at room temperature, the temperature was increased to 80˚C, which swiftly led to complete silylation giving donor **21** in 86% yield.

*Scheme 2: Synthesis of galactosamine donors **15**, **16**, **18**, **19** and **21**.*

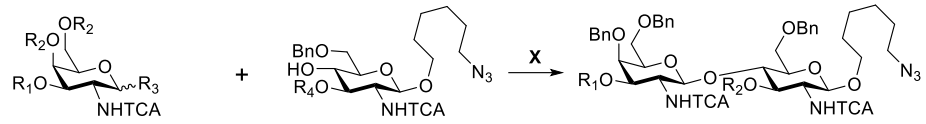


Reagents and conditions: **a**: Bz-Cl, DMAP, pyr., DCM, 99%, **b**: NBS, acetone, H_2O, 92%, **c**: CCl_3CN, DBU (cat.), ACN, 71%, **d**: NaH, Nap-Br, DMF, 85%, **e**: *p*-TsOH, MeOH, DCE, 80%, **f**: NaH, Bn-Br, DMF, 0˚C to 50˚C, 84%, **g**: NBS, acetone, H_2O, 98%, **h**: CCl_3CN, DBU (cat.), ACN, 78%, **i**: 1) Tf_2O, pyr., DCM, 0˚C, 2) Bn-OH, Et_3N, DMF, 50˚C, 40%, **j**: DDQ, DCM, MeOH, 85%, **k**: TBDMS-Cl, pyr, DMAP, DMF, 80˚C, 86%.

An overview of all attempted glycosylations to obtain the LDN backbone is shown in Table 1. Initially, thioglycoside **15** and acceptor **4** were condensed using NIS/TMSOTf as the activator couple (entries 1) but in this reaction the donor formed a stable oxazoline,

which did not react any further. Boutet *et al.* decribed a method to activate TCA oxazoline donors with $CuCl_2$, but this method failed.[23] The combination of donor **17** with acceptor **10** also provided an unproductive glycosylation (entry 2). The TCA oxazoline has been shown to be a good donor to use in β-selective glycosylations.[24] The reason for its apparent stability in this case is probably due the low reactivity of the C4-OH on the acceptor. When imidate donor **16** was combined with **4**, the desired dimer was formed, but separation from formed side products proved impossible (entry 3). Next the more reactive di-benzyl donor **18** was used in a glycosylation with acceptor **10** using NIS/TfOH. Unexpectedly, the β-(1-3) linked product **26** instead of the desired β-(1-4) linked product **22** was obtained (entry 4). Apparently, the C3-O-benzoyl group migrates to the C4-O position under these conditions, liberating the more reactive C3-OH, which in turn reacted with the activated donor.[25], [26] The thioglycoside was exchanged for imidate donor **19**, which reacted within 1 hour, opposed to the >18 hours of the previous entry, and gave the desired β-(1-4) linked product **22** in 45% yield (entry 5). Since the benzoyl proved difficult to remove in a later stage, the other donors were explored next. Condensation of TBDMS bearing donor **21** with naphthyl bearing acceptor **18** using the NIS/TfOH activator couple resulted in the formation of product **23** in 16% and 47% of oxazoline (**18BP**) (entry 6).[27] Several attempts to improve the yield turned out to be unsuccessful (entries 7 and 8). Next, attention was directed to the levulinoyl protected coupling partners. Naphthyl bearing donor **19** and levulinoyl bearing acceptor **7** were condensed using TfOH to give the dimer **24**, which -surprisingly- was formed as a mixture of α/β-anomers with the undesired α-isomer prevailing (α/β = 9/1, entry 9). To prevent the formation of the α-anomer, the solvent was changed from dichloromethane to the more β-directing solvent acetonitrile.[28] The change of solvent did improve the β-selectivity, but, not enough to render these building blocks useful for the construction of the backbone dimer (entries 10 and 11). The last reaction pair tried was naphthyl donor **19** and acetyl acceptor **13**. Like with levulinoyl protected acceptor **7**, acceptor **13** showed a lower β-selectivity, but less than the former (entry 12). The β-selectivity was improved by using a combination of DCM and acetonitrile as the solvent (entries 13-15). Employing this solvent mixture to condense donor **19** and acceptor **13** with TfOH as the activator resulted in the formation of disaccharide **25** in 82% yield (entry 15).

Table 1: Overview of glycosylations to form the LDN backbone.



15 R_1 = Bz, R_2 = CHPh, R_3 = SPh
16 R_1 = Bz, R_2 = CHPh, R_3 =O(N=H)CCl_3
17 R_1 = Nap, R_2 = CHPh, R_3 = SPh
18 R_1 = Nap, R_2 = Bn, R_3 = SPh
19 R_1 = Nap, R_2 = Bn, R_3 = O(N=H)CCl_3
21 R_1 = TBDMS, R_2 = Bn, R_3 = SPh

4 R_4 = Nap
7 R_4 = Lev
10 R_4 = Bz
13 R_4 = Ac

22 R_1 = Nap, R_2 = Bz
23 R_1 = TBDMS, R_2 = Nap
24 R_3 = Nap, R_2 = Lev
25 R_3 = Nap, R_2 = Ac
26 β-(1-3) product

entry	Don.	Acc.	T (˚C)	X[a]	prod.	yield	α/β
1	**15**	**4**	-40 → 0	NIS, TMSOTf	-	-	-
2	**17**	**10**	-40 → 0	NIS, TMSOTf	-	-	-
3	**16**	**4**	-40 → -20	TMSOTf	-	-[b]	-
4	**18**	**10**	-20	NIS, TfOH	**26**	47	0/1
5	**19**	**10**	-20 → 0	TfOH	**22**	45	0/1
6	**21**	**4**	-40 → -20	NIS, TfOH	**23**	16	0/1
7	**21**	**4**	-20	NIS, TfOH	**23**	17	0/1
8	**21**	**4**	0	NIS, TfOH	**23**	5	0/1
9	**19**	**7**	-20	TfOH	**24**	43	9/1
10	**19**	**7**	-20	TfOH[c]	**24**	44	1/9
11	**19**	**7**	0	TfOH[d]	**24**	37	1/3
12	**19**	**13**	-20 → 0	TfOH	**25**	35	1/8
13	**19**	**13**	-40 → -30	TfOH	**25**	62	1/8
14	**19**	**13**	-40 → -30	TfOH[d]	**25**	65	1/20
15	**19**	**13**	-40 → -30	TfOH[c]	**25**	82	1/20

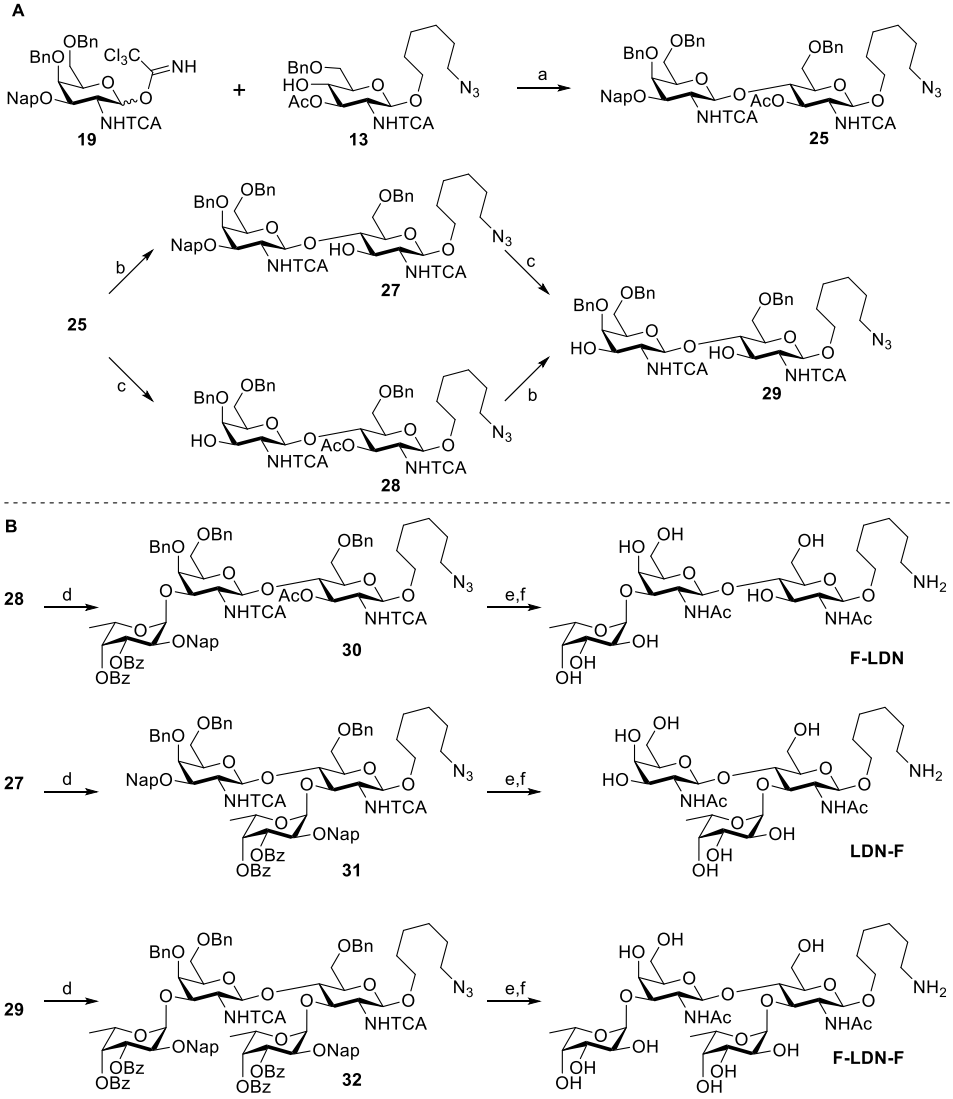
[a] All reactions were performed in presence of freshly dried molecular sieves (3Å) at a concentration of 0.1M under inert atmosphere in DCM unwise indicated otherwise
[b] obtained as an inseparable mixture.
[c] reaction was performed in a mixture of DCM/ACN, 4/1, v/v.
[d] reaction was performed in ACN

In order to obtain the three desired backbone acceptors, the orthogonal protective groups on either the C3-O, or C'3-O or both had to be removed (Scheme 3A). Disaccharide **22** was subjected to Zemplén conditions to hydrolyze the benzoyl group. Unfortunately, the benzoyl group proved to be very stable, presumably due to steric hindrance. When the temperature was increased, the TCA groups were hydrolyzed as well, reducing the usefulness of the benzoyl group. The hydrolysis of the more labile acetyl group on **25** under Zemplén conditions proceeded sluggishly as well. Therefore, sodium hydroxide, a smaller nucleophile was used. Although this did increase both the

reaction speed and the yield of compound **27** (58%), a significant amount of TCA removal was still observed. In order to obtain disaccharide **28** the naphthyl group was selectively removed by DDQ oxidation. This reaction proceeded very sluggishly, and the desired disaccharide was obtained in a low yield (16%). Addition of β-pinene did not significantly improve the yield, and therefore a different protocol was employed, which involves the use of HCl in HFIP with triethylsilane as a scavenger.[29] These conditions led to the selective removal of the naphthyl group giving disaccharide **28** in a 55% yield.[30] Approximately 40% of unreacted starting material was recovered and this could be retreated with the same conditions. Leaving the reaction for longer than one hour led to significant byproduct formation. Compound **28** had to be stored at -20˚C in order to prevent degradation. Diol acceptor **29** was synthesized from either **27** or **28**, by either hydrolyzing the ester or removing the naphthyl ether. Both reactions proceeded in similar yields as before.

With the properly protected dimers **27**-**29** available the fucosyl residues were introduced using the optimized protocol that is described in Chapter 2. The disaccharide backbones were condensed using two equivalents of fucosyl donor **A** (Figure 2) per hydroxyl present on the dimer acceptor, and NIS/TMSOTf as the activator couple (Scheme 3B). This resulted in trisaccharides **30** and **31** and tetrasaccharide **32** in yields ranging between 65% and 69%. NMR analysis confirmed the selective formation of *cis* linkages ($^{3}J_{1,2}$ = 3.6 Hz and $^{1}J_{C\text{-}1,\,H\text{-}1}$ = 170 Hz).[31] Of note, the C-2 peak of trisaccharide **31** and tetrasaccharide **32** was barely visible on their ^{13}C-APT NMR at room temperature.

Scheme 3: A) Synthesis of LDN acceptors, B) Synthesis of (F)-LDN-(F) fragments.



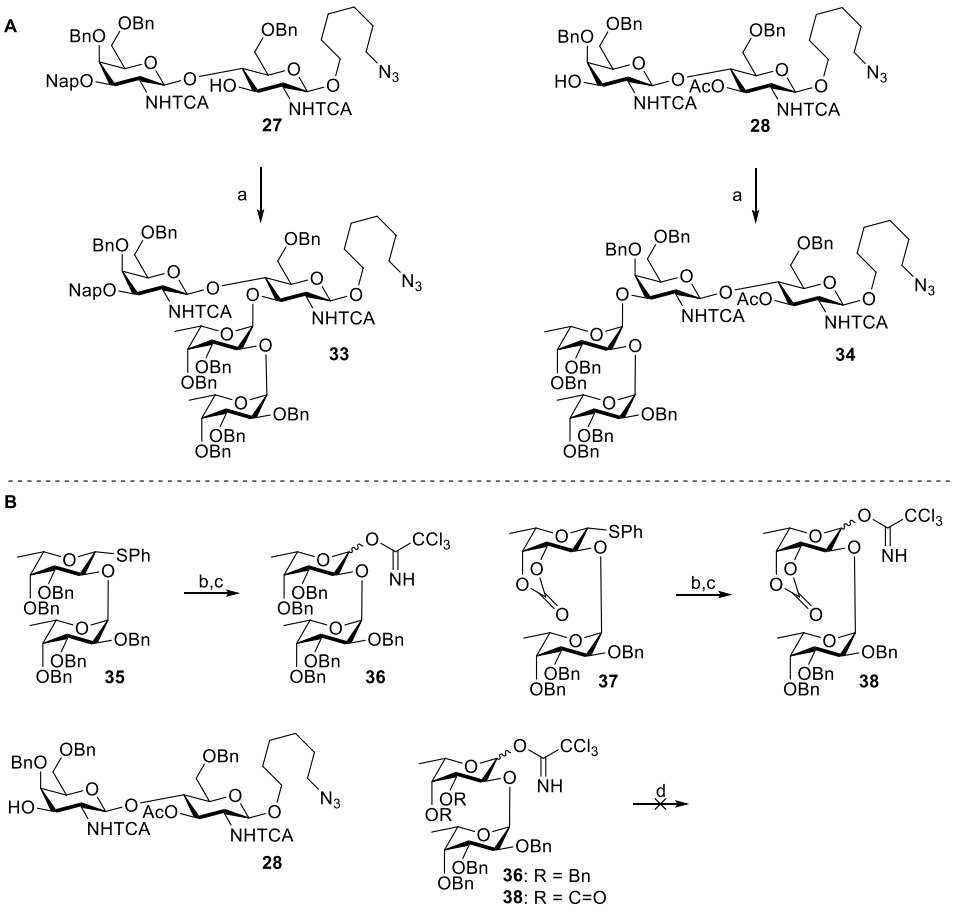
Reagents and conditions: **a**: **13**, TfOH, MS (3Å), DCM, ACN, -40 ˚C to -20˚C, 82% , **b**: NaOH, dioxane, H_2O, **27** 58%, **29** 47% **c**: HCl, HFIP, DCM, **28** 55%, **29** 61%, **d**: **A**, NIS, TMSOTf, MS (3Å), DCM, -40˚C→ -20˚C, **30** 65%, **31** 69%, **32** 69%, **e**: NaOMe (cat.), THF/MeOH, **30** 64%, **31** 65%, **32** 63%, **f**: Pd/C (cat.) H_2, dioxane, H_2O, **F-LDN** 38%, **LDN-F** 24%, **F-LDN-F** 24%.

Finally, the protective groups on **30-32** were removed in two steps. First, the esters were hydrolysed by sodium methoxide in a mixture of THF and MeOH. Although the benzoyl esters could all be removed by stirring overnight at room temperature, the removal of the acetyl group on the C3-O position required the temperature to be increased to 40˚C. As benzoyl groups are generally less susceptible to hydrolysis than acetyl groups, this

indicates that the C3-O is in a difficult position to react because of steric congestion, as also found in the deprotection reactions described above. Second, hydrolysed compounds **30-32** were subjected to catalytic hydrogenation. This converted the azide into a free amine, the TCA into an acetyl and removed the benzyl and naphthyl ethers. **F-LDN**, **LDN-F** and **F-LDN-F** were obtained in yields of 38%, 25% and 24%. Besides the desired products significant amounts of de-fucosylated products were observed, which were probably formed due to acidic hydrolysis of the fucosyl linkages as a result of the HCl that was released by the reduction of the TCA groups.

Lastly, the synthesis of LDN bearing di-fucosyl side chains was undertaken. To this end, the fucosyl dimers were attached to the C3-OH positions on the LDN backbones employing a [2+2] block coupling approach (Scheme 4). The optimized coupling method, described in Chapter 3, using two equivalents of fucosyl donor **35** with IDCP as the activator, was applied. Unfortunately, the condensations with acceptors **27** and **28** proceeded with poor yields (7% for **33** and 14% for **34**).

Scheme 4: A) Synthesis of (F2)-LDN-(F2) fragments, B) synthesis of imidate di-fucosyl donors and attempted glycosylations.

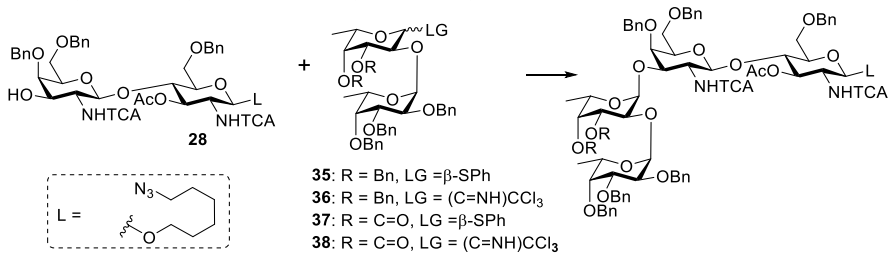


Reagents and conditions: **a**: **35**, IDCP, MS (3Å), DCM, 0˚C → RT, **33** 7%, **34** 14%, **b**: NBS, H_2O, acetone, 71% (from **35**), 64% (from **37**), **c**: CCl_3CN, DCM, DBU (cat.) **36** 97%, **38** 99%, **d**: **36** or **38**, TMSOTf (cat.), MS (3Å), DCM, -40˚C → -20˚C.

To improve the yield of the difucosylated tetrasaccharides, several glycosylation procedures were evaluated, the results of which are summarized in Table 2. In this study, acceptor **28** was used for optimization as it was reasoned that the C3'-OH is more accessible than the C3-OH. Initially the mild IDCP activation method was replaced by the pre-activation method using diphenylsulfoxide (DPS), 2,4,6-tri-*tert*-butylpyrimidine (TTBP) and triflic anhydride (entry 2).[32] Although this did result in a net higher yield of tetrasaccharide **34**, the stereoselectivity of the reaction was lower and the tetrasaccharide was isolated as an anomeric mixture. Bennet and co-workers showed that the α-selectivity of the pre-activation protocol could be increased by addition of TBAI (entry 3).[33] Unfortunately, when these glycosylation conditions were used no

product formation was observed. Next, thioglycoside **35** was turned into imidate **36**, by first hydrolyzing the thiophenyl group, followed by imidoylation of the formed hemi-acetal, to give imidate donor **36** in 71% over two steps.[34] Condensation of donor **36** with acceptor **28** by addition of a catalytic amount of TMSOTf was disappointing, as no significant quantity of the target compound could be isolated (entry 4). Besides activated donor **35**, disarmed di-fucosyl donor **37** was explored. The condensation of thioglycoside **37** with acceptor **28** using the NIS/TMSOTf activator couple (entry 5) resulted in the formation of the succinimide adduct of **37** (not isolated). In order to prevent the formation of this adduct, thioglycoside **37** was converted to an imidate. A similar method was used by hydrolyzing the thiophenyl group using NBS in aqueous acetone. The formed hemi-acetal was then imidoylated using trichloroacetonitrile with a catalytic amount of DBU to give imidate **38** in a yield of 64% over two steps.[34] Acceptor **28** was condensed with imidate donor **38**, and although LC-MS indicated product formation, the product could not be isolated in sufficient quantities for NMR analysis (entry 6).

Table 2: Optimization of the introduction of the di-fucosyl chains



entry	donor	reagents	Conditions[a]	product	Yield (%)
1	**35**	IDCP	0.2M, 0˚C → RT	**34**	14
2	**35**	DPS, TTBP, Tf_2O	0.05M, -80˚C → 0˚C	**34**[b]	20
3	**35**	DPS, TTBP, Tf_2O, TBAI	0.05M, -80˚C → RT	-	-
4	**36**	TMSOTf	0.1M, -40˚C → 0˚C	-	trace[c]
5	**37**	NIS, TMSOTf	0.1M, -20˚C → RT	-	-
6	**38**	TMSOTf	0.1M, -40˚C → 0˚C	-	trace[c]

[a] all reactions were performed under inert atmosphere in dry DCM, with MS (3Å) present using 0.05 mmol of acceptor **28**.

[b] Obtained as an anomeric mixture (α/β, 1/1).

[c] the mass was observed on LC-MS but not enough could be isolated for NMR.

As both armed and disarmed donors were used, it is assumed that the reactivity of the acceptor is the leading cause of the low yields. It has been documented that the reactivity of C3-OH glucosamine derivatives, with an amide on the C2 position is significantly lower due to both inter- and intra- molecular hydrogen bonding and similar effects may play a role in the galactosamine system studied here.[10], [35], [36] Of note, Kanaya *et al.* managed to install a di-fucosyl moiety on a similar backbone, but they used Troc groups instead of a TCA groups to mask the amines.[37]

Conclusion

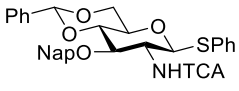
In order to synthesize a small library of fucosylated LDN fragments depicted in Figure 1, five different GlcNAc acceptors and five different GalNAc donors were synthesized, both bearing an orthogonal protecting group on the C3-O position. The synthesis of the LDN backbone proved to be troublesome, requiring reactive benzyl ether prptected donors to avoid oxaziline formation. Of the different protecting groups explored on the GlcNAc building block (naphthyl, benzoyl, levulinoyl and acetyl), the benzoyl showed the best stereoselectivity but this group proved difficult to remove at a later stage. The levulinoyl protected acceptor surprisingly led to the selective formation of the α-linked products, in spite of the TCA group in the donor glycosides. The acetyl protected acceptor showed a bit lower β-selectivity in comparison to its benzoyl counterpart, but the lower stereoselectivity could be remedied by using acetonitrile as a co-solvent. Mono-fucosides could be introduced on the GalN-GlcN backbone using NIS/TMSOTf mediated to provide tri- and tetrasaccharides that were successfully deprotected to obtain F-LDN, LDN-F, and F-LDN-F. The di-fucosyl chains could not be installed and the exact reason for this is currently attributed to steric hindrance.

Experimental

General

Glassware used for reactions was oven dried before use at 80°C. Anhydrous solvents were prepared by drying them over activated molecular sieves (3Å) for at least 24 hours before use. Molecular sieves were activated by flame-drying under reduced pressure. Reactions that required anhydrous conditions were co-evaporated with anhydrous toluene or anhydrous 1,4-dioxane to remove traces of water and the reactions were performed under argon or nitrogen atmosphere. EtOAc and toluene used for extractions and silica gel column chromatography were distilled before use, all other chemicals were used as received. One- and two-dimensional NMR spectra were recorded at 298 K unless stated otherwise on a Bruker AV-300 (300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei), AV-400 (400 MHz for ^{1}H nuclei and 101 MHz for ^{13}C nuclei) or a Bruker AV-500 (500 MHz for ^{1}H nuclei and 126 MHz for ^{13}C nuclei). Chemical shifts (δ) are given in ppm relative to tetramethylsilane or the deuterated solvent. IR-spectra were recorded on a Shimadzu FTIT-8300. HRMS spectra were recorded on a Thermo Finnigan LTQ orbitrap mass spectrometer. Unless stated otherwise all reaction were carried out at room temperature and monitored by thin layer chromatography (TLC). TLC was carried out on Merck aluminium sheets (silica gel 60 F254). TLC analysis was performed by detecting UV adsorption (254 nm) where suitable and spraying the TLC plate with 20% H_2SO_4 in EtOH or with a solution of $(NH_4)_6Mo_7.4H_2O$ (25 g/L), KOH (1 g/L) in water or a solution of $KMnO_4$ (20 g/L) and K_2CO_3 (10 g/L) in water or an anisaldehyde solution containing H_2SO_4, glacial acetic acid and p-anisaldehyde in absolute EtOH followed by charring the TLC plate at 150°C. TLC-MS analysis was performed by extracting spots of interest off a TLC plate with a CAMAG TLC interface connected to an API 165 mass spectrometer. Silica gel column chromatography was performed on silica gel (40 - 63 µm particle size, 60 Å pore size). Size exclusion chromatography was carried out on Sephadex™ LH-20 gel.

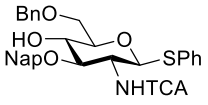
Phenyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-(2-methylnaphthyl)-1-thio-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (2)



NaH (0.12 g, 3.0 mmol, 3.0 eq.) was added portionwise to a solution of **1** (0.50 g, 1.0 mmol, 1.0 eq.) in dry DMF (10 mL, 0.1M) at -20˚C. The reaction was left to stir until the evolution of gas stopped, at which point the Nap-Br (0.24 g, 1.1 mmol, 1.1 eq.) was added. The solution was allowed to warm up to RT. Upon completion (~3 hours) the reaction mixture was slowly poured into H_2O. The white precipitate was filtered over a glass filter, washed with H_2O (3x) and cold Et_2O (3x). This gave the title compound as a white solid (0.54 g, 0.84 mmol, 84%). ^{1}H NMR (Acetone-d_6, 400 MHz): δ = 8.59 (d, 1H, *J*=8.4 Hz, NH), 7.93 – 7.64 (m, 4H, arom.), 7.61 – 7.45 (m, 7H, arom.), 7.45 – 7.22 (m, 6H, arom.), 5.78 (s, 1H,

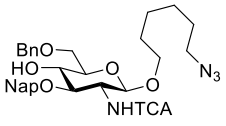
CHPh), 5.24 (d, 1H, *J*=9.8 Hz, H-1), 5.05 (d, 1H, *J*=12.1 Hz, CH_2Nap), 4.95 (d, 1H, *J*=11.5 Hz, CH_2Nap), 4.33 (dd, 1H, *J*=10.3, 5.0 Hz, H-6), 4.24 – 4.04 (m, 2H, H-2, H-3), 4.02 – 3.84 (m, 2H, H-4, H-6), 3.60 (td, 1H, *J*=9.8, 5.0 Hz, H-5) ppm. ^{13}C-APT NMR (Acetone-d_6, 101 MHz): δ 161.5 (C=O, TCA), 138.0, 136.1, 133.3, 133.1, 131.7, 129.0, 128.7, 128.1, 127.8, 127.6, 127.6, 126.3, 126.2, 126.1, 126.0, 125.7 (arom.), 101.0 (CHPh), 87.2 (C-1), 81.8 (C-3), 79.2 (C-4), 74.2 (CH_2Nap), 70.4 (C-5), 68.1 (C-6), 56.0 (C-2) ppm. HRMS $[M+NH_4]^+$ calcd for $C_{32}H_{28}Cl_3O_5SNH_4$: 661.10920, found 661.11008.

Phenyl 6-*O*-benzyl-2-deoxy-3-*O*-(2-methylnaphthyl)-1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside (3)



Compound **2** (3.03 g, 4.7 mmol, 1.0 eq.) was suspended in DCM (47 mL, 0.1M) and the flask was cooled to 0˚C. TES (9.0 mL, 56.4 mmol, 12 eq.) was added followed by dropwise addition of $BF_3{\cdot}OEt_2$ (1.16 mL, 9.40 mmol, 2.0 eq.). The suspension was stirred at 0˚C until all was dissolved, at which point TLC analysis showed full conversion of the starting material. The solution was diluted with EtOAc and washed with sat. $NaHCO_3$ (aq.) and brine, followed by drying over $MgSO_4$, filtered and concentrated. Pure **3** was obtained after purification by silicagel chromatography (tol:EtOAc, 1:0 → 4:1) as a white solid (1.84 g, 2.84 mmol, 61%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.99 – 7.68 (m, 4H, arom.), 7.62 – 7.42 (m, 5H, arom.), 7.42 – 7.13 (m, 8H, arom.), 6.87 (d, 1H, *J*=8.0 Hz, NH), 5.15 (d, 1H, *J*=10.3 Hz, H-1), 4.92 (q, 2H, *J*=11.3 Hz, CH_2arom), 4.74 – 4.45 (m, 2H, CH_2arom), 4.01 (dd, 1H, *J*=10.0, 8.5 Hz, H-3), 3.92 – 3.69 (m, 3H, H-4, H-6), 3.66 – 3.45 (m, 2H, H-2, H-5), 2.84 (d, 1H, *J*=2.6 Hz, 3-OH) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz): δ 161.7 (C=O, TCA), 137.7, 135.3, 133.4, 133.3, 133.2, 132.0, 129.2, 128.7, 128.5, 128.1, 128.1, 127.9, 127.8, 127.2, 126.3, 126.2, 126.1 (arom.), 85.0 (C-1), 81.3 (C-3), 78.0 (C-5), 75.2 (CH_2arom), 73.9 (CH_2arom), 73.5 (C-4), 70.7 (C-6), 56.7 (C-2) ppm.

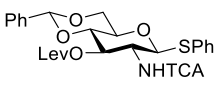
6-azidohexyl 6-*O*-benzyl-2-deoxy-3-*O*-(2-methylnaphthyl)-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (4)



Donor **3** (0.97 g, 1.61 mmol, 1.0 eq.) and 6-azidohexan-1-ol (0.3 g, 2.1 mmol, 1.3 eq.) were co-evaporated together thrice with dry toluene, before dissolving them in dry DCM (16 mL, 0.1M). Freshly dried MS (3Å) were added and the mixture was stirred for 15 min. at room temperature. Next NIS (0.43 g, 1.93 mmol, 1.2 eq.) was added and the mixture was cooled to -20˚C, at which temperature it was stirred for an additional 30 min. TMSOTf (58 µL, 0.32 mmol, 0.2 eq.) was added and the mixture was allowed to warm up to 0˚C and kept at that temperature. After 2 hours the reaction was stopped by addition of Et_3N (0.5 mL). The reaction mixture was diluted in EtOAc, washed twice with sat. $Na_2S_2O_3$ (aq.), followed by sat. $NaHCO_3$ (aq.) and brine. After drying over $MgSO_4$ and

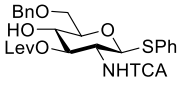
filtration the solvents were removed by evaporation. The title compound was separated from byproducts by silicagel chromatography (tol:EtOAc, 1:0 → 4:1) and isolated as a white solid (1.03 g, 0.64 mmol, 64%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.87 – 7.66 (m, 4H, arom.), 7.53 – 7.42 (m, 3H, arom.), 7.42 – 7.22 (m, 5H, arom.), 6.98 (d, 1H, *J*=7.7 Hz, NH), 5.07 – 4.85 (m, 2H, CH_2arom), 4.83 (d, 1H, *J*=8.2 Hz, H-1), 4.57 (q, 2H, *J*=12.0 Hz, CH_2arom), 4.04 (dd, 1H, *J*=10.5, 8.5 Hz, H-3), 3.84 (dt, 1H, *J*=9.6, 6.2 Hz, OCH_2), 3.79 – 3.62 (m, 3H, H-4, H-6), 3.59 – 3.48 (m, 2H, H-2, H-5), 3.43 (dt, 1H, *J*=9.6, 6.7 Hz, OCH_2), 3.21 (t, 2H, *J*=6.9 Hz, CH_2N_3), 2.93 (s, 1H, 4-OH), 1.62 – 1.46 (m, 4H, CH_2, hexyl), 1.39 – 1.26 (m, 4H, CH_2, hexyl) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ 162.0 (C=O, TCA), 137.6, 135.5, 133.3, 133.1, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8, 127.0, 126.3, 126.1, 126.1 (arom.), 99.5 (C-1), 92.6 (C_q, TCA), 79.6 (C-3), 74.8 (CH_2arom), 73.8 (CH_2arom), 73.7 (C-5), 73.6 (C-4), 70.6 (C-6), 69.9 (OCH_2), 58.3 (C-2), 51.4 (CH_2N_3), 29.5, 28.8, 26.5, 25.6 (CH_2, hexyl) ppm. HRMS $[M+H]^+$ calcd for $C_{32}H_{37}Cl_3N_4O_6H$: 679.18587, found 679.18846.

Phenyl 3-*O*-levulinoyl-4,6-*O*-benzylidene-2-deoxy-1-thio-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (5)



Sugar **1** (8.6 g, 17,1 mmol, 1.0 eq.) was dissolved in DCM (60 mL, 0.3M) and cooled to 0˚C. Levulinic acid (5.9 g, 51.3 mmol, 3.0 eq.) was added to this solution followed by DIC (5.0 g, 24 mmol, 1.4 eq.) and DMAP (0.22 g, 1.71 mmol, 0.1 eq.). The solution was left to stir at RT for 1 hour, when TLC analysis showed complete conversion. The reaction mixture was diluted in EtOAc and washed thrice with sat. $CuSO_4$ (aq.) , thrice with sat. $NaHCO_3$ (aq.) and once with brine. The organic layer was dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The obtained brown oil was purified via column chromatography (PE:EtOAc, 9:1 → 6:4) to afford compound as a white solid (10.3 g, 17.1 mmol, 99 %). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.54 – 7.38 (m, 3H, arom.), 7.38 – 7.22 (m, 9H, NH, arom.), 5.57 – 5.42 (m, 2H, H-3, CHPh), 4.95 (d, 1H, *J*=10.4 Hz, H-1), 4.17 (dd, 1H, *J*=10.4, 4.9 Hz, H-6), 4.04 (q, 1H, *J*=10.2, 9.3 Hz, H-2), 3.86 – 3.66 (m, 3H, H-4, H-6), 3.55 (dt, 1H, *J*=9.5, 4.8 Hz, H-5), 2.81 – 2.47 (m, 4H, CH_2, Lev), 2.09 (s, 3H, CH_3, Lev) ppm. ^{13}C-APT NMR ($CDCl_3$, 75 MHz) δ 133.0, 129.3, 129.2, 128.5, 128.3, 126.3, 126.2 (arom.), 101.4 (CHPh), 87.3 (H-1), 78.5 (C-3), 72.5 (C-5), 70.8 (C-4), 68.4 (C-6), 55.2 (C-2), 38.1 (CH_2, Lev), 28.2 (CH_2, Lev), 23.5 (CH_3, Lev). HRMS $[M+H]^+$ calcd for $C_{26}H_{30}Cl_3NO_7SNa$: 624.03932, found 624.04485.

Phenyl 3-*O*-levulinoyl-6-*O*-benzyl-2-deoxy-1-thio-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (6)

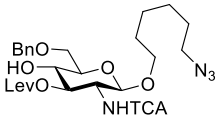


Sugar **5** (1 mmol, 0.6 g, 1.0 eq.) was co-evaporated thrice with toluene before dissolving it in dry DCM (10 mL, 0.1M). Molecular sieves (3Å) were added and the solution was left to stir at RT under inert

atmosphere for 30 min. TES (1.93 mL, 12 mmol, 12 eq.) was added and the solution was again left to stir for 10 minutes under inert atmosphere. $BF_3{\cdot}OEt_2$ (0.24 mL, 2 mmol, 2.0 eq.) was added and the solution was left to stir for 30 minutes. When TLC analysis showed complete conversion, the reaction mixture was diluted in EtOAc and washed with 1M HCl (aq.), thrice with sat. $NaHCO_3$ (aq.) and once with brine. The organic layer was dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The obtained liquid was dissolved in 10 mL DCM (0,1M), to this Trt-Cl (0.31 g, 1.1 mmol, 1.1 eq.) and triethylamine (0.21 mL, 1.5 mmol, 1.5 eq.) were added and the mixture was left to stir overnight. The solvents were removed under reduced pressure and the obtained liquid was purified by column chromatography (tol:EtOAc, 1:0 → 6:4) to afford compound as a white solid (0.36 g, 0.6 mmol, 60%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.61 – 7.41 (m, 2H, arom.), 7.43 – 7.08 (m, 9H, NH, arom.), 5.36 (t, 1H, *J*=10.0, 8.5 Hz, H-3), 4.84 (d, 1H, *J*=10.3 Hz, H-1), 4.64 – 4.48 (m, 2H, CH_2Bn), 4.01 (q, 1H, *J*=10.1 Hz, H-2), 3.88 – 3.65 (m, 4H, H-4, H-5, H-6), 3.55 (s, 1H, 4-OH), 2.68 (t, 2H, *J*=6.5 Hz, CH_2, Lev), 2.59 – 2.31 (m, 2H, CH_2, Lev), 2.05 (s, 3H, CH_3, Lev) ppm. ^{13}C-APT NMR ($CDCl_3$, 75 MHz) δ 207.9 (CH_3C=O, Lev), 173.7 (C=O, Lev), 161.9 (C=O, TCA), 138.1, 132.5, 132.5, 132.5, 129.0, 128.5, 128.0, 127.8, 127.7 (arom.), 92.5 (C_q, TCA), 85.9 (C-1), 78.7 (C-5), 76.8 (C-3), 73.6 (CH_2Bn), 69.8 (C-6), 69.7 (C-4), 54.2 (C-2), 38.3 (CH_2, Lev), 29.8 (CH_3, Lev), 28.3 (CH_2, Lev) ppm. HRMS $[M+H]^+$ calcd for $C_{26}H_{28}Cl_3NO_7SNa$: 626.05498, found 626.05394.

4

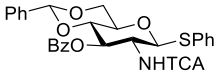
6-azidohexyl 3-*O*-levulinoyl-6-*O*-benzyl-2-deoxy-1-thio-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (7)



Donor **6** (0.16 g, 0.26 mmol, 1.0 eq.) and 6-azidohexan-1-ol (0.074 g, 0.52 mmol, 2.0 eq.) were co-evaporated together thrice with dry toluene, before dissolving them in dry DCM (2.5 mL, 0.1M). Freshly dried MS (4Å) were added and the mixture was stirred for 15 min. at room temperature. Next NIS (0.071 g, 0.31 mmol, 1.2 eq.) was added and the mixture was cooled to -20˚C, at which temperature it was stirred for an additional 30 min. TMSOTf (52 µL, 0.55 mmol, 0.2 eq., of a 0.1M in DCM) was added and the mixture was allowed to warm up to 0˚C. After 2 hours the reaction was stopped by addition of Et_3N (0.1 mL). The reaction mixture was diluted in EtOAc, washed twice with sat. $Na_2S_2O_3$ (aq.), followed by sat. $NaHCO_3$ (aq.) and brine. After drying over $MgSO_4$ and filtration the solvents were removed by evaporation. The title compound was separated from byproducts by silicagel chromatography (PE:EtOAc, 9:1 → 1:1) and isolated (0.092 g, 0.14 mmol, 55%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.37 – 7.26 (m, 5H, arom.), 7.13 (d, 1H, *J*=9.1 Hz, arom.), 5.27 (dd, 1H, *J*=10.8, 8.8 Hz, H-3), 4.67 – 4.49 (m, 3H, H-1, CH_2Bn), 4.03 – 3.69 (m, 5H, H-2, H-4, H-6, OCH_2), 3.69 – 3.53 (m, 1H, H-5), 3.46 (m, 2H, OCH_2, 4-OH), 3.23 (t, 2H, *J*=6.9 Hz, CH_2N_3), 2.76 (m, 2H, CH_2, Lev), 2.63 – 2.44 (m, 2H, CH_2, Lev), 2.15 (s, 3H, CH_3, Lev), 1.63 – 1.49 (m, 4H, CH_2, hexyl), 1.41 – 1.30 (m, 4H, CH_2, hexyl) ppm. ^{13}C-APT

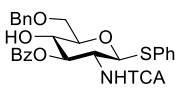
NMR ($CDCl_3$, 75 MHz): δ 207.8 (CH_3C=O, Lev), 173.5 (C=O, Lev), 162.1 (C=O, TCA), 128.5, 127.9, 127.8 (Ph), 100.7 (C-1), 75.4 (C-3), 74.5 (C-5), 73.7 (CH_2Bn), 70.2 (C-4), 69.8 (C-6, OCH_2), 55.7 (C-2), 51.4 (OCH_2N_3), 38.4 (CH_2, Lev), 29.5 (CH_2, Lev), 28.8, 28.3, 26.5, 25.6 (CH_2, hexyl) ppm.

Phenyl 3-*O*-benzoyl-4,6-*O*-benzylidene-2-deoxy-1-thio-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (8)



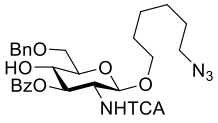
Benzoyl chloride (1.4 mL, 12.0 mmol, 2 eq.) was slowly added to a solution of **1** (3.0 g, 5.95 mmol, 1.0 eq.) in DCM and pyridine (60 mL, 0.1M, 3/1, v/v). The reaction was stirred for 1 hour at room temperature. After this time MeOH (2 mL) was added and the reaction was diluted in EtOAc. The organic layer was washed with sat. $CuSO_4$ (aq., 3x), sat. $NaHCO_3$ (aq., 1x) and brine, before drying over $MgSO_4$, filtration and concentration *in vacuo*. The crude mixture was purified by silicagel chromatography (PE:EtOAc, 99:1 → 4:1) and isolated as a white solid (2.94 g, 4.8 mmol, 81%). Spectral data was in accordance with those reported previously.[38]

Phenyl 3-*O*-benzoyl-6-*O*-benzyl-2-deoxy-1-thio-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (9)



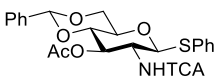
Compound **8** (0.065 g, 0.10 mmol, 1.0 eq.) was dissolved in dry DCM (1.1 mL, 0.1M) and the solution was cooled to 0˚C. TES (68 µL, 0.42 mmol, 4.0 eq.) and TFA (32 µL, 0.42 mmol, 4.0 eq.) were added after 3 hours of stirring at 0˚C. TLC analysis showed complete consumption of the starting material. The reaction mixture was transferred to a separatory funnel, diluted with EtOAc, washed thrice with sat. $NaHCO_3$ (aq.) and once with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Silicagel chromatography (PE:EtOAc, 99:1 → 7:3) gave the title compound as a colourless oil (0.045 g, 0.074 mmol, 69%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.05 – 7.72 (m, 2H, arom.), 7.66 – 7.46 (m, 4H, NH, arom.), 7.46 – 7.04 (m, 10H, arom.), 5.78 (t, 1H, *J*=10.2 Hz, H-3), 4.99 (d, 1H, *J*=10.3 Hz, H-1), 4.67 – 4.43 (m, 2H, CH_2Bn), 4.27 (q, 1H, *J*=10.1 Hz, H-2), 3.92 (m, 1H, H-4), 3.88 – 3.70 (m, 3H, H-5, H-6), 3.23 (s, 1H, 4-OH) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz): δ 167.9 (C=O, Bz), 162.1 (C=O, TCA), 137.7, 133.9, 132.8, 132.4, 130.0, 129.1, 128.8, 128.7, 128.6, 128.2, 128.0, 127.8 (arom.), 92.3 (C_q, TCA), 86.7 (C-1), 78.3 (C-5), 77.5, 77.2, 76.9, 76.8 (C-3), 73.8 (CH_2Benzyl), 70.8 (C-4), 70.3 (C-6), 54.4 (C-2) ppm. HRMS $[M+Na]^+$ calcd for $C_{28}H_{26}Cl_3NO_6SNa$: 632.04441, found 632.04386.

6-azidohexyl 3-*O*-benzoyl-6-*O*-benzyl-2-deoxy-1-thio-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (10)



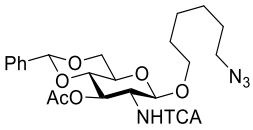
Donor **9** (1.68 g, 2.75 mmol, 1.0 eq.) and 6-azidohexan-1-ol (0.59 g, 4.12 mmol, 1.5 eq.) were co-evaporated together thrice with dry toluene, before dissolving them in dry DCM (27 mL, 0.1M). Freshly dried MS (3Å) were added and the mixture was stirred for 15 min. at room temperature. Next NIS (0.93 g, 4.12 mmol, 1.5 eq.) was added and the mixture was cooled to 0˚C, at which temperature it was stirred for an additional 30 min. TMSOTf (100 µL, 0.55 mmol, 0.2 eq.) was added and the mixture was stirred at 0˚C. After 2 hours the reaction was stopped by addition of Et_3N (0.5 mL). The reaction mixture was diluted in EtOAc, washed twice with sat. $Na_2S_2O_3$ (aq.), followed by sat. $NaHCO_3$ (aq.) and brine. After drying over $MgSO_4$ and filtration the solvents were removed by evaporation. The title compound was separated from byproducts by silicagel chromatography (PE:EtOAc, 19:1 → 4:1) and isolated (1.28 g, 2.0 mmol, 73%). Spectral data was in accordance with those reported previously.[38]

Phenyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-1-thio-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (11)



Acetic anhydride (0.94 mL, 10 mmol, 2.0 eq.) was added to a solution containing sugar **1** (2.52 g, 5.0 mmol, 1.0 eq.) and pyridine (1.2 mL, 15 mmol, 3eq.). The mixture was left to stir at room temperature for 2 hours, diluted in EtOAc and transferred to a separatory funnel. The organic layer was washed with sat. $CuSO_4$ (aq., 3x), sat. $NaHCO_3$ (aq.) and brine, before being dried over $MgSO_4$, filtered and concentrated. Compound **11** was obtained after purification by silicagel chromatography (PE:EtOAc, 19:1 → 4:1) as a white solid (2.60 g, 4.74 mmol, 95%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.53 (d, 1H, *J*=9.7 Hz, NH), 7.49 – 7.42 (m, 2H, arom.), 7.42 – 7.35 (m, 2H, arom.), 7.35 – 7.27 (m, 5H, arom.), 7.27 – 7.20 (m, 3H, arom), 5.55 (t, 1H, *J*=9.8 Hz, H-3), 5.47 (s, 1H, CHPh), 4.79 (d, 1H, *J*=10.4 Hz, H-1), 4.17 (q, 1H, *J*=10.0 Hz, H-2), 3.98 (dd, 1H, *J*=10.5, 4.7 Hz, H-6), 3.67 (t, 2H, *J*=9.8 Hz., H-4, H-6), 3.50 (td, 1H, *J*=9.6, 4.8 Hz, H-5), 2.05 (s, 3H, CH_3, Ac) ppm ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ 171.9 (C=O, Ac), 162.1 (C-O, TCA), 136.9, 133.1, 132.2, 129.2, 128.5, 128.3, 126.0 (arom.), 101.1 (ChPh), 87.8 (C-1), 78.4 (C-3), 72.9 (C-5), 70.7 (C-4), 68.3 (C-6), 54.8 (C-2), 21.0 (CH_3) ppm.

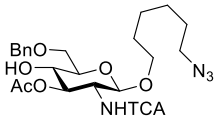
6-azidohexyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (12)



Compound **11** (3.03 g, 6.0 mmol, 1.0 eq.) was dissolved in EtOAc (20 mL, 0.3M) and cooled to 0˚C. Pyridine (1.5 mL, 18 mmol, 3.0 eq.) and Ac_2O (1.13 mL, 12.0 mmol, 2.0 eq.) were added and the ice bath was removed. TLC analysis showed full conversion after 2 hours and the reaction was diluted in EtOAc and transferred to a separatory funnel. The organic layer was washed with sat. $CuSO_4$ (aq., 3x), sat. $NaHCO_3$ (aq., 3x) and brine, followed by drying over $MgSO_4$, filtration and concentration. The yellow solid was purified by silicagel chromatography (tol:ACN, 1:0 → 9:1) to give **12** as a white solid (3.32 g, 5.73 mmol, 95%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.86 (d, 1H, *J*=9.7 Hz, NH), 7.43 (dd, 2H, *J*=7.1, 2.6 Hz, arom.), 7.33 (dd, 3H, *J*=5.2, 2.1 Hz, arom.), 5.57 (t, 1H, *J*=10.1 Hz, H-3), 5.49 (s, 1H, CHPh), 4.33 (d, 1H, *J*=8.3 Hz, H-1), 4.28 – 4.02 (m, 2H, H-2, H-5), 3.84 – 3.66 (m, 2H, H-4, H-6), 3.66 – 3.46 (m, 2H, H-6, OCH_2), 3.23 (t, 2H, *J*=6.9 Hz, CH_2N_3), 3.14 (dt, 1H, *J*=9.7, 6.5 Hz, OCH_2), 2.11 (s, 3H, Ac), 1.69 – 1.41 (m, 3H, CH_2, hexyl), 1.41 – 1.20 (m, 4H, CH_2, hexyl) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ 171.9 (C=O), 162.4 (C=O, TCA), 137.2, 128.8, 128.1, 125.7 (arom.), 101.5 (C-1), 100.8 (CHPh), 92.8 (C_q, TCA), 78.8 (C-4), 72.0 (C-3), 70.1 (OCH_2), 68.3 (C-6), 65.7 (C-5), 55.4 (C-2), 51.3 (CH_2N_3), 29.2, 28.7, 26.4, 25.4 (CH_2-hexyl), 20.8 (CH_3, Ac) ppm. HRMS $[M+Na]^+$ calcd for $C_{23}H_{29}Cl_3N_4O_7Na$: 601.09995, found 601.09940.

4

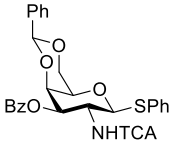
6-azidohexyl 3-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (13)



Compound **12** (3.3 g, 5.7 mmol, 1.0 eq.) was dissolved in dry DCM (60 mL, 0.1M). Freshly dried molecular sieves (3Å) were added and the solution was cooled to 0˚C. TES (4.6 mL, 28.7 mmol, 5.0 eq.) and TFA (2.2 mL, 28.7 mmol, 5.0 eq.) were added after 1 hour of stirring at 0˚C. After 2.5 hours TLC analysis showed spot to spot conversion to a more polar compound. The reaction mixture was transferred to a separatory funnel, diluted with DCM, washed thrice with sat. $NaHCO_3$ (aq.) and once with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Silicagel chromatography (PE:EtOAc, 4:1 → 1:1) gave the title compound as a colourless oil (3.2 g, 5.5 mmol, 96%).^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.44 – 7.28 (m, 5H, arom.), 7.02 (d, 1H, *J*=9.2 Hz, NH), 5.25 (dd, 1H, *J*=10.9, 9.0 Hz, H-3), 4.73 – 4.41 (m, 3H, H-1, CH_2Bn), 3.95 (dt, 1H, *J*=10.8, 8.7 Hz, H-2), 3.87 (dt, 1H, *J*=9.5, 6.1 Hz, OCH_2), 3.83 – 3.71 (m, 3H, H-6, H-4), 3.59 (dt, 1H, *J*=9.7, 4.8 Hz, H-5), 3.44 (dt, 1H, *J*=9.6, 6.7 Hz, OCH_2), 3.23 (t, 2H, *J*=6.9 Hz, CH_2N_3), 3.13 (s, 1H, OH), 2.09 (s, 3H, Ac), 1.70 – 1.44 (m, 4H, CH_2, hexyl), 1.34 (td, 3H, *J*=6.2, 4.7, 2.6 Hz, CH_2, hexyl) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ 172.0 (C=O, Ac), 162.2 (C=O, TCA), 128.7, 128.1, 127.9 (arom.), 100.9 (C-1), 74.6 (C-3), 74.0 (C-5), 73.9 (CH_2Bn), 71.1 (C-4),

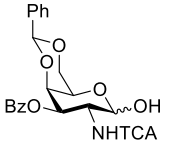
70.4 (C-6), 69.9 (OCH_2), 55.8 (C-2), 51.5 (CH_2N_3), 29.4, 28.8, 26.6, 25.6 (CH_2-hexyl), 21.0 (CH_3, Ac) ppm. HRMS $[M+Na]^+$ calcd for $C_{23}H_{31}Cl_3N_4O_7Na$: 603.11560, found 603.11505.

Phenyl 3-*O*-benzoyl-4,6-*O*-benzylidene-2-deoxy-1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside (15)



Compound **14** (2.52 g, 5.0 mmol, 1.0 eq.) was dissolved in a mixture of DCM and pyridine (50 mL, 0.1M, 2/1, 1/1) and cooled to 0˚C with an ice bath. Bz-Cl (1.2 mL, 10.0 mmol, 2.0 eq.) was added slowly and the ice bath was removed. After 45min. TLC analysis showed full consumption of the starting material and the reaction mixture was poured into H_2O (50 mL). The layers were separated and the water layer was extracted twice with DCM. The organic layers were combined and washed with sat. $CuSO_4$ (aq. 4x), sat. $NaHCO_3$ (aq., 2x) and brine, followed by drying over $MgSO_4$, filtration and concentration *in vacuo*. Compound **15** was obtained after purification by silicagel chromatography (PE:EtOAc, 4:1 → 3:2) as a white solid (3.0 g, 4.9 mmol, 99%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.24 – 8.02 (m, 2H, arom.), 8.01 – 7.85 (m, 2H, arom.), 7.73 – 7.61 (m, 3H, arom.), 7.59 – 7.47 (m, 4H, arom.), 7.47 – 7.40 (m, 2H, arom.), 7.40 – 7.19 (m, 4H, arom.), 6.95 (d, 1H, *J*=8.8 Hz, NH), 5.65 (dd, 1H, *J*=10.8, 3.2 Hz, H-3), 5.52 (s, 1H, CHPh), 5.20 (d, 1H, *J*=10.1 Hz, H-1), 4.58 – 4.30 (m, 3H, H-2, H-4, H-6), 4.07 (dd, 1H, *J*=12.5, 1.7 Hz, H-6), 3.76 (q, 1H, *J*=1.5 Hz, H-5) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ 166.4 (C=O, Bz), 161.6 (C=O, TCA), 137.7, 134.7, 133.8, 133.6, 131.0, 130.6, 130.1, 129.2, 129.1, 129.0, 128.5, 128.5, 128.2, 126.5 (arom.), 100.8 (CHPh), 84.7 (C-1), 73.5 (C-4), 72.2 (C-3), 70.0 (C-5), 69.3 (C-6), 50.7 (C-2) ppm. HRMS [M+Na] calcd for $C_{28}H_{24}Cl_3NO_6SNa$: 630.02876, found 630.0291.

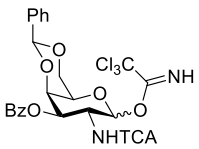
3-*O*-benzoyl-4,6-*O*-benzylidene-2-deoxy-2-(2,2,2-trichloroacetamido)-α/β-D-galactopyranoside (15a)



Thioglycoside **15** (1.33 g, 2.2 mmol, 1.0 eq.) was dissolved in a mixture of acetone and water (22 mL, 0.1M, 9/1, v/v). NBS (1.96 g, 11 mmol, 5 eq.) was added and the reaction was stirred in the dark under inert atmosphere for 30 min., before addition of sat. $Na_2S_2O_3$ (aq., 10 mL). The reaction mixture was stirred until colourless and afterwards reduced *in vacuo* to approximately 10 ml. The concentrated solution was extracted with Et_2O thrice. The combined organic layers were then washed with sat. $NaHCO_3$ (aq.) and brine, followed by drying over $MgSO_4$, filtration and concentration. The resulting yellow oil was purified by silicagel chromatography (PE: EtOAc, 9:1 → 4:1), which gave **15a** as a single isomer (1.04 g, 2.02, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.09 – 7.98 (m, 2H, arom.), 7.53 (m, 3H, arom.), 7.46 – 7.30 (m, 5H, arom.), 7.22 (d, 1H, *J*=9.4 Hz, NH), 5.57 – 5.50 (m, 2H, H-3, CHPh), 5.46 (d, 1H, *J*=3.4 Hz, H-1), 5.10 – 5.00 (s, 1H, 1-OH), 4.81 (ddd, 1H, *J*=11.1, 9.3,

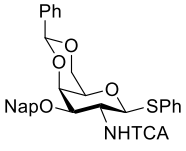
3.4 Hz, H-2), 4.35 (d, 1H, *J*=3.3 Hz, H-4), 4.26 (dd, 1H, *J*=12.7, 1.5 Hz, H-6), 4.03 (dd, 1H, *J*=12.7, 1.7 Hz, H-6), 3.97 (s, 1H, H-5) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ 166.8 (C=O, Bz), 162.3 (C=O, TCA), 137.4, 133.6, 130.1, 130.0, 129.1, 129.0, 128.5, 128.4, 128.3, 126.0 (arom.), 100.4 (CHPh), 92.1 (C_q, TCA), 91.7 (C-1), 73.6 (C-4), 69.6 (C-3), 69.3 (C-6), 62.4 (C-5), 50.1 (C-2) ppm. HRMS [M+Na] calcd for $C_{22}H_{20}Cl_3NO_7Na$: 538.02031, found 538.0204.

3-*O*-benzoyl-4,6-*O*-benzylidene-2-deoxy-2-(2,2,2-trichloroacetamido)-α/β-D-galactopyranoside (16)



Hemi-acetal **15a** (0.52 g, 1.0 mmol, 1.0 eq.) and trichloro acetonitrile (1.0 mL, 10 mmol, 10 eq.) were dissolved in dry DCM (10 mL, 0.1M). DBU (0.050 mL, 0.1 mmol, 0.1 eq.) was added and after 15 min. The reaction mixture was concentrated. The black residue was purified by silicagel chromatography over neutralized silica (PE:EtOAc, 9:1 → 3:2) to yield **16** as a yellow oil (0.47 g, 0.71 mmol, 71%). ^{1}H NMR (Acetone-d_6, 400 MHz): δ = 9.51 (s, 1H, C=NH), 8.19 (d, 1H, *J*=7.9 Hz, NH), 8.14 – 7.95 (m, 3H, arom.), 7.71 – 7.57 (m, 1H, arom.), 7.57 – 7.41 (m, 6H, arom.), 7.41 – 7.28 (m, 4H, arom.), 6.76 (d, 1H, *J*=3.3 Hz, H-1), 5.90 – 5.67 (m, 2H, H-3, CHPh), 5.00 (ddd, 1H, *J*=11.4, 7.9, 3.4 Hz, H-2), 4.95 (dd, 1H, *J*=3.2, 1.2 Hz, H-4), 4.39 – 4.16 (m, 3H, H-5, H-6) ppm. ^{13}C-APT NMR (Acetone-d_6, 101 MHz,) δ 166.1 (C=O, Bz), 162.2 (C=O, TCA), 159.7 (C=NH), 138.5, 133.7, 129.7, 129.6, 128.9, 128.7, 128.6, 128.1, 126.3 arom., 100.4 (CHPh), 95.0 (C-1), 72.9 (C-4), 69.3 (C-3), 68.6 (C-6), 65.3 (C-5), 50.1 (C-2) ppm.

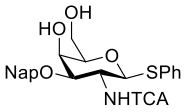
Phenyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-(2-methylnaphthyl)-1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside (17)



Galactopyranoside **14** (8.5 g, 16.8 mmol, 1.0 eq.) was dissolved in dry DMF (170 mL, 0.1 mL) and cooled to 0˚C. NaH (2.7 g, 67.3 mmol, 3.0 eq.) was added portionwise over a period of 30 min., followed by Nap-Br (4.1 g, 18.5 mmol, 1.1 eq.). The ice bath was removed and the reaction was left to stir for 3 hours. Upon completion the reaction mixture was slowly poured into H_2O. The white precipitate was filtered over a glass filter, washed with H_2O (3x) and cold Et_2O (3x). This gave the title compound as a white solid (9.3 g, 14.3 mmol, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.85 – 7.65 (m, 6H, arom.), 7.53 – 7.33 (m, 8H, arom), 7.33 – 7.15 (m, 3H, arom.), 6.85 (d, 1H, *J*=7.0 Hz, NH), 5.50 – 5.41 (m, 2H, H-1, CHPh), 4.83 – 4.68 (m, 2H, CH_2Nap), 4.49 (dd, 1H, *J*=10.5, 3.3 Hz, H-3), 4.38 (dd, 1H, *J*=12.4, 1.7 Hz, H-6), 4.20 (d, 1H, *J*=3.3 Hz, H-4), 3.98 (dd, 1H, *J*=12.4, 1.7 Hz, H-6), 3.78 (td, 1H, *J*=10.3, 7.0 Hz, H-2), 3.54 (s, 1H, H-5) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz): δ 161.7 (C=O, TCA), 137.8, 135.0, 134.1, 133.2, 129.2, 128.5, 128.4, 128.2, 127.9, 127.7, 126.9, 126.5, 126.3, 126.2, 125.8 (arom.), 100.9 (CHPh), 82.5 (C-1), 75.1 (C-3), 72.8

(C-4), 71.9 (CH_2Nap), 70.1 (C-5), 69.5 (C-6), 52.9 (C-2) ppm. HRMS $[M+Na]^+$ calcd for $C_{32}H_{28}Cl_3NO_5SNa$: 666.06515, found 666.06460.

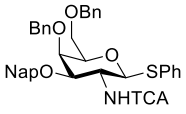
Phenyl 4,6-di-*O*-benzyl-2-deoxy-3-*O*-(2-methylnaphthyl)-1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside (17a)



Thioglycoside **17** (9.3 g, 14.3 mmol, 1.0 eq.) was suspended in a mixture of DCE and methanol (170 mL, 0.1 M, 3/1, v/v). *p*-TsOH (0.27 g, 1.43 mmol, 0.1 eq.) and the mixture was heated to 50˚C. When TLC analysis showed full consumption of the starting material, Et_3N was added and the mixture was concentrated *in vacuo*. The resulting pale yellow solid was washed with heptane (2x), water (2x) and dried *in vacuo* to obtain the title compound as a pure white solid (6.3 g, 11.4 mmol, 80%). ^{1}H NMR (Acetone-d_6, 400 MHz): δ = 8.37 (d, 1H, *J*=9.5 Hz, NH), 7.94 – 7.76 (m, 4H, arom.), 7.59 – 7.42 (m, 5H, arom.), 7.40 – 7.17 (m, 3H, arom.), 5.07 (d, 1H, *J*=10.6 Hz, H-1), 4.93 (d, 1H, *J*=12.0 Hz, CH_2Nap), 4.76 (d, 1H, *J*=12.0 Hz, CH_2Nap), 4.48 – 4.33 (m, 2H, H-2, H-4), 4.22 (d, 1H, *J*=3.8 Hz, 4-OH), 4.02 – 3.89 (m, 2H, H-3, 6-OH), 3.86 – 3.79 (m, 2H, H-6), 3.61 (t, 1H, *J*=6.4, Hz, H-5) ppm. ^{13}C-APT NMR (101 MHz, Acetone): δ 162.3 (C=O, TCA), 136.9, 135.9, 134.2, 133.9, 131.7, 129.7, 128.7, 128.6, 128.5, 127.8, 127.1, 126.9, 126.8, 126.6 (arom.), 87.9 (C-1), 80.4 (C-3), 80.2 (C-5), 71.4 (CH_2Nap), 65.7 (C-4), 62.4 (C-6), 52.9 (C-2) ppm. HRMS $[M+Na]^+$ calcd for $C_{25}H_{24}Cl_3NO_5SNa$: 578.03385, found 578.03330.

4

Phenyl 4,6-di-*O*-benzyl-2-deoxy-3-*O*-(2-methylnaphthyl)-1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside (18)



From **17a:**

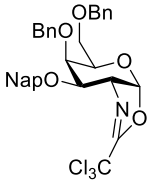
Diol **17a** (6.3 g, 11.4 mmol, 1.0 eq.) was dissolved in dry DMF (110 mL, 0.1M) and cooled to 0˚C, before portionwise addition of NaH (2.3 g, 57 mmol, 5.0 eq.). Bn-Br (3.0 mL, 25.1, 2.2 eq.) was added after 30 min. of stirring and the ice bath was removed. After 1 hour the temperature was increased to 50˚C and stirred at that temperature for an additional hour. When TLC analysis showed full consumption of the starting material, the reaction was quenched by slow addition of methanol. Once cooled the mixture was transferred to a separatory funnel, diluted with EtOAc, washed with H_2O (3x) and brine (2x). The organic layer was dried over $MgSO_4$, filtered and concentrated. The title compound was obtained by silicagel chromatography (tol:ACN, 1:0 → 19:1) as a white amorphous solid (7.1 g, 9.6 mmol, 84%).

From **3:**

Glucopyranoside **3** (2.4 g, 3.72 mmol, 1.0 eq.) was dissolved in a mixture of DCM and pyridine (37 mL, 0.1M, 3/1, v/v) and cooled to 0˚C. Tf_2O (0.81 mL, 4.84 mmol, 1.3 eq.) was added slowly. The colourless solution turned orange after addition of Tf_2O. After 30 min. the mixture was diluted in DCM and transferred to a separatory funnel. The organic

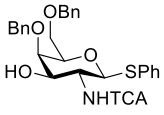
layer was washed with sat. $CuSO_4$ (aq., 5x) and brine. Before being dried over $MgSO_4$, filtered and concentrated at room temperature. The orange oil was redissolved in dry DMF (40 mL, 0.1M) and benzyl alcohol (1.9 mL, 18.6 mmol, 5.0 eq.) and Et_3N (1.0 mL, 7.44 mmol, 2.0 eq.) were added. The solution was heated to 50˚C and left to stir overnight. The reaction mixture was poured into EtOAc and washed with H_2O and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The brown oil was purified by silicagel chromatography (PE:EtOAc, 19:1 → 7:3) to give the title compound as a white amorphous solid (1.1 g, 1.49 mmol, 40%).
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.87 – 7.69 (m, 4H, arom.), 7.58 – 7.38 (m, 5H, arom.), 7.38 – 7.11 (m, 13H, arom.), 6.82 (d, 1H, *J*=7.5 Hz, NH), 5.27 (d, 1H, *J*=10.2 Hz, H-1), 4.91 (d, 1H, *J*=11.4 Hz, CH_2arom.), 4.80 (d, 1H, *J*=11.4 Hz, CH_2arom.), 4.67 (d, 1H, *J*=11.4 Hz, CH_2arom.), 4.60 (d, 1H, *J*=11.4 Hz, CH_2arom.), 4.56 – 4.42 (m, 2H, CH_2arom.), 4.31 (dd, 1H, *J*=10.5, 2.7 Hz, H-3), 4.10 (d, 1H, *J*=2.6 Hz, H-4), 3.96 (td, 1H, *J*=10.4, 7.4 Hz, H-2), 3.81 – 3.72 (m, 1H, H-5), 3.72 – 3.60 (m, 2H, H-6) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ 161.7 (C=O, TCA), 138.5, 137.8, 134.7, 133.2, 133.1, 132.8, 132.2, 129.0, 128.5, 128.5, 128.2, 128.0, 127.9, 127.9, 127.7, 127.6, 127.0, 126.3, 126.2, 125.9 (arom.), 84.4 (C-1), 78.3 (C-3), 77.5 (C-5), 74.6 (CH_2arom.), 73.6 (CH_2arom.), 72.5 (CH_2arom.), 72.4 (C-4), 68.4 (C-6), 53.8 (C-2) ppm. HRMS: $[M+Na]^+$ calcd for $C_{39}H_{36}Cl_3NO_5SNa$: 758.12775, found 758.12720.

3,4-di-*O*-benzyl-2-deoxy-3-*O*-(2-methylnaphthyl)-1,2-trichlorooxazolino-α-D-galactopyranoside (18BP)



^{1}H NMR (CD_3CN, 400 MHz): δ 7.96 – 7.83 (m, 4H, arom.), 7.62 – 7.48 (m, 3H, arom.), 7.41 – 7.25 (m, 10H, arom.), 6.30 (d, 1H, *J*=6.7 Hz, H-1), 5.01 – 4.83 (m, 3H, CH_2arom.), 4.63 (d, 1H, *J*=11.4 Hz, CH_2arom.), 4.58 – 4.47 (m, 2H, CH_2arom), 4.39 (dd, 1H, *J*=7.8, 6.7 Hz, H-2), 4.10 – 3.97 (m, 2H, H-4, H-5), 3.73 – 3.54 (m, 3H, H-3, H-6) ppm. ^{13}C-APT NMR (CD_3CN, 101 MHz): δ 162.3 (C=N), 139.2, 138.9, 136.5, 133.9, 133.6, 129.0, 129.0, 128.8, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 128.3, 127.0, 126.9, 126.7, 126.5, 107.7 (C-1), 80.2 (C-3), 74.9 (CH_2arom.), 74.3 (C-5), 73.6 (CH_2arom.), 72.3 (C-4), 71.9 (CH_2arom), 69.4 (C-6), 67.4 (C-2) ppm.

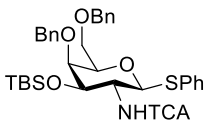
Phenyl 4,6-di-*O*-benzyl-2-deoxy-1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside (20)



Glycan **18** (1.90 g, 2.57 mmol, 1.0 eq.) was dissolved in a mixture of methylene chloride and methanol (25 mL, 0.1M, 9/1, 1/1). DDQ (1.75 g, 7.72 mmol, 3.0 eq.) was added portionwise (1.0 eq. per 30 min.) and the reaction was left to stir under inert atmosphere. When TLC analysis showed full conversion to a single more polar spot, 20 mL of sat. $Na_2S_2O_3$ (aq.) was added. The mixture was stirred until the solution turned colourless. The colourless mixture was

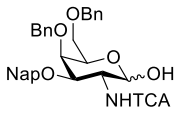
transferred to a separatory funnel, the water layer was removed and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. After purification by silicagel chromatography the title compound was obtained as a white amorphous solid (1.31 g, 2.2 mmol, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.56 – 7.46 (m, 2H, arom.), 7.39 – 7.16 (m, 13H, arom.), 6.88 (d, 1H, *J*=7.4 Hz, NH), 4.86 (d, 1H, *J*=9.8 Hz, H-1), 4.65 (d, 2H, *J*=1.4 Hz, CH_2Bn), 4.56 – 4.39 (m, 2H, CH_2Bn), 3.90 (m, 3H, H-2, H-3, H-4), 3.78 – 3.56 (m, 3H, H-5, H-6), 2.85 – 2.31 (m, 1H, 3-OH) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ 162.4 (C=O, TCA), 138.1, 137.6, 132.5, 132.4, 129.0, 128.6, 128.5, 128.0, 128.0, 127.7 (arom.), 92.5 (C_q, TCA), 85.7 (C-1), 77.5 (C-5), 75.9 (C-4), 75.2 (CH_2Bn), 73.6 (CH_2Bn), 72.5 (C-3), 68.3 (C-6), 54.8 (C-2) ppm. HRMS $[M+Na]^+$ calcd for $C_{28}H_{28}Cl_3NO_5SNa$: 618.06515, found 618.06460.

Phenyl 4,6-di-*O*-benzyl-2-deoxy-3-*O*-(*tert*-butyldimethylsilyl)-1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside (21)



Thioglycoside **20** (1.31 g, 2.2 mmol, 1.0 eq.) was dissolved in DMF (22 mL, 0.1M) together with DMAP (2.68 g, 22 mmol, 10 eq.). TBDMS-Cl (2.3 mL of a 50% solution in toluene) was added and the reaction was heated to 80˚C and left to stir overnight. The mixture was cooled and subsequently diluted with EtOAc. The mixture was then transferred to a separatory funnel and the organic layer was washed with 1M HCl (aq., 2x), sat. $NaHCO_3$ (aq., 1x) and brine (4x), before being dried over $MgSO_4$, filtered and concentrated. The crude mixture was purified by silicagel chromatography (PE:EtOAc, 99:1 → 9:1) to give the title compound as a white solid (1.35 g, 1.90 mmol, 86%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.61 – 7.42 (m, 2H, arom.), 7.42 – 7.08 (m, 13H, arom.), 6.79 (d, 1H, *J*=8.0 Hz, NH), 5.25 (d, 1H, *J*=10.3 Hz, H-1), 4.98 (d, 1H, *J*=11.1 Hz, CH_2Bn), 4.54 – 4.40 (m, 3H, CH_2Bn), 4.29 (d, 1H, *J*=10.0 Hz, H-3), 3.97 (d, 1H, *J*=9.2 Hz, H-2), 3.83 (d, 1H, *J*=2.7 Hz, H-4), 3.75 (t, 1H, *J*=6.5 Hz, H-5), 3.66 (d, 2H, *J*=6.4 Hz, H-6), 0.89 (s, 9H, *t*-Bu, TBDMS), 0.17 (s, 3H, CH_3, TBDMS), 0.10 (s, 3H, CH_3, TBDMS) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ 161.4 (C=O, TCA), 138.7, 138.0, 133.0, 132.4, 129.0, 128.5, 128.3, 128.0, 127.9, 127.8, 127.6, 127.5 (arom.), 92.6 (C_q, TCA), 84.8 (C-1), 77.4 (C-5), 76.8 (C-4), 75.2 (CH_2Bn), 73.6 (CH_2Bn), 73.2 (C-3), 68.6 (C-6), 55.0 (C-2), 25.9 (*t*-Bu, TBDMS) 18.0 (C_q, TBDMS), -3.4 (CH_3, TBDMS), -4.9 (CH_3, TBDMS) ppm.

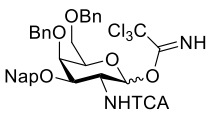
4,6-di-*O*-benzyl-3-*O*-(2-methylnaphthyl)-2-deoxy-2-(2,2,2-trichloroacetamido)-α/β-D-galactopyranoside (18a)



Thioglycoside **18** (7.1 g, 9.6 mmol, 1.0 eq.) was dissolved in a mixture of water in acetone (1/9, v/v, 100 mL, 0.1M). NBS (5.1 g, 28.7 mmol, 3.0 eq.) was added and the mixture was stirred in the dark for 30 min. under inert atmosphere. A solution of sat. $Na_2S_2O_3$ (aq.) (30 mL) was

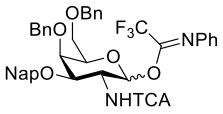
added and the mixture was stirred until the solution turned colourless. The acetone was removed in vacuo and the water layer was extracted thrice with Et_2O. The combined organic layers were washed with sat. $NaHCO_3$ (aq.) followed by brine. The organic layer was dreid over $MgSO_4$, filtered and concentrated. The crude compound was purified by silicagel chromatography (tol: ACN, 1:0 → 9:1) to give **18a** as a pale white solid (6.1 g, 9.46 mmol, 98%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.86 – 7.67 (m, 4H, arom.), 7.51 – 7.38 (m, 3H, arom), 7.33 – 7.19 (m, 11H, arom), 6.83 (d, 1H, *J*=9.1 Hz, NH), 5.29 (t, 1H, *J*=3.6 Hz, H-1), 4.93 (d, 1H, *J*=11.6 Hz, CH_2arom), 4.79 (d, 1H, *J*=12.3 Hz, CH_2arom), 4.70 – 4.50 (m, 4H, CH_2arom), 4.45 (d, 1H, *J*=11.9 Hz, CH_2arom), 4.35 (d, 1H, *J*=11.9 Hz), 4.10 (t, 1H, *J*=6.2 Hz, H-5), 3.91 (d, 1H, *J*=2.5 Hz, H-4), 3.77 (dd, 1H, *J*=10.7, 2.5 Hz, H-3), 3.57 (dd, 1H, *J*=9.8, 7.2 Hz, H-6), 3.36 (dd, 1H, *J*=9.6, 5.2 Hz, H-6) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ 161.4 (C=O, TCA), 137.7, 137.0, 134.7, 132.9, 132.7, 128.1, 128.1, 128.0, 128.0, 127.8, 127.7, 127.7, 127.6, 127.6, 127.5, 127.4, 126.1, 125.9, 125.7, 125.2 (arom.), 92.4 (C_q, TCA), 91.2 (C-1), 76.5 (C-3), 74.1 (CH_2arom.), 73.2 (CH_2arom.), 72.0 (C-4), 71.5 (CH_2arom.), 69.3 (C-5), 69.2 (C-6), 51.1 (C-2) ppm. HRMS $[M+Na]^+$ calcd for $C_{33}H_{32}Cl_3NO_6Na$: 666.11929, found 666.11874.

Trichloroacetimidoyl 4,6-di-*O*-benzyl-3-*O*-(2-methylnaphthyl)-2-deoxy-2-(2,2,2-trichloroacetamido)-α/β-D-galactopyranoside (19)



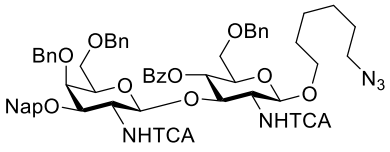
DBU (0.28 mL, 1.9 mmol, 0.2 eq.) was added to a solution of hemi-acetal **18a** (6.1 g, 9.5 mmol, 1.0 eq.) and trichloro acetonitrile (9.5 mL, 94.6 mmol, 10 eq.) in dry DCM (95 mL, 0.1M). Upon stirring for 15 min. TLC indicated full conversion and the mixture was concentrated in vacuo. The brown oil was purified over neutralized silica (tol:ACN, 1:0 → 19:1) to give imidate **19** as a yellow oil (5.9 g, 7.5 mmol, 78%, α/β, 5/1). NMR of the α-anomer: ^{1}H NMR ($CDCl_3$, 400 MHz, 400 MHz): δ 8.57 (s, 1H, C=NH), 7.94 – 7.70 (m, 6H, arom.), 7.60 – 7.40 (m, 5H, arom.), 7.40 – 7.22 (m, 12H, arom.), 6.46 (d, 1H, *J*=3.4 Hz, H-1), 6.38 (d, 1H, *J*=8.1 Hz, NH), 5.06 – 4.75 (m, 3H, H-2, CH_2arom), 4.72 – 4.56 (m, 2H, CH_2arom), 4.54 – 4.35 (m, 2H, CH_2arom), 4.24 (d, 1H, *J*=2.4 Hz, H-4), 4.20 – 4.07 (m, 1H, H-5), 3.94 (dd, 1H, *J*=8.5, 2.4 Hz, H-3), 3.76 – 3.46 (m, 2H, H-6) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ 162.0 (C=NH), 160.1 (C=O, TCA), 138.1, 138.0, 137.6, 134.8, 134.3, 133.2, 133.1, 129.0, 128.6, 128.6, 128.5, 128.5, 128.4, 128.4, 128.4, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 128.0, 128.0, 127.9, 127.8, 127.7, 127.4, 127.0, 126.8, 126.6, 126.5, 126.3, 126.2, 126.0, 125.9, 125.8 (arom.), 95.1 (C-1), 92.3 (C_q, TCA), 90.8 (C_q, imidate), 74.8 (CH_2arom), 74.7 (C-3), 73.6 (CH_2arom), 72.5 (C-5), 71.4 (C-4), 71.1 (CH_2arom), 68.0 (C-6), 50.8 (C-2) ppm.

N-Phenyl-trifluoroacetimidoyl 4,6-di-*O*-benzyl-3-*O*-(2-methylnaphthyl)-2-deoxy-2-(2,2,2-trichloroacetamido)-α/β-D-galactopyranoside (19a)



Hemiacetal **18a** (3.1 g, 4.7 mmol, 1.0 eq.) was dissolved in acetone (47 mL, 0.1M) and cooled to 0˚C. Cs_2CO_3 (4.59 g, 14.1 mmol, 3.0 eq.) was added, followed by $CF_3(C{=}NPh)Cl$ (1.52 mL, 9.4 mmol, 2.0 eq.). The reaction mixture was left to stir overnight under inert atmosphere. After filtration over celite the volatiles were evaporated *in vacuo*. The residue was purified by silicagel chromatography using neutralized silica (tol:Et_2O, 1:0 → 9:1) to give **19a** as a yellow oil (3.65 g, 4.47 mmol, 95%). ^{1}H NMR (CD_3CN, 300 MHz, 323K): δ = 7.94 – 7.77 (m, 4H, arom.), 7.64 – 7.45 (m, 3H, arom.), 7.45 – 7.19 (m, 10H, arom.), 7.18 – 7.05 (m, 1H, arom.), 6.88 – 6.70 (m, 2H, arom.), 6.31 (s, 1H, H-1), 5.01 – 4.74 (m, 2H, CH_2arom), 4.70 – 4.44 (m, 3H, H-2, CH_2arom), 4.36 – 4.10 (m, 3H, H-3, H-4, H-5), 3.76 – 3.52 (m, 2H, H-6) ppm. ^{13}C-APT NMR (CD_3CN, 75 MHz, 323 K) δ 163.4 (C=O, TCA), 144.7, 139.7, 139.6, 136.9, 134.5, 134.2, 130.0, 129.5, 129.4, 129.2, 129.1, 128.9, 128.9, 128.8, 128.8, 127.7, 127.4, 127.2, 125.6, 120.4 (arom.), 96.0 (C-1), 76.8 (C-3), 75.9 (CH_2arom), 74.1 (C-4 + CH_2arom), 73.7 (C-5), 72.5 (CH_2arom), 70.0 (C-6), 52.3 (C-2) ppm.

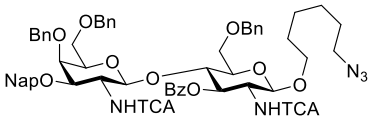
6-azidohexyl 4-*O*-benzoyl-6-*O*-benzyl-2-deoxy-4-*O*-(4,6-di-*O*-benzyl-2-deoxy-3-*O*-(2-methylnaphthyl)-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside)-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (26)



Acceptor **10** (0.037 g, 0.058 mmol, 1.0 eq.) and donor **18** (0.065 g, 0.088 mmol, 1.5 eq.) were co-evaporated thrice with dry toluene, before dissolving in dry DCM (0.6 mL, 0.1M). NIS (0.022 g, 0.098 mmol, 1.7 eq.) and freshly dried molecular sieves (4Å) were added and the reaction mixture was cooled to -20˚C and left to stir for 1 hour at that temperature. TfOH (100 µL, 0.011 mmol, 0.2 eq. of a 0.1M solution in DCM) was added and the reaction kept at -20˚C for 8 hours, after which it was left overnight at 0˚C. TLC analysis showed full consumption of donor **18** and Et_3N (0.05 mL) was added. The reaction mixture was diluted in EtOAc and transferred to a separatory funnel. The organic layer was washed with HCl (1M, aq.), sat. $NaHCO_3$ (aq.) and brine. Any traces of water were removed by drying over $MgSO_4$ followed by filtration and concentration *in vacuo*. The title compound **26** was obtained by silicagel chromatography (tol:ACN, 1:0 → 19:1) followed by size exclusion (LH-20, DCM/MeOH, 1/1, v/v) as a viscous colourless oil (0.035 g, 0.027 mmol, 47%) ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.95 – 7.87 (m, 2H, arom.), 7.85 – 7.66 (m, 4H, arom.), 7.51 – 7.38 (m, 4H, arom.), 7.38 – 7.28 (m, 7H, arom.), 7.28 – 7.08 (m, 14H, arom.), 7.02 (d, 1H, *J*=9.1 Hz, NH), 6.84 (d, 1H, *J*=7.3 Hz, NH'), 5.43 (dd, 1H, *J*=10.5, 8.7 Hz, H-4), 4.93 (d, 1H, *J*=8.2 Hz, H-1'), 4.78 – 4.68 (m, 2H, CH_2arom), 4.68 – 4.51 (m, 4H, H-1, CH_2arom), 4.41 (d, 1H,

J=11.5 Hz, CH_2arom), 4.26 – 4.09 (m, 4H, H-2, H-3, CH_2arom), 4.06 (dd, 1H, *J*=11.0, 2.8 Hz, H-3'), 3.92 (d, 1H, *J*=2.7 Hz, H-4'), 3.90 – 3.84 (m, 1H, OCH_2), 3.78 – 3.57 (m, 4H, H-5, H-6, H-2'), 3.46 (dt, 1H, *J*=9.5, 6.6 Hz, OCH_2), 3.30 (dd, 1H, *J*=8.8, 5.3 Hz, H-5'), 3.21 (t, 2H, *J*=6.9 Hz, CH_2N_3), 3.17 – 3.04 (m, 2H, H-6'), 1.62 – 1.48 (m, 4H, CH_2, hexyl), 1.40 – 1.27 (m, 4H, CH_2, hexyl) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ 166.9 (C=O, Bz), 162.1 (C=O, TCA), 138.6, 138.2, 137.8, 135.0, 133.3, 133.2, 133.1, 130.1, 129.8, 128.6, 128.5, 128.4, 128.3, 128.3, 128.0, 128.0, 128.0, 127.8, 127.8, 127.8, 127.6, 126.7, 126.4, 126.2, 125.8 (arom.), 100.9 (C-1), 98.5 (C-1'), 92.6, 92.5 (C_q, TCA), 76.8 (C-3'), 75.0 (C-5), 74.7 (CH_2arom), 73.8 (C-3), 73.4 (CH_2arom), 73.2 (CH_2arom), 73.1 (C-4), 73.0 (C-5'), 72.1 (CH_2arom), 71.9 (C-4'), 69.7 (OCH_2), 68.2 (C-6), 67.3 (C-6'), 56.3 (C-2'), 55.7 (C-2), 51.5 (CH_2N_3), 29.5, 28.9, 26.6, 25.7 (CH_2, hexyl) ppm.

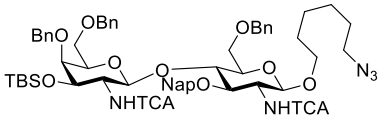
6-azidohexyl 3-*O*-benzoyl-6-*O*-benzyl-2-deoxy-4-*O*-(4,6-di-*O*-benzyl-2-deoxy-3-*O*-(2-methylnaphthyl)-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside)-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (22)



Acceptor **10** (1.0 g, 1.5 mmol, 1.0 eq.) and donor **19** (1.32 g, 1.6 mmol, 1.1 eq.) were co-evaporated separately with dry toluene and dissolved in DCM (7.5 mL, 0.2M each). Molecular sieves (3Å) were added to both flasks and the solutions were stirred for 1 hour at RT. Both solutions were cooled to -20˚C and stirred for 15 min. TfOH (40 µL, 0.45 mmol, 0.3 eq.) was added to the acceptor and the solution containing donor **19** was slowly added to the solution containing acceptor **10** and TfOH. The mixture was kept at -20˚C and for the duration of the reaction. After 2 hours TLC indicated full conversion of the donor. The reaction was quenched by addition of Et_3N (0.5 mL), diluted and transferred to a separatory funnel. The organic layer was washed with sat. $NaHCO_3$ (aq.) and brine, followed by drying over $MgSO_4$, filtration and concentration. The brown mixture was purified by size exclusion (LH-20, DCM/MeOH, 1/1, v/v) to give compound **22** (0.76 g, 0.6 mmol, 40%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.98 – 7.89 (m, 2H, arom.), 7.83 – 7.62 (m, 4H, arom.), 7.50 – 7.40 (m, 3H, arom.), 7.39 – 7.09 (m, 21H, NH, arom.), 7.04 (d, 1H, *J*=7.3 Hz, NH'), 5.53 (dd, 1H, *J*=10.5, 8.8 Hz, H-3), 4.97 (d, 1H, *J*=8.2 Hz, H-1), 4.76 – 4.50 (m, 6H, H-1, CH_2Bn), 4.41 (d, 1H, *J*=11.7 Hz, CH_2Bn), 4.22 (ddd, 1H, *J*=10.5, 9.3, 8.1 Hz, H-2), 4.18 – 4.11 (m, 3H, H-4, H-3', CH_2Bn), 4.08 (dd, 1H, *J*=10.9, 2.8 Hz), 3.91 (d, 1H, *J*=2.8 Hz, H-4'), 3.84 (dd, 1H, *J*=10.8, 4.7 Hz, OCH_2), 3.81 – 3.60 (m, 4H, H-5, H-6, H-2'), 3.47 (dt, 1H, *J*=9.5, 6.4 Hz, OCH_2), 3.29 (dd, 1H, *J*=8.3, 6.0 Hz, H-5'), 3.16 (t, 2H, *J*=6.9 Hz, CH_2N_3), 3.10 – 2.97 (m, 2H, H-6'), 1.60 – 1.43 (m, 4H, CH_2, hexyl), 1.40 – 1.20 (m, 4H, CH_2, hexyl) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ 166.9 (C=O, Bz), 162.2, 162.0 (C=O, TCA), 138.6, 138.2, 137.8, 135.0, 133.3, 133.2, 133.0, 130.1, 129.7, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 127.9, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 126.6, 126.3, 126.1, 125.7 (arom.), 100.5 (C-1),

98.9 (C-1'), 92.6, 92.5 (C_q, TCA), 76.9 (C-3'), 75.0 (C-5), 74.6 (CH_2arom), 74.5 (C-4), 73.4 (C-3), 73.3 (CH_2arom), 73.1 (CH_2arom), 72.9 (C-5'), 72.1 (CH_2arom), 71.8 (C-4'), 69.2 (OCH_2), 68.0 (C-6), 67.2 (C-6'), 56.3 (C-2'), 55.4 (C-2), 51.4 (CH_2N_3), 29.5, 28.8, 26.5, 25.7 (CH_2, hexyl) ppm. HRMS $[M+Na]^+$ calcd for $C_{61}H_{63}Cl_6N_5O_{12}Na$: 1290.25021, found 1290. 24966.

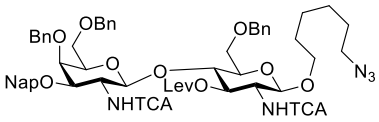
6-azidohexyl 6-*O*-benzyl-2-deoxy-4-*O*-(4,6-di-*O*-benzyl-2-deoxy-3-*O*-(*tert*-butyldimethylsilyl)-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside)-3-*O*-(2-methylnaphthyl)-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (23)



Acceptor **4** (0.068 g, 0.10 mmol, 1.0 eq.) and donor **21** (0.14 g, 0.2 mmol, 2.0 eq.) were co-evaporated separately with dry toluene and dissolved in DCM (0.5 mL, 0.2M each). Molecular sieves (3Å) were added to both flasks and the solutions were stirred for 1 hour at RT. NIS (0.050 g, 0.22 mmol, 2.2 eq.) was added to the solution containing acceptor **4**. Both solutions were cooled to -40˚C and stirred for 15 min. TfOH (200 µL, 0.02 mmol, 0.2 eq. of a 0.1M solution in DCM) was added to the acceptor and the solution containing donor **21** was slowly added to the solution containing acceptor **4**, NIS and TfOH. The mixture was allowed to warm up to -20˚C and kept at that temperature for the duration of the reaction. After 8 hours TLC indicated full conversion of the donor. The reaction was quenched by addition of Et_3N (0.05 mL), diluted and transferred to a separatory funnel. The organic layer was washed with sat. $Na_2S_2O_3$ (aq.), sat. $NaHCO_3$ (aq.) and brine, followed by drying over $MgSO_4$, filtration and concentration. The brown mixture was purified by silicagel chromatography (PE:EtOAc, 99:1 → 4:1), followed by size exclusion (LH-20, DCM/MeOH, 1/1, v/v) to give compound **23** as a pale yellow oil (0.021 g, 0.016 mmol, 16%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.82 – 7.55 (m, 4H, arom.), 7.53 – 6.95 (m, 23H, NH, arom.), 6.63 (d, 1H, *J*=7.9 Hz, NH'), 5.01 (dd, 2H, *J*=23.8, 11.0 Hz, CH_2arom.), 4.81 (d, 1H, *J*=7.3 Hz, H-1), 4.79 (d, 1H, *J*=7.8 Hz, H-1'), 4.73 – 4.63 (m, 2H, CH_2arom), 4.51 (d, 1H, *J*=12.1 Hz, CH_2arom), 4.43 (d, 1H, *J*=11.1 Hz, CH_2arom), 4.33 – 4.10 (m, 4H, H-4, CH_2arom), 4.08 – 3.91 (m, 3H, H-3, H-2', H-3'), 3.89 – 3.68 (m, 4H, H-6, H-4', OCH_2), 3.67 – 3.53 (m, 2H, H-2, H-5), 3.50 – 3.28 (m, 4H, H-5', H-6', OCH_2), 3.20 (t, 3H, *J*=6.9 Hz, CH_2N_3), 1.60 – 1.48 (m, 4H, CH_2, hexyl), 1.37 – 1.28 (m, 4H, CH_2, hexyl), 0.90 (s, 9H, *t*-Bu, TBDMS), 0.17 (s, 3H, CH_3, TBDMS), 0.11 (s, 3H, CH_3, TBDMS) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz): δ 161.8, 161.6 (C=O, TCA), 138.7, 138.3, 138.0, 135.8, 133.3, 133.0, 129.0, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 126.8, 126.5, 126.4, 125.9, 125.7 (arom.), 99.4 (C-1'), 98.8 (C-1), 92.7, 92.6 (C_q, TCA), 77.4 (C-3), 76.5 (C-4'), 75.6 (CH_2arom), 75.2 (C-4), 75.1 (C-5), 74.2 (CH_2arom), 73.5 (CH_2arom), 73.3 (CH_2arom), 73.2 (C-5'), 72.1 (C-3'), 69.7 (OCH_2), 68.8 (C-

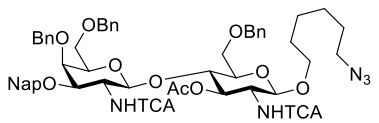
6), 68.0 (C-6'), 57.2 (C-2'), 56.9 (C-2), 51.5 (CH_2N_3), 29.4, 28.8, 26.6 (CH_2, hexyl), 25.9 (*t*-Bu, TBDMS), 25.7 (CH_2, hexyl), 18.0 (C_q, TBDMS), -3.3, -4.8 (CH_3, TBDMS) ppm.

6-azidohexyl 6-*O*-benzyl-2-deoxy-4-*O*-(4,6-di-*O*-benzyl-2-deoxy-3-*O*-(2-methylnaphthyl)-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside)-3-*O*-levulinoyl-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (24)



Donor **19** (0.050 g, 0.065 mmol, 1.3 eq.) and acceptor **10** (0.032 g, 0.050 mmol, 1.0 eq.) were co-evaporated together with dry toluene (3x) and dissolved in a mixture of dry DCM and ACN (0.5 mL, 0.1M, 4/1, v/v). Freshly dried molecular sieves (3Å) were added and the mixture was cooled to -20˚C and stirred for 30 min. before TfOH (100 µL, 0.2 eq. of a 0.1M solution in DCM) was added. Upon completion the reaction was stopped by addition of Et_3N (50 µL), diluted in EtOAc, washed with sat $NaHCO_3$ (aq.) and brine, followed by drying over $MgSO_4$, filtering and concentration *in vacuo*. The resulting yellow oil was purified by silicagel chromatography (tol:ACN, 19:1 → 9:1) to give the title compound (0.028 g, 0.022 mmol, 44%) ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.86 – 7.71 (m, 4H, arom.), 7.47 (m, 2H, arom.), 7.44 – 7.12 (m, 21H, arom.), 7.01 (d, 1H, *J*=7.7 Hz, NH'), 6.73 (d, 1H, *J*=8.8 Hz, NH), 5.17 (dd, 1H, *J*=10.5, 9.1 Hz, H-3), 4.88 (d, 1H, *J*=11.1 Hz, CH_2arom.), 4.85 – 4.76 (m, 2H, H-1', CH_2arom.), 4.70 – 4.48 (m, 7H, H-1, CH_2arom.), 4.13 – 3.98 (m, 3H, H-4, H-3', H-4'), 3.90 – 3.69 (m, 4H, H-2, H-2', H-6, OCH_2), 3.69 – 3.46 (m, 5H, H-5, H-6, H-5', H-6'), 3.44 – 3.32 (m, 1H, OCH_2), 3.22 (t, 2H, *J*=6.9 Hz, CH_2N_3), 2.49 – 2.21 (m, 4H, CH_2Lev)), 1.91 (s, 3H, CH_3, Lev), 1.63 – 1.47 (m, 4H, CH_2, hexyl), 1.41 – 1.26 (m, 4H, CH_2, hexyl) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ 206.9 (CH_3C=O, Lev), 173.0 (OC=O, Lev), 162.0, 162.0 (C=O, TCA), 138.6, 138.3, 137.8, 135.1, 133.3, 133.2, 129.2, 128.7, 128.6, 128.5, 128.5, 128.4, 128.4, 128.4, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.8, 126.8, 126.4, 126.2, 125.8, 125.4 (arom.), 100.8 (C-1), 97.5 (C-1'), 92.7, 92.5 (C_q, TCA), 77.3 (C-3'), 75.0 (CH_2arom.), 74.9 (C-5/5'), 73.7 (CH_2arom.), 73.2 (C-5/5'), 73.2 CCH_2arom.), 72.7 (C-4), 72.5 (C-4'), 72.4 (CH_2arom.), 71.6 (C-3), 69.8 (OCH_2), 68.2 (C-6), 68.1 (C-6'), 56.2 (C-2'), 56.0 (C-2), 51.5 (CH_2N_3), 37.6 (CH_2, Lev), 29.7 (CH_3, Lev), 29.4, 28.9, 28.0, 26.6, 25.6 (CH_2, hexyl, Lev) ppm. HRMS $[M+Na]^+$ calcd for $C_{59}H_{65}Cl_6N_5O_{13}Na$: 1284.26077, found 1284.26022.

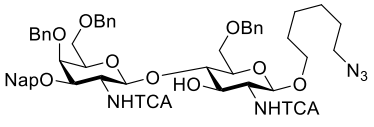
6-azidohexyl 3-*O*-acetyl-6-*O*-benzyl-2-deoxy-4-*O*-(4,6-di-*O*-benzyl-2-deoxy-3-*O*-(2-methylnaphthyl)-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside)-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (25)



Donor **19** (2.46 g, 3.12 mmol, 1.5 eq.) and acceptor **13** (1.21 g, 2.08 mmol, 1.0 eq.) were co-evaporated thrice with dry toluene, before dissolving in a mixture of dry DCM and dry ACN (10 mL, 0.1M, 4/1,

v/v). Freshly dried molecular sieves (4Å) were added and the reaction mixture was cooled to -40˚C and left to stir for 1 hour at that temperature. TfOH (36 µL, 0.42 mmol, 0.2 eq.) was added and the reaction was warmed to -30˚C and kept at that temperature. TLC analysis showed full consumption of acceptor **13** (~5 hours). Et_3N (0.4 mL) was added and the reaction mixture was diluted in EtOAc. The organic layer was washed with HCl (1M, aq.), sat. $NaHCO_3$ (aq.) and brine. Any traces of water were removed by drying over $MgSO_4$ followed by filtration and concentration *in vacuo*. The title compound **25** was obtained by silicagel chromatography (tol:ACN, 1:0 → 19:1) followed by size exclusion (LH-20, DCM/MeOH, 1/1, v/v) as a viscous colourless oil (1.55 g, 1.28 mmol, 82%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.89 – 7.71 (m, 4H, arom.), 7.53 – 7.46 (m, 2H, arom.), 7.44 – 7.13 (m, 20H, arom.), 6.80 (d, 1H, *J*=7.3 Hz, NH'), 6.73 (d, 1H, *J*=8.6 Hz, NH), 5.10 (t, 1H, *J*=10.6 Hz, H-3), 4.88 (m, 2H, H-1', CH_2arom.), 4.79 (d, 1H, *J*=11.5 Hz, CH_2arom.), 4.70 – 4.59 (m, 2H, CH_2arom.), 4.58 – 4.40 (m, 5H, H-1, CH_2arom.), 4.14 (dd, 1H, *J*=11.0, 2.7 Hz, H-3'), 4.09 – 4.00 (m, 2H, H-4, H-4'), 3.95 (dt, 1H, *J*=10.6, 8.6 Hz, H-2), 3.86 (dt, 1H, *J*=9.5, 6.1 Hz, OCH_2), 3.75 – 3.65 (m, 2H, H-6, H-2'), 3.65 – 3.58 (m, 2H, H-6'), 3.55 (dd, 1H, *J*=8.8, 5.1 Hz, H-6), 3.53 – 3.45 (m, 2H, H-5, H-5'), 3.42 (dt, 1H, *J*=9.5, 6.6 Hz, OCH_2), 3.22 (t, 2H, *J*=6.9 Hz, CH_2N_3), 1.82 (s, 3H, CH_3, Ac), 1.58 – 1.50 (m, 4H, CH_2, hexyl), 1.32 (m, 4H, CH_2, hexyl) ppm. ^{13}C-APT NMR ($CDCl_3$, 126 MHz) δ 171.4 (C=O, Ac), 162.0, 161.9 (C=O, TCA), 138.5, 138.2, 137.8, 135.0, 133.3, 133.2, 128.7, 128.5, 128.5, 128.4, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.8, 126.8, 126.4, 126.3, 125.9 (arom.), 101.1 (C-1), 97.6 (C-1'), 92.6 (C_q, TCA), 77.4 (C-3'), 75.0 (C-5), 74.9 (CH_2arom), 73.7 (CH_2arom), 73.2 (C-5, CH_2arom), 72.6 (C-4), 72.3 (CH_2arom), 72.3 (C-4'), 72.1 (C-3), 69.7 (OCH_2), 68.1 (C-6), 68.0 (C-6'), 56.5 (C-2'), 55.6 (C-2), 51.5 (CH_2N_3), 29.4, 28.9, 26.6, 25.6 (CH_2-hexyl), 20.7 (CH_3, Ac) ppm. HRMS $[M+Na]^+$ calcd for $C_{56}H_{61}Cl_6N_5O_{12}Na$: 1228.23456, found 1228.23401.

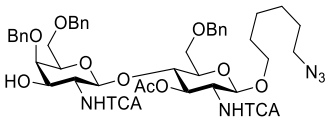
6-azidohexyl 6-*O*-benzyl-2-deoxy-4-*O*-(4,6-di-*O*-benzyl-3-*O*-(2-methylnaphthyl)-2-deoxy-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside)-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (27)



NaOH (83 µL, 0.1 eq., 0.1M, aq.) was added to a solution of disaccharide **25** (1.0 g, 0.83 mmol, 1.0 eq.) in dioxane (4 mL, 0.2M). The solution was left to stir until TLC analysis showed full consumption of the starting material (~8 hours), before the reaction was stopped by addition of AcOH (0.1M in H_2O). The volatiles were evaporated and the residue was taken up in EtOAc and subsequently washed with sat. $NaHCO_3$ (aq.) and brine. The title compound was obtained by silicagel chromatography (tol:ACN, 1:0 → 17:3) as a white solid (0.56 g, 0.48 mmol, 58%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.87 – 7.73 (m, 4H, arom.), 7.53 – 7.47 (m, 2H, arom.), 7.42 (dd, 1H, *J*=8.4, 1.7 Hz, arom.), 7.39 – 7.10 (m, 16H, arom), 6.83 – 6.73 (m,

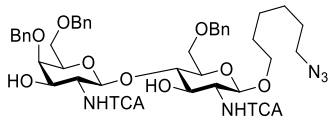
2H, NH, NH'), 4.87 (d, 1H, *J*=11.5 Hz, CH_2arom), 4.83 – 4.73 (m, 3H, H-1, H-1', CH_2arom), 4.70 – 4.61 (m, 2H, CH_2arom), 4.52 (dd, 2H, *J*=11.8, 5.2 Hz, CH_2arom), 4.49 – 4.35 (m, 2H, CH_2arom), 4.09 – 3.95 (m, 3H, H-2, H-4, H-3'), 3.92 (d, 1H, *J*=1.8 Hz, H-4'), 3.86 (dt, 1H, *J*=9.6, 6.1 Hz, OCH_2), 3.75 – 3.57 (m, 5H, H-3, H-6, H-5', H-6'), 3.54 (ddd, 1H, *J*=7.7, 6.0, 4.2 Hz, H-5), 3.51 – 3.35 (m, 3H, H-2', H-6', OCH_2), 3.22 (t, 2H, *J*=6.9 Hz, CH_2N_3), 1.62 – 1.49 (m, 4H, CH_2, hexyl), 1.39 – 1.30 (m, 4H, CH_2, hexyl) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ 162.1, 161.8 (C=O, TCA), 138.5, 138.0, 137.4, 134.7, 133.3, 133.2, 128.7, 128.6, 128.5, 128.5, 128.4, 128.2, 128.2, 128.0, 128.0, 128.0, 127.9, 127.8, 127.0, 126.5, 126.4, 125.9 (arom.), 99.9 (C-1), 99.7 (C-1'), 92.5 (C_q, TCA), 80.7 (C-5'), 77.6 (C-3'), 74.8 (CH_2arom), 74.3 (C-5), 74.0, (C-3) 73.8 (CH_2arom), 73.5 (CH_2arom), 72.5 (CH_2arom), 71.7 (C-4'), 71.4 (C-4), 69.8 (OCH_2), 68.6 (C-6), 68.5 (C-6'), 58.6 (C-2'), 55.5 (C-2), 51.5 (CH_2N_3), 29.5, 28.9, 26.6, 25.7 (CH_2, hexyl) ppm. HRMS $[M+Na]^+$ calcd for $C_{54}H_{59}Cl_6N_5O_{11}Na$: 1186.22399, found 1186.22344.

6-azidohexyl 3-*O*-acetyl-6-*O*-benzyl-2-deoxy-4-*O*-(4,6-di-*O*-benzyl-2-deoxy-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside)-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (28)



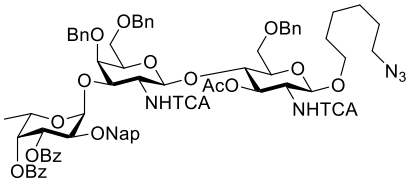
Disaccharide **25** (0.14 g, 0.12 mmol, 1.0 eq.) was dissolved in a mixture of DCM and HFIP (1.2 mL, 0.1M, 1/1, v/v). TES (58 µL, 0.36 mmol, 3.0 eq.) was added followed by 83 µL of HCl (1.0M, in HFIP). After 3 hours TLC analysis showed full conversion of the starting material and the reaction was stopped by addition of Et_3N (0.2 mL). The mixture was taken up in EtOAc and washed with sat. $NaHCO_3$ (aq.) and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude mixture was purified by silicagel chromatography (tol:ACN, 1:0 → 17:3), giving disaccharide **28** (0.070 g, 0.065 mmol, 55%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.42 – 7.20 (m, 16H, arom.), 6.96 (d, 1H, *J*=9.2 Hz, NH), 6.67 (d, 1H, *J*=7.6 Hz, NH'), 5.10 (dd, 1H, *J*=10.7, 9.0 Hz, H-3), 4.75 – 4.60 (m, 3H, CH_2Bn), 4.57 – 4.43 (m, 5H, H-1, H-1', CH_2Bn), 4.05 – 3.93 (m, 2H, H-2, H-4), 3.90 – 3.81 (m, 2H, H-4', OCH_2), 3.72 – 3.63 (m, 3H, H-6, H-3'), 3.63 – 3.57 (m, 2H, H-6'), 3.57 – 3.51 (m, 1H, H-2'), 3.51 – 3.38 (m, 3H, H-5, H-5', OCH_2), 3.21 (t, 2H, *J*=6.9 Hz, CH_2N_3), 2.36 (d, 1H, *J*=9.7 Hz, OH), 1.89 (s, 3H, CH_3, Ac), 1.59 – 1.46 (m, 4H, CH_2, hexyl), 1.36 – 1.27 (m, 4H, CH_2, hexyl) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ 171.3 (C=O, Ac), 162.5, 162.1 (C=O, TCA), 138.0, 137.8, 137.5, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9 (arom.), 101.0 (C-1), 98.8 (C-1'), 92.6 , 92.6 (C_q, TCA), 75.6 (C-4'), 75.4 (CH_2Bn), 74.6 (C-5), 74.0 (C-4), 73.7 (CH_2Bn), 73.6 (CH_2Bn), 73.2 (C-5'), 72.2 (C-3), 70.9 (C-3'), 69.7 (OCH_2), 68.4 (H-6), 67.8 (H-6'), 57.4 (C-2'), 55.4 (C-2), 51.4 (CH_2N_3), 29.4, 28.8, 26.5, 25.6 (CH_2-hexyl), 20.8 (CH_3, Ac) ppm. HRMS $[M+Na]^+$ calcd for $C_{45}H_{53}Cl_6N_5O_{12}Na$: 1088.17196, found 1088.17141.

6-azidohexyl 6-*O*-benzyl-2-deoxy-4-*O*-(4,6-di-*O*-benzyl-2-deoxy-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside)-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (29)



Disaccharide **28** (0.185 g, 0.174 mmol, 1.0 eq.) was dissolved in a mixture of THF and MeOH (1.7 mL, 0.1M, 6/1, v/v). NaOMe (2.0 mg, 0.034 mmol, 0.2 eq.) was added and the mixture was stirred heated to 40˚C. When TLC analysis showed full consumption of the starting material (~6 hours) the reaction mixture was neutralized by addition of AcOH (0.1M in H_2O). The reaction mixture was diluted in EtOAc, transferred to a separatory funnel and washed with sat. $NaHCO_3$ (aq.) and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The title compound was obtained after purification by silicagel chromatography (tol:EtOAc, 1:0 → 3:2) as a white amorphous solid (0.12 g, 0.12 mmol, 68%).^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.40 – 7.22 (m, 15H,), 6.90 (d, 1H, *J*=8.2 Hz, NH), 6.80 (d, 1H, *J*=7.9 Hz, NH), 4.77 – 4.57 (m, 4H, H-1', CH_2Bn), 4.55 – 4.37 (m, 4H, H-1, CH_2Bn), 4.04 – 3.90 (m, 2H, H-3', H-2), 3.85 (dt, 1H, *J*=9.6, 6.2 Hz, OCH_2), 3.79 (dd, 1H, *J*=11.4, 4.3 Hz, H-6), 3.75 – 3.66 (m, 2H, H-4, H-6), 3.67 – 3.58 (m, 4H, H-3, H-4', H-5', H-6'), 3.58 – 3.50 (m, 2H, H-5, H-2'), 3.49 – 3.40 (m, 2H, H-6', OCH_2), 3.23 (t, 2H, *J*=6.9 Hz, CH_2N_3), 2.44 (s, 1H, OH), 1.81 (s, 1H, OH), 1.63 – 1.50 (m, 4H, CH_2, hexyl), 1.42 – 1.26 (m, 4H, CH_2, hexyl) ppm. ^{13}C-APT NMR ($CDCl_3$, 126 MHz) δ 163.3, 161.9 (C=O, TCA), 138.2, 137.6, 137.3, 128.8, 128.7, 128.7, 128.3, 128.3, 128.2, 128.2 (arom.), 100.7 (C-1), 99.9 (C-1'), 92.8 (C_q, TCA), 92.5 (C_q, TCA), 81.4 (C-3), 75.6 (CH_2Bn), 75.5 (C-4), 74.1 (C-5), 74.0 (C-5'), 73.8 (CH_2Bn), 73.8 (CH_2Bn), 72.2 (C-4'), 71.6 (C-3'), 69.9 (OCH_2), 68.7 (C-6), 68.4 (C-6'), 58.4 (C-2'), 56.4 (C-2), 51.5 (CH_2N_3), 29.5, 28.9, 26.6, 25.7 (CH_2-hexyl) ppm. HRMS $[M+Na]^+$ calcd for $C_{43}H_{51}Cl_6N_5O_{11}Na$: 1046.16139, found 1046.16084.

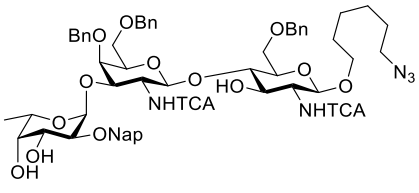
6-azidohexyl 3-*O*-acetyl-6-*O*-benzyl-2-deoxy-4-*O*-(4,6-di-*O*-benzyl-2-deoxy-3-*O*-(3,4-di-*O*-benzoyl-2-*O*-(2-methylnaphthyl)-α-L-fucopyranoside)-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside)-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (30)



Donor **A** (0.121 g, 0.2 mmol, 2.0 eq.) and acceptor **28** (0.107 g, 0.1 mmol) were co-evaporated together thrice with dry toluene, before dissolving them in dry DCM (1 mL, 0.1M). Freshly dried MS (4Å) were added and the mixture was stirred for 15 min. at room temperature. Next NIS (0.049 g, 0.022 mmol, 2.2 eq.) was added and the mixture was cooled to -40˚C, at which temperature it was stirred for an additional 30 min. TMSOTf (100 µL, 0.1 eq., of a 0.1M solution in DCM) was added and the mixture was allowed to warm up to -20˚C and kept at that temperature. After 6 hours the reaction was stopped

by addition of Et_3N (0.05 mL). The reaction mixture was diluted in EtOAc, washed twice with sat. $Na_2S_2O_3$ (aq.), followed by sat. $NaHCO_3$ (aq.) and brine. After drying over $MgSO_4$ and filtration the solvents were removed by evaporation. The title compound was separated by silicagel chromatography (tol:EtOAc, 1:0 → 4:1), followed by size exclusion (LH-20, MeOH/DCM, 1/1, v/v). This gave the title compound as a white solid (0.102 g, 0.065 mmol, 65%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.67 – 7.55 (m, 3H, arom.), 7.55 – 7.46 (m, 5H, arom.), 7.42 – 7.28 (m, 4H, arom.), 7.27 – 6.99 (m, 22H, NH', arom.), 6.84 (d, 1H, *J*=9.3 Hz, NH), 5.54 (dd, 1H, *J*=10.5, 3.3 Hz, H-3''), 5.45 (dd, 1H, *J*=3.4, 1.3 Hz, H-4''), 5.01 – 4.88 (m, 2H, H-3, H-1''), 4.84 – 4.72 (m, 2H, H-1', CH_2arom), 4.64 (s, 2H, CH_2arom), 4.49 – 4.39 (m, 3H, CH_2arom), 4.38 – 4.21 (m, 4H, H-1, H-5'', CH_2arom), 4.13 (dd, 1H, *J*=11.1, 2.9 Hz, H-3'), 4.03 (dd, 1H, *J*=10.5, 3.3 Hz, H-2''), 3.95 – 3.82 (m, 2H, H-2, H-4), 3.80 (d, 1H, *J*=2.9 Hz, H-4'), 3.68 – 3.57 (m, 2H, H-2', OCH_2), 3.57 – 3.41 (m, 5H, H-5, H-6, H-6'), 3.37 (dd, 1H, *J*=8.4, 5.0 Hz, H-5'), 3.12 (dt, 1H, *J*=9.6, 6.6 Hz, OCH_2), 3.04 (t, 2H, *J*=6.9 Hz, CH_2N_3), 1.66 (s, 3H, CH_3, Ac), 1.44 – 1.28 (m, 4H, CH_2, hexyl), 1.20 – 1.07 (m, 4H, CH_2, hexyl), 0.86 (d, 3H, *J*=6.5 Hz, H-6'') ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz): δ 171.2 (C=O, Ac), 166.1, 165.6 (C=O, Bz), 162.1, 162.0 (C=O, TCA), 138.4, 137.7, 135.0, 133.4, 133.2, 133.1, 129.7, 129.6, 129.4, 128.7, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.1, 128.0, 128.0, 127.8, 127.8, 127.7, 127.7, 127.6, 127.5, 126.4, 126.3, 126.3 (arom.), 100.9 (C-1), 97.8 (C-1'), 97.8 (C-1''), 92.8, 92.6 (C_q, TCA), 77.4 (C-3'), 75.1 (C-5), 74.8 (CH_2arom), 73.6 (CH_2arom), 73.5 (CH_2arom), 73.5 (C-4'), 73.3 (C-2''), 73.1 (CH_2arom), 73.0 (C-5'), 72.4 (C-4), 72.3 (C-3), 72.2 (C-4''), 70.8 (C-3''), 69.7 (OCH_2), 68.5 (C-6), 67.8 (C-6'), 66.5 (C-5'), 55.9 (C-2'), 55.3 (C-2), 51.4 (CH_2N_3), 29.4, 28.8, 26.5, 25.6, 20.7 (CH_2-hexyl), 16.0 (C-6'') ppm. HRMS $[M+Na]^+$ calcd for Chemical Formula: $C_{76}H_{79}Cl_6N_5O_{18}Na$: 1582.34490, found 1582.34435.

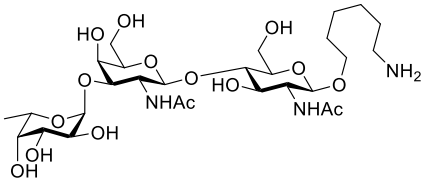
6-azidohexyl 6-*O*-benzyl-2-deoxy-4-*O*-(4,6-di-*O*-benzyl-2-deoxy-3-*O*-(2-*O*-(2-methylnaphthyl)-α-L-fucopyranoside)-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside)-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (30a)



Trisaccharide **30** (0.080 g, 0.05 mmol, 1.0 eq.) was dissolved in a mixture of THF and MeOH (0.5 mL, 0.1M, 4/1, v/v). NaOMe (100 µL of a 0.1M solution of NaOMe in MeOH, 0.2 eq.) was added and the mixture was left to stir overnight at room temperature. The reaction mixture was diluted with THF (0.5 mL) and neutralized with Dowex H^+ resin. The resin was filtered off and the volatiles were removed *in vacuo*. The crude was purified by size exclusion (DCM/MeOH, 1/1, v/v) to give the title compound as a colourless film (0.043 g, 0.032 mmol, 64%). ^{1}H NMR (CD_3CN, 500 MHz): δ = 7.87 (m, 4H, arom.), 7.58 (d, 1H, *J*=10.5 Hz, NH'), 7.53 – 7.47 (m, 2H, arom.), 7.45 (d, 1H, *J*=8.7 Hz, NH), 7.38 (d, 4H, *J*=5.7 Hz, arom.),

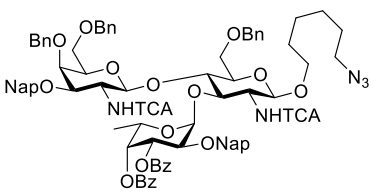
7.35 – 7.22 (m, 11H, arom.), 5.22 (d, 1H, *J*=3.5 Hz, H-1''), 4.91 – 4.81 (m, 3H, CH_2arom), 4.57 – 4.51 (m, 1H, CH_2arom), 4.51 – 4.43 (m, 4H, H-1, CH_2arom), 4.40 – 4.32 (m, 3H, H-1', CH_2arom), 4.17 – 4.09 (m, 1H, H-2'), 4.06 (dd, 1H, *J*=11.2, 2.6 Hz, H-3'), 3.98 (q, 1H, *J*=6.7, 5.7 Hz, H-5''), 3.95 – 3.88 (m, 2H, H-4', H-3''), 3.85 – 3.78 (m, 1H, H-5), 3.78 – 3.70 (m, 2H, H-2'', OCH_2), 3.68 – 3.58 (m, 4H, H-2, H-6, H-5', H-4''), 3.55 – 3.46 (m, 2H, H-6, H-6'), 3.46 – 3.40 (m, 2H, H-4, OCH_2), 3.39 – 3.36 (m, 1H, H-6'), 3.31 (dd, 1H, *J*=9.5, 7.4 Hz, H-3), 3.23 (t, 2H, *J*=7.0 Hz, CH_2N_3), 3.15 (d, 1H, *J*=5.8 Hz, 3''-OH), 3.03 (d, 1H, *J*=4.1 Hz, 4''-OH), 1.51 (m, 4H, CH_2, hexyl), 1.35 – 1.24 (m, 4H, CH_2, hexyl), 1.11 (d, 3H, *J*=6.5 Hz, H-6'') ppm. ^{13}C-APT NMR (CD_3CN, 126 MHz): δ 163.4, 162.9 (C=O, TCA), 139.8, 139.5, 139.0, 137.3, 134.2, 134.0, 129.4, 129.3, 129.2, 129.2, 129.2, 129.0, 128.8, 128.7, 128.7, 128.4, 128.3, 128.0, 127.5, 127.4, 127.1 (arom.), 102.5 (C-1'), 101.1 (C-1), 98.0 (C-1''), 93.8, 93.3 (C_q, TCA), 82.2 (C-3), 78.4 (C-2''), 77.5 (C-3'), 75.6 (CH_2arom), 74.9 (C-4), 74.7 (C-4'), 74.6 (C-5), 74.3 (CH_2arom), 73.9 (CH_2arom), 73.6 (CH_2arom), 73.3 (C-5'), 72.8 (C-4''), 70.4 (C-3''), 70.2 (C-6', OCH_2), 69.6 (C-6), 68.4 (C-5''), 58.2 (C-2), 54.9 (C-2'), 52.0 (CH_2N_3), 30.1, 29.4, 27.1, 26.2 (CH_2-hexyl), 16.7 (C-6'') ppm. HRMS $[M+Na]^+$ calcd for $C_{60}H_{69}Cl_6N_5O_{15}Na$: 1332.28190, found 1332.28135.

6-aminohexyl 2-acetamido-2-deoxy-4-*O*-(2-acetamido-2-deoxy-3-*O*-(α-L-fucopyranoside)-β-D-galactopyranoside)-β-D-glucopyranoside (F-LDN)



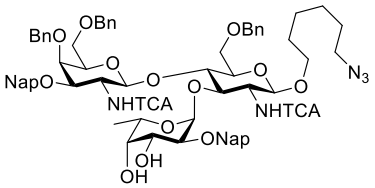
Pd/C (10 mg) was added to a degassed solution of **30a** (0.032 g, 0.024 mmol, 1.0 eq.) in EtOH (0.5 mL). The solution was kept under hydrogen atmosphere for 24 hours. The hydrogen atmosphere was replaced by a nitrogen atmosphere and the solution was filtered over a whatman filter. The filtrate was concentrated *in vacuo*, redissolved in H_2O and purified by HW-40 size exclusion chromatography. After lyophilisation **F-LDN** was obtained as a white solid. (6.1 mg, 9.1 µmol, 38%). ^{1}H NMR (D_2O, 500 MHz): δ = 4.99 (d, 1H, *J*=4.1 Hz, H-1''), 4.58 (d, 1H, *J*=8.5 Hz, H-1'), 4.49 (d, 1H, *J*=8.2 Hz, H-1), 4.11 (q, 1H, *J*=6.6 Hz, H-5''), 4.04 (dd, 1H, *J*=10.9, 8.4 Hz, H-2'), 3.97 (d, 1H, *J*=3.2 Hz), 3.93 – 3.60 (m, 11H), 3.57 (dt, 1H, *J*=10.4, 6.4 Hz, OCH_2), 3.50 (ddd, 1H, *J*=9.8, 5.5, 2.1 Hz), 2.98 (t, 2H, *J*=7.7 Hz, CH_2N_3), 2.04 (s, 3H, CH_3, Ac), 2.02 (s, 3H, CH_3, Ac), 1.68 – 1.50 (m, 4H, CH_2, hexyl), 1.42 – 1.32 (m, 4H, CH_2, hexyl), 1.19 (d, 3H, *J*=6.6 Hz, H-6'') ppm. ^{13}C-APT NMR (D_2O, 126 MHz): δ 175.0, 174.4 (C=O, Ac), 101.5 (C-1'', C-1'), 101.1 (C-1), 79.1, 78.4, 75.3, 74.5, 72.6, 71.8, 71.6, 70.4 (OCH_2), 69.3, 68.2, 67.9, 67.2 (C-5''), 60.9 (C-6'), 60.2 (C-6), 54.9 (C-2), 51.7 (C-2'), 39.5 (CH_2N_3), 28.4, 26.7, 25.3, 24.6 (CH_2-hexyl), 22.2 (CH_3, Ac), 15.4 (C-6'') ppm. HRMS $[M+H]^+$ calcd for $C_{28}H_{51}N_3O_{15}H$: 670.33985, found 670. 670.33929.

6-azidohexyl 6-*O*-benzyl-2-deoxy-3-*O*-(3,4-di-*O*-benzoyl-2-*O*-(2-methylnaphthyl)-α-L-fucopyranoside)-4-*O*-(4,6-di-*O*-benzyl-3-*O*-(2-methylnaphthyl)-2-deoxy-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside)-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (31)



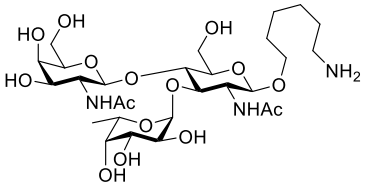
Disaccharide acceptor **27** (0.088 g, 0.075 mmol, 1.0 eq.) and donor **A** (0.091 g, 0.075 mmol, 2.0eq.) were co-evaporated together thrice with dry toluene, before dissolving them in dry DCM (0.75 mL, 0.1M). Freshly dried MS (4Å) were added and the mixture was stirred for 15 min. at room, before addition of NIS (0.037 g, 0.165 mmol, 2.2 eq.). The mixture was cooled to -40˚C, at which temperature it was stirred for an additional 30 min. TMSOTf (150 µL, 0.2 eq. of a 0.1M solution in DCM) was added and the mixture was allowed to warm up to -20˚C and kept at that temperature. After 5 hours the reaction was stopped by addition of Et_3N (0.05 mL). The reaction mixture was diluted in EtOAc, washed twice with sat. $Na_2S_2O_3$ (aq.), followed by sat. $NaHCO_3$ (aq.) and brine. After drying over $MgSO_4$ and filtration the solvents were removed by evaporation. The title compound was separated by silicagel chromatography (tol:EtOAc, 1:0 → 4:1), followed by size exclusion (LH-20, MeOH/DCM, 1/1, v/v). This gave trisaccharide **31** as colourless film (0.086 g, 0.052 mmol, 69%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.03 – 7.71 (m, 11H, arom.), 7.71 – 7.26 (m, 25H, arom.), 7.26 – 7.02 (m, 7H, NH', arom.), 6.52 (d, 1H, *J*=8.1 Hz, NH), 5.82 (dd, 1H, *J*=10.5, 3.4 Hz, H-3''), 5.74 (dd, 1H, *J*=3.5, 1.3 Hz, H-4''), 5.48 (d, 1H, *J*=3.7 Hz, H-1''), 5.05 (q, 1H, *J*=6.1 Hz, H-5'') 4.97 – 4.73 (m, 7H, H-1, H-1', CH_2arom), 4.68 (d, 1H, *J*=11.8 Hz, CH_2arom), 4.64 – 4.48 (m, 4H, CH_2arom), 4.40 (t, 1H, *J*=7.9 Hz, H-3), 4.31 – 4.20 (m, 2H, H-4, H-2''), 4.16 (d, 1H, *J*=2.7 Hz, H-4'), 4.01 (m, 2H, H-2', H-6'), 3.93 (dd, 1H, *J*=9.0, 4.9 Hz, H-6'), 3.90 – 3.71 (m, 5H, H-2, H-6, H-3', OCH_2), 3.59 (dt, 1H, *J*=8.3, 3.3 Hz, H-5), 3.53 – 3.38 (m, 2H, H-5', OCH_2), 3.21 (t, 2H, *J*=6.9 Hz, CH_2N_3), 1.61 – 1.46 (m, 4H, CH_2, hexyl), 1.39 – 1.25 (m, 4H, CH_2, hexyl), 1.16 (d, 3H, *J*=6.5 Hz, H-6'') ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz): δ 166.1, 165.3 (C=O, Bz), 161.9, 161.6 (C=O, TCA), 138.3, 138.1, 138.0, 135.6, 134.9, 133.3, 133.2, 133.2, 133.1, 133.0, 132.9, 130.1, 130.0, 129.8, 129.7, 129.5, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.0, 126.4, 126.3, 126.3, 126.1, 126.0, 125.9, 125.7 (arom.), 99.0 (C-1), 98.9 (C-1'), 97.2 (C-1''), 92.7, 92.5 (C_q, TCA), 77.6 (C-3'), 74.9 (C-5), 74.6 (C-3), 74.5 (CH_2arom), 74.1 (C-2''), 73.5 (C-5'), 73.4 (CH_2arom), 73.3 (CH_2arom), 73.2 (C-4), 73.1 (CH_2arom), 72.9 (C-4''), 71.5 (CH_2arom), 70.9 (C-3''), 70.1 (C-4'), 69.7 (OCH_2), 68.5 (C-6), 67.9 (C-6'), 65.3 (C-5''), 59.1 (C-2), 55.4 (C-2'), 51.4 (CH_2N_3), 29.4, 28.8, 26.5, 25.6 (CH_2-hexyl), 15.9 (CH_3, Ac) ppm. HRMS $[M+Na]^+$ calcd for $C_{85}H_{85}Cl_6N_5O_{17}Na$: 1680.39693, found 1680.39638.

6-azidohexyl 6-*O*-benzyl-2-deoxy-3-*O*-(2-*O*-(2-methylnaphthyl)-α-L-fucopyranoside)-4-*O*-(4,6-di-*O*-benzyl-3-*O*-(2-methylnaphthyl)-2-deoxy-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside)-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (31a)



NaOMe (100 µL of a 0.1M solution of NaOMe in MeOH, 0.2 eq.) was added to a solution of trisaccharide **31** (0.080 g, 0.048 mmol, 1.0 eq.) in a mixture of THF and MeOH (0.5 mL, 0.1M, 5/2, v/v). The reaction mixture was left to stir overnight at room temperature. The reaction mixture was diluted with THF (1 mL) and neutralized by addition of a solution of AcOH (0.1M in H_2O). The mixture was concentrated and purified by size exclusion (DCM/MeOH, 1/1, v/v) to give the title compound as a colourless film. (0.047 g, 0.032 mmol, 65%) ^{1}H NMR (CD_3CN, 500 MHz): δ = 7.92 – 7.75 (m, 8H, arom.), 7.61 (d, 1H, *J*=9.5 Hz, NH'), 7.55 – 7.45 (m, 5H, arom.), 7.42 (d, 1H, *J*=9.5 Hz, NH), 7.39 – 7.15 (m, 14H, arom.), 5.37 (d, 1H, *J*=3.6 Hz, H-1''), 4.85 (d, 1H, *J*=11.7 Hz, CH_2arom), 4.82 – 4.72 (m, 2H, CH_2arom), 4.68 (d, 1H, *J*=11.7 Hz, CH_2arom), 4.64 – 4.52 (m, 7H, H-1, CH_2arom), 4.50 – 4.39 (m, 2H, H-1', CH_2arom), 4.16 – 3.99 (m, 4H, H-2, H-3', H-4', H-3''), 3.91 (t, 1H, *J*=8.8 Hz, H-3), 3.87 – 3.69 (m, 5H, H-2', H-5', H-6', OCH_2), 3.69 – 3.56 (m, 3H, H-6, H-2''), 3.53 (t, 1H, *J*=6.4 Hz, H-5), 3.48 – 3.36 (m, 3H, H-4, H-4'', OCH_2), 3.23 (t, 2H, *J*=7.0 Hz, CH_2N_3), 2.91 (d, 1H, *J*=5.4 Hz, 3''-OH), 2.39 (d, 1H, *J*=3.9 Hz, 4''-OH), 1.57 – 1.42 (m, 4H, CH_2, hexyl), 1.34 – 1.22 (m, 4H, CH_2, hexyl), 1.06 (d, 3H, *J*=6.6 Hz, H-6'') ppm. ^{13}C-APT NMR (CD_3CN, 126 MHz) δ 163.1, 162.5 (C=O, TCA), 139.6, 139.5, 139.5, 137.6, 136.7, 134.2, 134.2, 134.0, 133.8, 129.8, 129.4, 129.3, 129.2, 129.1, 128.9, 128.8, 128.8, 128.8, 128.6, 128.6, 128.5, 128.4, 128.4, 128.3, 128.2, 127.7, 127.3, 127.3, 127.3, 127.2, 127.0, 126.9, 126.7 (arom.), 101.5 (C-1'), 100.9 (C-1), 96.4 (C-1''), 93.8 (C_q, TCA), 79.4 (C-5'), 77.7 (C-2''), 75.8 (C-4), 75.7 (CH_2arom), 74.5 (C-5), 74.4 (C-3), 74.1 (CH_2arom), 73.6 (C-3'), 73.4 (CH_2arom), 73.2 (C-4'), 72.9 (C-4''), 72.6 (CH_2arom), 72.5 (CH_2arom), 70.4 (OCH_2), 69.7 (H-6'), 69.5 (H-6), 69.3 (C-3''), 66.7 (C-5''), 59.2 (C-2'), 55.2 (C-2), 52.0 (CH_2N_3), 30.2, 29.3, 27.1, 26.3 (CH_2-hexyl), 16.6 (C-6'') ppm. HRMS $[M+Na]^+$ calcd for $C_{71}H_{77}Cl_6N_5O_{15}Na$: 1472.34450, found 1472.34395.

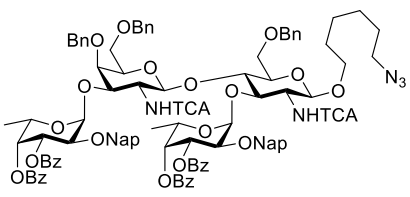
6-aminohexyl 2-acetamido-2-deoxy-3-*O*-(α-L-fucopyranoside)-4-*O*-(2-acetamido-2-deoxy-β-D-galactopyranoside)-β-D-glucopyranoside (LDN-F)



Pd/C (10 mg) was added to a degassed solution of **31a** (0.021 g, 0.014 mmol, 1.0 eq.) in EtOH (0.5 mL). The solution was kept under hydrogen atmosphere for 24 hours. The hydrogen atmosphere was replaced by a nitrogen atmosphere and the solution was filtered over a whatman filter. The filtrate was concentrated *in vacuo*, redissolved in H_2O and purified by HW-40 size exclusion chromatography. After lyophilisation **LDN-F**

was obtained as a white solid (2.3 mg, 0.0034 mmol, 24%). ^{1}H NMR (D_2O, 500 MHz): δ = 5.00 (d, 1H, *J*=3.9 Hz, H-1''), 4.78 – 4.72 (m, 1H, H-5''), 4.43 – 4.32 (m, 2H, H-1, H-1''), 3.89 – 3.70 (m, 11H), 3.70 – 3.49 (m, 9H), 3.49 – 3.41 (m, 1H), 3.41 – 3.34 (m, 1H), 3.07 – 3.01 (m, 1H), 2.86 (t, 2H, *J*=7.7 Hz, CH_2N), 1.93 (s, 3H, CH_3, Ac), 1.90 (s, 3H, CH_3, Ac), 1.58 – 1.50 (m, 2H, CH_2, hexyl), 1.44 (s, 2H, CH_2, hexyl), 1.30 – 1.20 (m, 4H, CH_2, hexyl), 1.15 (d, 3H, *J*=6.6 Hz, H-6'') ppm HRMS $[M+H]^+$ calcd for $C_{28}H_{51}N_3O_{15}H$: 670.33985, found 670.33929.

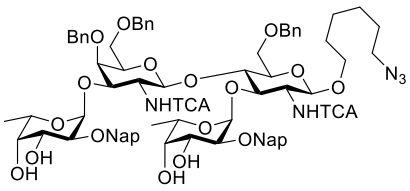
6-azidohexyl 6-*O*-benzyl-2-deoxy-3-*O*-(3,4-di-*O*-benzoyl-2-*O*-(2-methylnaphthyl)-α-L-fucopyranoside)-4-*O*-(4,6-di-*O*-benzyl-3-*O*-(3,4-di-*O*-benzoyl-2-*O*-(2-methylnaphthyl)-α-L-fucopyranoside)-2-deoxy-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside)-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (32)



Diol acceptor **29** (0.10 g, 0.10 mmol, 1.0 eq.) and donor **A** (0.30 g, 0.5 mmol, 5.0 eq.) were co-evaporated together thrice with dry toluene, before dissolving them in dry DCM (1 mL, 0.1M). Freshly dried MS (4Å) were added and the mixture was stirred for 15 min. at room temperature. Next NIS (0.14 g, 0.6 mmol, 6.0 eq.) was added and the mixture was cooled to -40˚C, at which temperature it was stirred for an additional 30 min. TMSOTf (100 µL, of a 0.1M solution in DCM) was added and the mixture was allowed to warm up to -20˚C and kept at that temperature. After 6 hours the reaction was stopped by addition of Et_3N (0.05 mL). The reaction mixture was diluted in EtOAc, washed twice with sat. $Na_2S_2O_3$ (aq.), followed by sat. $NaHCO_3$ (aq.) and brine. After drying over $MgSO_4$ and filtration the solvents were removed by evaporation. The title compound was separated by silicagel chromatography (tol:EtOAc, 1:0 → 4:1), followed by size exclusion (LH-20, MeOH/DCM, 1/1, v/v). This gave tetrasaccharide **32** as a white solid (0.14 g, 0.069 mmol, 69%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.94 – 7.81 (m, 6H, arom), 7.81 – 7.65 (m, 8H, arom), 7.65 – 7.43 (m, 9H, arom), 7.44 – 7.14 (m, 31H, NH, NH', arom.), 5.76 – 5.54 (m, 5H, H-1'', H-3'', H-4'', H-3''', H-4'''), 5.17 (d, 1H, *J*=3.5 Hz, H-1'''), 4.93 (m, 3H, CH_2arom), 4.81 (m, 2H, CH_2arom), 4.74 – 4.59 (m, 4H, H-1, CH_2arom), 4.54 – 4.30 (m, 6H, H-1', H-5'', H-2''', H-5''', CH_2arom), 4.30 – 4.08 (m, 4H, H-3, H-4, H-2', H-2''), 4.07 – 3.95 (m, 2H, H-2, H-4'), 3.89 – 3.60 (m, 7H, H-5, H-6, H-3', H6', OCH_2), 3.43 (dd, 1H, *J*=8.7, 4.6 Hz, H-5'), 3.35 (dt, 1H, *J*=9.5, 6.7 Hz, OCH_2), 3.13 (t, 2H, *J*=7.0 Hz, CH_2N_3), 1.52 – 1.39 (m, 4H, CH_2, hexyl), 1.28 – 1.18 (m, 4H, CH_2, hexyl), 1.14 – 1.01 (m, 6H, H-6'', H-6''') ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ 166.1, 165.8, 165.5, 165.4 (C=O, Bz), 162.7, 162.1 (C=O, TCA), 138.3, 138.1, 137.9, 135.5, 134.4, 133.4, 133.3, 133.3, 133.3, 133.2, 133.2, 133.0, 132.9, 130.1, 129.8, 129.8, 129.7, 129.7, 129.7, 129.5, 129.1, 128.6, 128.6, 128.6, 128.5, 128.5, 128.3, 128.1, 128.1, 128.0, 128.0, 128.0, 127.9, 127.7, 126.8, 126.8, 126.7, 126.1, 126.1, 125.9, 125.8 (arom.),

100.9 (C-1'), 99.5 (C-1), 98.1 (C-1'''), 96.0 (C-1''), 92.8, 92.7 (C_q, TCA), 79.8 (C-3'), 76.4 (C-5), 75.8 (C-3), 74.9 (CH_2arom), 74.9 (C-2'''), 74.6 (CH_2arom), 73.5 (C-5'), 73.5 (CH_2arom), 73.4 (CH_2arom), 73.0 (C-2''), 72.7 (C-4), 72.6 (C-4''), 72.2 (CH_2arom), 71.9 (C-4'''), 71.7 (C-4'), 71.6 (-3'''), 70.5 (C-3''), 69.5 (C-6, C-6'), 67.7 (OCH_2), 66.9 (C-5''), 65.4 (C-5'''), 56.7 (C-2), 53.9 (C-2'), 51.4 (CH_2N_3), 29.5, 28.8, 26.5, 25.6 (CH_2-hexyl), 16.2 (C-6''), 16.1 (C-6''') ppm. HRMS $[M+Na+H]^{2+}$ calcd $C_{105}H_{103}Cl_6N_5O_{23}NaH$: 1017.75755, found 1017.75700.

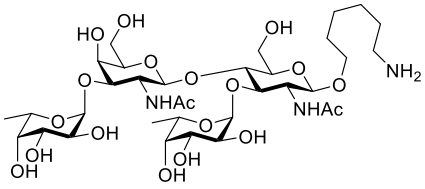
6-azidohexyl 6-*O*-benzyl-2-deoxy-3-*O*-(2-*O*-(2-methylnaphthyl)-α-L-fucopyranoside)-4-*O*-(4,6-di-*O*-benzyl-2-deoxy-3-*O*-(2-*O*-(2-methylnaphthyl)-α-L-fucopyranoside)-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside)-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (32a)



NaOMe (130 µL of a 0.1M solution of NaOMe in MeOH, 0.2 eq.) was added to a suspension of tetrasaccharide **32** (0.14 g, 0.067 mmol, 1.0 eq.) in dry methanol (0.7 mL, 0.1M). The reaction was left to stir overnight, diluted in MeOH (5 mL) and neutralized by addition of Dowex H^+ resin. The resin was filtered off, washed and the filtrate was concentrated and purified by size exclusion (DCM/MeOH, 1/1, v/v) to give tetraol **32a** as a colourless film (0.067 g, 0.042 mmol, 63%). ^{1}H NMR (CD_3CN, 500 MHz): δ = 7.94 – 7.78 (m, 8H, arom.), 7.62 (d, 1H, *J*=9.4 Hz, NH), 7.60 – 7.45 (m, 9H, NH', arom.), 7.41 – 7.36 (m, 2H, arom.), 7.36 – 7.30 (m, 6H, arom.), 7.30 – 7.20 (m, 7H, arom.), 5.34 (d, 1H, *J*=3.6 Hz, H-1''), 5.31 (d, 1H, *J*=3.6 Hz, H-1'''), 4.90 – 4.76 (m, 4H, CH_2arom), 4.65 – 4.54 (m, 3H, CH_2arom), 4.54 – 4.33 (m, 6H, H-1, H-1', H-5'', CH_2arom), 4.25 – 4.14 (m, 1H, H-2'), 4.08 (dd, 1H, *J*=11.1, 2.8 Hz, H-3'), 4.06 – 3.95 (m, 3H, H-3, H-3'', H-5'''), 3.94 – 3.88 (m, 3H, H-4, H-4', H-3'''), 3.83 (q, 1H, *J*=9.2, 8.3, 7.9 Hz, H-2), 3.75 – 3.63 (m, 5H, H-6, H-6', H-2''', OCH_2), 3.63 – 3.59 (m, 3H, H-5', H-6', H-4'), 3.57 (dd, 1H, *J*=10.0, 3.6 Hz, H-2''), 3.50 – 3.43 (m, 1H, H-5), 3.41 – 3.30 (m, 2H, H-4'', OCH_2), 3.21 (t, 2H, *J*=6.9 Hz, CH_2N_3), 3.17 (d, 1H, *J*=5.8 Hz, 3'''-OH), 3.01 (d, 1H, *J*=4.1 Hz, 4'''-OH), 2.91 (d, 1H, *J*=5.3 Hz, 3''-OH), 2.34 (d, 1H, *J*=3.8 Hz, 4''-OH), 1.57 – 1.37 (m, 4H, CH_2, hexyl), 1.26 (h, 4H, *J*=3.4 Hz, CH_2, hexyl), 1.12 (d, 3H, *J*=6.6 Hz, H-6'''), 1.03 (d, 3H, *J*=6.5 Hz, H-6'') ppm. ^{13}C-APT NMR (CD_3CN, 126 MHz): δ 163.0, 162.5 (C=O, TCA), 139.6, 139.5, 137.5, 137.2, 134.2, 134.2, 133.9, 133.8, 129.9, 129.6, 129.4, 129.2, 129.2, 129.0, 128.9, 128.9, 128.6, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 127.9, 127.4, 127.4, 127.3, 127.1, 127.0, 126.9, 126.7, 126.2 (arom.), 101.6 (C-1'), 101.4 (C-1), 97.8 (C-1'''), 96.3 (C-1''), 93.8, 93.7 (C_q, TCA), 78.1 (C-2'''), 77.6 (C-2''), 76.4 (C-3'), 76.2 (C-5), 76.1 (CH_2arom), 75.4 (C-4'), 74.6 (C-5'), 74.2 (C-3, C-4), 74.1 (CH_2arom), 73.7 (CH_2arom), 73.5 (CH_2arom), 72.9 (C-4''), 72.8 (C-4'''), 72.5 (CH_2arom), 70.4 (C-3'''), 70.3 (OCH_2), 69.8 (C-6), 69.5 (C-6'), 69.4 (C-3''), 68.1 (C-5'''), 66.8 (C-5''), 58.9 (C-2), 55.4 (C-2'), 52.0 (CH_2N_3),

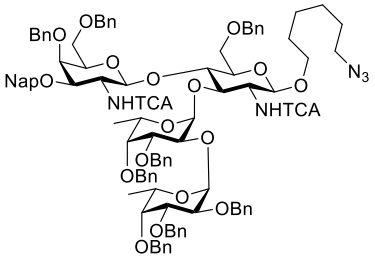
30.2, 29.3, 27.1, 26.2 (CH_2-hexyl), 16.7 (H-6'''), 16.6 (C-6'') ppm. HRMS $[M+Na]^+$ calcd for $C_{77}H_{87}Cl_6N_5O_{19}Na$: 1618.40241, found 1618.40186.

6-aminohexyl 2-acetamido-2-deoxy-3-*O*-(α-L-fucopyranoside)-4-*O*-(2-acetamido-2-deoxy-3-*O*-(α-L-fucopyranoside)-β-D-galactopyranoside)-β-D-glucopyranoside (F-LDN-F)



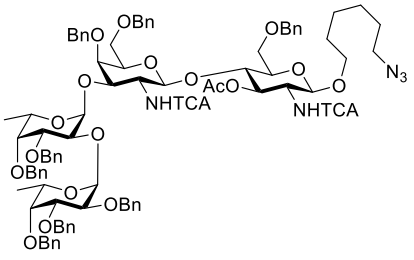
Tetraol **32a** (57 mg, 28 µmol, 1.0 eq.) was dissolved in degassed, sodium treated EtOH (1 mL). Pd/C (20 mg) was added after purging the flask with nitrogen. The reaction was kept under hydrogen atmosphere for 24 hours at room temperature. After this time period the hydrogen atmosphere was replaced by a nitrogen atmosphere and the solution was filtered over a whatman filter. The solvent was removed *in vacuo* and the colourless film was redissolved in degassed H_2O (1 mL). Pd black (10 mg) was added and the reaction was put under hydrogen atmosphere for an additional 24 hours. After this time period the temperature was increased to 50˚C and the mixture was stirred for another 24 hours. Upon completion, indicated by LC-MS analysis, the hydrogen atmosphere was replaced by a nitrogen atmosphere and the solution was filtered over a whatman filter. The mixture was concentrated and purified by HW-40 size exclusion chromatography and lyophilized. This gave fully deprotected tetramer as a fluffy white solid (5.4 mg, 6.6 µmol, 24%). ^{1}H NMR (D_2O, 500 MHz): δ = 5.11 (d, 1H, *J*=4.0 Hz), 4.97 (d, 1H, *J*=4.2 Hz), 4.84 (q, 1H, *J*=6.6 Hz), 4.50 (d, 1H, *J*=8.5 Hz), 4.48 (d, 1H, *J*=8.1 Hz), 4.15 – 4.03 (m, 2H), 3.99 – 3.79 (m, 10H), 3.79 – 3.65 (m, 5H), 3.61 (dd, 1H, *J*=8.1, 4.1 Hz), 3.59 – 3.53 (m, 1H), 3.50 (ddd, 0H, *J*=9.3, 4.9, 2.3 Hz), 2.99 (dt, 2H, *J*=13.5, 7.6 Hz), 2.02 (s, 3H), 2.01 (s, 3H), 1.69 – 1.62 (m, 2H), 1.58 – 1.51 (m, 2H), 1.38 – 1.32 (m, 4H), 1.26 (d, 3H, *J*=6.6 Hz), 1.20 (d, 3H, *J*=6.6 Hz) ppm. ^{13}C-APT NMR (D_2O, 126 MHz) δ 175.1, 174.1 (C=O, Ac), 101.6, 101.0, 100.7, 98.4, 78.7, 75.4, 75.0, 74.3, 73.5, 72.0, 71.8, 70.5, 69.3, 69.2, 68.3, 67.8, 67.8, 67.2, 66.9, 61.4, 60.0, 55.8, 51.4, 47.0, 42.8, 39.5, 28.4, 26.7, 25.5, 25.4, 25.3, 24.7, 22.3, 22.2, 15.4, 15.3, 10.5 ppm. HRMS $[M+Na]^+$ calcd for $C_{34}H_{61}N_3O_{19}H$: 816.39776, found 816.39720.

6-azidohexyl 6-*O*-benzyl-2-deoxy-3-*O*-(3,4-di-*O*-benzyl-2-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranose)-α-L-fucopyranose)-4-*O*-(4,6-di-*O*-benzyl-3-*O*-(2-methylnaphthyl)-2-deoxy-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside)-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (33)



Di-fucosyl donor **35** (0.11 g, 0.13 mmol, 1.5 eq.) and acceptor **27** (0.10 g, 0.086 mmol, 1.0 eq.) were co-evaporated thrice with dry toluene and dissolved in dry DCM (0.9 mL, 0.1M). MS (3Å) were added and the solution was stirred at 0˚C for 1 hour. IDCP (0.12 g, 0.26 mmol, 3.0 eq.) was added and the mixture was allowed to warm to RT. The mixture was stirred for 24 hours. As TLC analysis showed little to no conversion after this time the reaction was diluted with EtOAc and quenched by addition of sat. $Na_2S_2O_3$ (aq.) (0.2 mL). The two-phase system was transferred to a separatory funnel and the water layer was removed. The organic layer was washed with sat. $CuSO_4$ (aq.) and brine, dried over $MgSO_4$, filtered and concentrated. The brown mixture was purified by silicagel chromatography (tol:ACN, 1:0 → 4:1) followed by size exclusion over LH-20 (DCM/MeOH, 1/1. v/v) to give compound **33** as a colourless film (0.012 g, 0.0063 mmol, 7%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.82 (m, 5H), 7.54 – 7.11 (m, 48H), 6.82 (d, 1H, *J*=7.3 Hz), 5.17 (d, 1H, *J*=3.5 Hz), 5.00 – 4.92 (m, 3H), 4.92 – 4.78 (m, 5H), 4.76 – 4.34 (m, 15H), 4.24 – 4.07 (m, 6H), 3.99 (dd, 1H, *J*=10.2, 2.7 Hz), 3.86 (dd, 1H, *J*=10.5, 2.7 Hz), 3.80 – 3.70 (m, 2H), 3.70 – 3.62 (m, 3H), 3.60 – 3.52 (m, 1H), 3.47 – 3.39 (m, 2H), 3.36 – 3.29 (m, 2H), 3.25 (s, 1H), 3.15 (t, 2H, *J*=6.9 Hz), 1.62 – 1.43 (m, 4H), 1.25 (m, 4H), 1.04 (d, 3H, *J*=6.5 Hz), 0.77 (d, 3H, *J*=6.5 Hz) ppm.

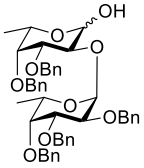
6-azidohexyl 3-*O*-acetyl-6-*O*-benzyl-2-deoxy-4-*O*-(4,6-di-*O*-benzyl-2-deoxy-3-*O*-(3,4-di-*O*-benzyl-2-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranose)-α-L-fucopyranose)-2-(2,2,2-trichloroacetamido)-β-D-galactopyranoside)-2-(2,2,2-trichloroacetamido)-β-D-glucopyranoside (34)



Acceptor **28** (0.053 g, 0.050 mmol, 1.0 eq.) and di-fucosyl donor **35** (0.085 g, 0.10 mmol, 2.0 eq.) were co-evapotared thrice with dry toluene and dissolved in dry DCM (0.5 mL, 0.1M). MS (3Å) were added and the solution was stirred at 0˚C for 1 hour. IDCP (0.094 g, 0.20 mmol, 4.0 eq.) was added and the mixture was allowed to warm to RT. The mixture was stirred for 24 hours. As TLC analysis showed little to no conversion after this time the reaction was diluted with EtOAc and quenched by addition of sat. $Na_2S_2O_3$ (aq.) (0.2 mL). The two-phase system was transferred to a separatory funnel and the water layer was removed. The organic layer was washed with sat. $CuSO_4$

(aq.) and brine, dried over $MgSO_4$, filtered and concentrated. The brown mixture was purified by silicagel chromatography (tol:ACN, 1:0 → 4:1) followed by size exclusion over LH-20 (DCM/MeOH, 1/1. v/v) to give compound **34** as a colourless film (0.013 g, 0.0072 mmol, 14%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.66 (d, 1H, *J*=8.4 Hz, NH'), 7.46 – 7.09 (m, 38H, NH, arom.), 7.04 (dd, 2H, *J*=6.4, 2.9 Hz, arom.), 5.09 (d, 1H, *J*=3.3 Hz, H-1''), 5.04 – 4.96 (m, 2H, H-3, CH_2Bn), 4.94 – 4.85 (m, 3H, H-1''', CH_2Bn), 4.81 – 4.73 (m, 3H, CH_2Bn), 4.71 – 4.61 (m, 4H, CH_2Bn), 4.57 – 4.32 (m, 7H, H-1, H-2', H-2'', CH_2Bn), 4.30 – 4.06 (m, 6H, H-1', H-5'', H-2''', H-5''', CH_2Bn), 4.05 – 3.91 (m, 4H, H-2, H-4', H-3'', H-3'''), 3.89 – 3.76 (m, 4H, H-4, H-3', H-4'', OCH_2), 3.70 (q, 1H, *J*=5.3 Hz, H-5), 3.59 – 3.50 (m, 2H, H-6, H-6'), 3.50 – 3.33 (m, 4H, H-6, H-6', H-4''', OCH_2), 3.23 (m, 3H, H-5', CH_2N_3), 1.73 (s, 3H, CH_3, Ac), 1.55 (q, 4H, *J*=6.1, 5.0 Hz, CH_2, hexyl), 1.34 (m, 4H, CH_2, hexyl), 1.07 (d, 3H, *J*=6.4 Hz, H-6''), 0.87 (d, 3H, *J*=6.4 Hz, H-6''') ppm. ^{13}C-APT NMR ($CDCl_3$, 126 MHz) δ 170.1 (C=O, Ac), 162.6, 161.9 (C=O, TCA), 138.6, 138.6, 138.5, 138.3, 138.2, 138.0, 137.9, 129.0, 128.7, 128.7, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 127.3 (arom.), 101.6 (C-1'), 100.9 (C-1), 95.6 (C-1'''), 95.4 (C-1''), 81.0 (C-3'''), 78.1 (C-3''), 77.0 (C-4''), 76.7 (C-5), 76.2 (C-4'''), 75.3 (CH_2Bn), 74.9 (CH_2Bn), 74.6 (CH_2Bn), 73.8 (C-2'''), 73.7 (CH_2Bn), 73.6 (CH_2Bn), 73.3 (CH_2Bn), 73.3 (C-5'), 73.1 (C-4), 72.2 (C-3), 72.1 (C-4'), 71.9 (CH_2Bn), 71.3 (CH_2Bn), 70.8 (C-2''), 69.8 (OCH_2), 68.6 (C-6), 68.3 (C-5''), 67.9 (C-6'), 66.2 (C-5'''), 54.9 (C-2), 53.8 (C-2'), 51.5 (CH_2N_3), 29.4, 28.9, 26.6, 25.6 (CH_2, hexyl), 20.7 (CH_3, Ac), 16.8 (C-6''), 16.3 (C-6''') ppm. HRMS $[M+Na]^+$ calcd for $C_{92}H_{103}Cl_6N_5O_{20}Na$: 1830.52253, found 1830.52198.

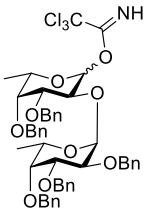
3,4-di-*O*-benzyl-2-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranose)-α/β-L-fucopyranose (35a)



Disaccharide **35** (0.050 g, 0.057 mmol, 1.0 eq.) was dissolved in a mixture of acetone and water (0.6 mL, 0.1M, 9/1, v/v). NBS (0.030 g, 0.172 mmol, 3.0 eq.) was added and the mixture was stirred for 10min. when TLC analysis indicated full conversion to two lower running spots. sat. $Na_2S_2O_3$ (aq. 0.5 mL) was added and the solution was stirred until the red solution turned colourless. The mixture was diluted in EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated. The title compound was obtained after purification by silicagel chromatography (tol:ACN, 1:0 → 9:1) as a yellow oil (0.025 g, 0.035 mmol, 71%, 5/3, α/β). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.69 – 6.99 (m, 39H, arom.), 5.35 (d, 0.6H, *J*=3.6 Hz, H-1'β), 5.26 (d, 1H, *J*=3.5 Hz, H-1'α), 5.01 – 4.89 (m, 3H, CH_2arom), 4.87 – 4.52 (m, 17H, H-1α, H-1β, CH_2arom), 4.17 (dd, 1H, *J*=9.7, 3.5 Hz, H-2'α), 4.15 – 4.06 (m, 2.6H, H-2'α, H-5'α, H-2β), 4.04 (dd, 1H, *J*=9.2, 3.7 Hz, H-2α), 4.01 – 3.89 (m, 2.8H, H-5α, H-2β, H-3β, H-5'β), 3.87 – 3.78 (m, 2H, H-3α, H-3'α), 3.67 (dd, 1H, *J*=2.8, 1.3 Hz, H-4'α), 3.61 (dd, 1H, *J*=2.9, 1.0 Hz, H-4β), 3.58 – 3.50 (m, 1.2H, H-5β, H-3'β), 3.47 (dd, 1H, *J*=2.9, 1.2 Hz, H-4α), 3.43 (dd, 0.6H, *J*=2.9, 1.2 Hz, H-4β), 1.25 (d, 2H, *J*=6.4 Hz, H-6β), 1.20 (d, 3H, *J*=6.5 Hz, H-6'α), 0.93 (d, 3H, *J*=6.5 Hz, H-6α), 0.88 (d, 2H, *J*=6.4 Hz, H-6'β) ppm. ^{13}C-APT NMR

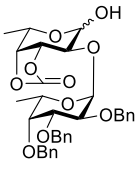
($CDCl_3$, 101 MHz) δ 139.0, 138.8, 138.7, 138.7, 138.6, 138.6, 138.2, 138.0, 138.0, 128.7, 128.6, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 128.0, 127.8, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 127.6, 127.6, 127.4 (arom.), 98.2 (C-1β), 97.8 (C-1'β), 96.1 (C-1α), 90.7 (C-1'α), 82.2 (C-3'β), 79.7 (C-3α), 79.4 (C-3β), 78.3 (C-3'α), 77.7 (C-4'β), 77.5 (C-2'β), 77.4 (C-4α), 76.8 (C-2β), 76.7 (C-4'α), 76.5 (C-4β), 75.7 (C-2α), 74.9 (CH_2arom), 74.9 (CH_2arom), 74.8 (CH_2arom), 74.7 (CH_2arom), 74.4 (CH_2arom), 73.8 (C-2'α), 73.6 (CH_2arom), 73.1 (CH_2arom), 72.9 (CH_2arom), 72.8 (CH_2arom), 72.6 (CH_2arom), 71.0 (C-5β), 67.3 (C-5'α), 66.9 (C-5α), 66.8 (C-5'β), 17.1, 16.9, 16.5, 16.5 (C-6α, C-6'α, C-6β, C-6'β) ppm. HRMS $[M+Na]^+$ calcd for $C_{47}H_{52}O_9Na$: 783.35090, found 783.35035.

(2,2,2-trichloroacetimidoyl) 3,4-di-*O*-benzyl-2-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranose)-α/β-L-fucopyranose (36)



Hemi acetal **35a** (0.025 g, 0.032 mmol, 1.0 eq.) was dissolved in dry DCM (0.5 mL, 0.06M). Cl_3CCN (34 µL, 0.32 mmol, 10 eq.) was added, followed by addition of DBU (33 µL, 3 µmol 0.1 eq. of a 0.1M solution in DCM). The mixture turned brown in 10 min. and the mixture was concentrated *in vacuo*. The dark oil was purified by silicagel chromatography using neutralized silica (tol:ACN, 1:0 → 9:1), which gave the title compound as a colourless oil (0.028 g, 0.031 mmol, 97%, 9/1, α/β). α-product: ^{1}H NMR (CD_3CN, 400 MHz): δ = 9.11 (s, 1H, NH), 7.73 – 7.04 (m, 36H, arom.), 5.81 (d, 1H, *J*=8.2 Hz, H-1), 5.41 (d, 1H, *J*=3.7 Hz, H-1'), 4.95 (d, 1H, *J*=10.7 Hz, CH_2Bn), 4.88 – 4.80 (m, 2H, CH_2Bn), 4.78 – 4.66 (m, 5H, CH_2Bn), 4.62 (d, 1H, *J*=11.2 Hz, CH_2Bn), 4.50 (m, 4H, CH_2Bn), 4.24 (q, 1H, *J*=7.5, 6.0 Hz, H-5), 4.12 – 4.02 (m, 1H, H-3), 3.93 – 3.68 (m, 5H, H-2, H-4, H-5, H-2', H-3'), 3.40 (dd, 1H, *J*=3.0, 1.3 Hz, H-4'), 1.24 (d, 3H, *J*=6.3 Hz, H-6), 0.80 (d, 3H, *J*=6.4 Hz, H-6') ppm. ^{13}C-APT NMR (CD_3CN, 101 MHz) δ 160.8 (C=NH), 140.1, 140.0, 139.7, 139.0, 129.4, 129.3, 129.3, 129.3, 129.2, 129.1, 129.1, 129.1, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3 (arom.), 99.5 (C-1), 96.7 (C-1'), 82.2 (C-3), 79.6 (C-2), 78.5 (C-4'), 77.1, (C-4, C-2') 76.1 (CH_2Bn), 75.6 (CH_2Bn), 73.5 (CH_2Bn), 73.3 (CH_2Bn), 73.1 (CH_2Bn), 72.0 (C-5), 71.4 (C-3), 66.9 (C-5'), 16.9 (C-6), 16.6 (C-6') ppm.

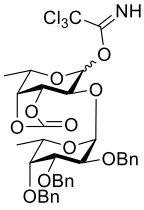
3,4-*O*-carbonate-2-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranose)-α/β-L-fucopyranose (37a)



NBS (0.035 g, 0.203 mmol, 3.0 eq.) was added to a solution containing disaccharide **37** (0.047 g, 0.067 mmol, 1.0 eq.) and left to stir in the dark for 15 min. Sat. $Na_2S_2O_3$ (aq. 0.5 mL) was added and the solution was stirred until the red solution turned colourless. The mixture was diluted in EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated. The title compound was obtained after purification by silicagel chromatography (tol:ACN, 1:0 → 9:1) as a yellow oil (0.026 g, 0.043 mmol, 64%, 5/3, α/β). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.43 – 7.22 (m, 19H, arom.), 5.31 (d, 0.2H, *J*=3.8 Hz,

H-1'β), 5.20 – 5.13 (m, 1H, H-1'α), 4.96 (d, 1H, *J*=11.5 Hz, CH_2Bn), 4.90 (d, 1H, *J*=11.6 Hz, CH_2Bn), 4.86 – 4.79 (m, 3H, H-1α, H-4α, CH_2Bn), 4.79 – 4.74 (m, 3H, H-1β), 4.74 – 4.71 (m, 1H, CH_2Bn), 4.69 – 4.66 (m, 2H, H-4β, CH_2Bn), 4.66 – 4.63 (m, 1H, CH_2Bn), 4.51 (dd, 0.2H, *J*=6.9, 2.1 Hz, H-3β), 4.47 (dd, 1H, *J*=8.1, 1.7 Hz, H-3α), 4.13 – 3.99 (m, 3.4H, H-2α, H-5α, H-2'α, H-5β, H-2'β), 3.90 (dd, 0.2H, *J*=10.1, 2.8 Hz, H-3'β), 3.86 (dd, 0.2H, *J*=6.6, 2.1 Hz, H-5'β), 3.83 – 3.73 (m, 2H, H-3'α, H-5'α), 3.73 – 3.68 (m, 1.4H, H-4'α, H-2β, H-4'β), 1.42 (d, 0.6H, *J*=6.6 Hz, H-6β), 1.29 (d, 3H, *J*=6.5 Hz, H-6α), 1.17 (d, 0.6H, *J*=6.4 Hz, H-6'β), 1.15 (d, 3H, *J*=6.5 Hz, H-6'α) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz): δ 153.8 (C=O), 138.8, 138.6, 138.2, 138.1, 137.3, 129.2, 128.8, 128.7, 128.6, 128.6, 128.5, 128.5, 128.5, 128.4, 128.3, 128.3, 128.0, 128.0, 128.0, 127.8, 127.7, 127.7, 127.5, 125.4 (arom.), 101.8 (C-1α), 98.1 (C-1'β), 95.6 (C-1β), 89.6 (C-1'α), 79.3 (C-3'β), 78.9 (C-3'α), 78.5 (C-4β), 77.9 (C-3'β), 77.5 (C-4'β), 76.6 (C-4'α), 76.3 (C-2β), 76.0 (C-3α, C-2'β), 75.1 (CH_2Bn), 75.0 (C-2α), 74.8 (CH_2Bn), 73.6 (CH_2Bn), 73.2 (CH_2Bn), 72.5 (C-2'α), 72.5 (CH_2Bn), 68.5 (C-5'β), 68.0 (C-5'α), 67.3 (C-5β), 64.2 (C-5α), 16.8 (C-6α), 16.6 (C-6β), 16.3 (C-6'β), 15.9 (C-6'α) ppm. HRMS $[M+Na]^+$ calcd for $C_{34}H_{38}O_{10}Na$: 629.23627, found 629.23572.

(2,2,2-trichloroacetimidoyl) 3,4-*O*-carbonate-2-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranose)-α/β-L-fucopyranose (38)



Hemiacetal **37a** (0.025 g, 0.041 mmol, 1.0 eq.) was dissolved in dry DCM (0.5 mL, 0.06M). Cl_3CCN (41 µL, 0.41 mmol, 10 eq.) was added, followed by addition of DBU (61 µL, 4 µmol, 0.1 eq. of a 0.1M solution in DCM). The mixture turned brown in 10 min. and the mixture was concentrated *in vacuo*. The dark oil was purified by silicagel chromatography using neutralized silica (tol:ACN, 1:0 → 9:1), which gave the title compound as a colourless oil (0.034 g, 0.041 mmol, 99%, 5/3, α/β). ^{1}H NMR (CD_3CN, 400 MHz): δ = 9.13 (s, 0.6H, C=NHβ), 8.99 (s, 1H, C=NHα), 7.47 – 7.12 (m, 22H, arom.), 6.40 (d, 1H, *J*=3.6 Hz, H-1α), 6.06 (d, 0.6H, *J*=5.8 Hz, H-1β), 5.33 (m, 0.6H, H-1'β), 5.17 (d, 1H, *J*=2.7 Hz, H-1'α), 4.98 – 4.80 (m, 4H, H-3α, H-3β, CH_2Bn), 4.80 – 4.55 (m, 19H, H-4α, H-4β, CH_2Bn), 4.40 (qd, 1H, *J*=6.6, 2.4 Hz, H-5α), 4.17 (qd, 0.6H, *J*=6.6, 1.9 Hz, H-5β), 4.10 (dd, 1H, *J*=7.4, 3.6 Hz, H-2α), 4.08 – 3.99 (m, 2.2H, H-2β, H-5'α, H-5'β), 3.94 – 3.92 (m, 1.2H, H-2'β, H-4'β), 3.90 – 3.87 (m, 2.6H, H-2α. H-3'α, H-3'β), 3.85 – 3.83 (m, 1H, H-4'α), 1.32 (d, 3H, *J*=6.7 Hz, H-6α), 1.32 (d, 3H, *J*=6.7 Hz, H-6β), 1.20 (d, 2H, *J*=6.4 Hz, H-6'β), 1.18 (d, 3H, *J*=6.5 Hz, H-6'α) ppm. ^{13}C-APT NMR (CD_3CN, 101 MHz): δ 160.8, 160.7 (C=NH), 140.1 (C=O) 129.2, 129.2, 129.1, 129.1, 128.9, 128.9, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.2 (arom.), 98.6 (C-1'β), 97.8 (C-1'α), 97.2 (C-1β), 94.1 (C-1α), 79.5 (C-4'β), 79.2, 78.8 (C-4'α), 78.7, 78.4, 77.6, 77.4, 76.5, 76.4, 75.9 (CH_2Bn), 75.8 (CH_2Bn), 73.7 (CH_2Bn), 73.1 (CH_2Bn), 72.9 (CH_2Bn), 72.9 (C-5'β), 72.3 (C-2α), 68.8 (C-5β), 68.1 (C-5'α), 65.8 (C-5α), 16.8, 16.3, 16.0 (C-6α, C-6'α, C-6β, C-6'β) ppm.

References

[1] A. v. Remoortere, C. H.Hokke, G. J. v. Dam, I. v. Die, A. M.Deelder, and D. H. v. d. Eijnden, "Various stages of Schistosoma express Lewisx, LacdiNAc, GalNAc 1-4 (Fuc 1-3)GlcNAc and GalNAc 1-4(Fuc 1-2Fuc 1-3)GlcNAc carbohydrate epitopes: detection with monoclonal antibodies that are characterized by enzymatically synthesized neoglycoproteins," *Glycobiology*, vol. 10, no. 6, pp. 601–609, 2000.

[2] S. R. Kantelhardt, M. Wuhrer, R. D. Dennis, M. J. Doenhoff, Q. Bickle, and R. Geyer, "Fuc(α1→3)GalNAc-: the major antigenic motif of Schistosoma mansoni glycolipids implicated in infection sera and keyhole-limpet haemocyanin cross-reactivity," *Biochem. J.*, vol. 366, no. 1, pp. 217–223, Aug. 2002.

[3] M. Wuhrer, S. R. Kantelhardt, R. D. Dennis, M. J. Doenhoff, G. Lochnit, and R. Geyer, "Characterization of glycosphingolipids from schistosoma mansoni eggs carrying Fuc(α1-3)GalNac-, GalNac(β1-4)[Fuc(α1-3)]GlcNac-and Gal(β1-4)[Fuc(α1-3)]GlcNac- (Lewis X) terminal structures," *Eur. J. Biochem.*, vol. 269, no. 2, pp. 481–493, 2002.

[4] A. Dell *et al.*, "Structural analysis of the oligosaccharides derived from glycodelin, a human glycoprotein with potent immunosuppressive and contraceptive activities," *J. Biol. Chem.*, vol. 270, no. 41, pp. 24116–24126, 1995.

[5] C. W. A. Naus *et al.*, "Specific antibody responses to three schistosome-related carbohydrate structures in recently exposed immigrants and established residents in an area of Schistosoma mansoni endemicity," *Infect. Immun.*, vol. 71, no. 10, pp. 5676–5681, 2003.

[6] M. L. Mickum, N. S. Prasanphanich, J. Heimburg-Molinaro, K. E. Leon, and R. D. Cummings, "Deciphering the glycogenome of schistosomes," *Front. Genet.*, vol. 5, no. AUG, pp. 1–15, Aug. 2014.

[7] M. L. Mickum, T. Rojsajjakul, Y. Yu, and R. D. Cummings, "Schistosoma mansoni α1,3-fucosyltransferase-F generates the Lewis X antigen," *Glycobiology*, vol. 26, no. 3, pp. 270–285, 2015.

[8] S. E. Zurabyan, T. S. Antonenko, and A. Y. Khorlin, "Oxazoline synthesis of 1,2-trans-2-acetamido-2-deoxyglycosides. Glycosylation of secondary hydroxyl groups in partially protected saccharides," *Carbohydr. Res.*, vol. 15, no. 1, pp. 21–27, 1970.

[9] M. Tsutsui, J. Sianturi, S. Masui, K. Tokunaga, Y. Manabe, and K. Fukase, "Efficient synthesis of antigenic trisaccharides containing N-acetylglucosamine: protection of NHAc as NAc2," *European J. Org. Chem.*, pp. 1–10, 2020.

[10] D. Crich and V. Dudkin, "Why are the hydroxy groups of partially protected N-acetylglucosamine derivatives such poor glycosyl acceptors, and what can be done about it? A comparative study of the reactivity of N-acetyl-, N-phthalimido-, and 2-azido-2-deoxy-glucosamine derivatives ," *J. Am. Chem. Soc.*, vol. 123, no.

28, pp. 6819–6825, 2001.

[11] S. Hou and P. Kováč, "Synthesis of the conjugation ready, downstream disaccharide fragment of the O-PS of Vibrio cholerae O:139.," *Carbohydr. Res.*, vol. 346, no. 12, pp. 1394–7, Sep. 2011.

[12] F. Bélot and J. C. Jacquinet, "Syntheses of chondroitin 4- and 6-sulfate pentasaccharide derivatives having a methyl β-D-glucopyranosiduronic acid at the reducing end," *Carbohydr. Res.*, vol. 326, no. 2, pp. 88–97, 2000.

[13] A. Vibert, C. Lopin-Bon, and J.-C. Jacquinet, "Efficient alternative for the reduction of N-trichloroacetyl groups in synthetic chondroitin oligosaccharide intermediates," *Tetrahedron Lett.*, vol. 51, no. 14, pp. 1867–1869, Apr. 2010.

[14] G. Despras, D. Urban, B. Vauzeilles, and J. M. Beau, "One-pot synthesis of d-glucosamine and chitobiosyl building blocks catalyzed by triflic acid on molecular sieves," *Chem. Commun.*, vol. 50, no. 9, pp. 1067–1069, 2014.

[15] M. DeNinno, J. Etienne, and K. Duplantier, "A method for the selective reduction of carbohydrate 4, 6- O-benzylidene acetals," *Tetrahedron Lett.*, vol. 36, no. 5, pp. 669–672, 1995.

[16] R. Panchadhayee and A. K. Misra, "Regioselective reductive ring opening of benzylidene acetals using triethylsilane and iodine," *Synlett*, no. 8, pp. 1193–1196, 2010.

[17] S. D. Debenham and E. J. Toone, "Regioselective reduction of 4 , 6- O - benzylidenes using triethylsilane and BF 3 · Et 2 O," *Tetrahedron: Asymmetry*, vol. 11, pp. 385–387, 2000.

[18] M. R. E. Aly, P. Rochaix, M. Amessou, L. Johannes, and J. C. Florent, "Synthesis of globo- and isoglobotriosides bearing a cinnamoylphenyl tag as novel electrophilic thiol-specific carbohydrate reagents," *Carbohydr. Res.*, vol. 341, no. 12, pp. 2026–2036, 2006.

[19] Z. Zhang, I. R. Ollmann, X. S. Ye, R. Wischnat, T. Baasov, and C. H. Wong, "Programmable one-pot oligosaccharide synthesis," *J. Am. Chem. Soc.*, vol. 121, no. 4, pp. 734–753, 1999.

[20] Y. Cai, C. C. Ling, and D. R. Bundle, "Concise and efficient synthesis of 2-acetamido-2-deoxy-β-D- hexopyranosides of diverse aminosugars from 2-acetamido-2-deoxy-β-D-glucose," *J. Org. Chem.*, vol. 74, no. 2, pp. 580–589, 2009.

[21] M. Ziaco *et al.*, "Synthesis of the tetrasaccharide outer core fragment of Burkholderia multivorans lipooligosaccharide," *Carbohydr. Res.*, vol. 403, pp. 182–191, 2015.

[22] E. J. Corey and A. Venkateswarlu, "Protection of Hydroxyl Groups as tert-Butyldimethylsilyl Derivatives," *J. Am. Chem. Soc.*, vol. 94, no. 17, pp. 6190–6191, 1972.

[23] J. Boutet and L. A. Mulard, “Synthesis of two tetra- and four pentasaccharide fragments of Shigella flexneri serotypes 3a and X O-antigens from a common tetrasaccharide intermediate,” *European J. Org. Chem.*, no. 33, pp. 5526–5542, 2008.

[24] G. Blatter, J. M. Beau, and J. C. Jacquinet, “The use of 2-deoxy-2-trichloroacetamido-d-glucopyranose derivatives in syntheses of oligosaccharides,” *Carbohydr. Res.*, vol. 260, no. 2, pp. 189–202, 1994.

[25] E. Skordi, I. D. Wilson, J. C. Lindon, and J. K. Nicholson, “Kinetic studies on the intramolecular acyl migration of β-1-O-acyl glucuronides: Application to the glucuronides of (R)- and (S)-ketoprofen, (R)- and (S)-hydroxy-ketoprofen metabolites, and tolmetin by1H-NMR spectroscopy,” *Xenobiotica*, vol. 35, no. 7, pp. 715–725, 2005.

[26] S. D. Markad and R. R. Schmidt, “Temporary carbohydrate diol protection with ester groups - orthogonality under solid-phase oligosaccharide synthesis conditions,” *European J. Org. Chem.*, no. 29, pp. 5002–5011, 2009.

[27] S. Hanessian *et al.*, “A constrained tricyclic nucleic acid analogue of α-l-LNA: Investigating the effects of dual conformational restriction on duplex thermal stability,” *J. Org. Chem.*, vol. 78, no. 18, pp. 9064–9075, 2013.

[28] S. S. Nigudkar and A. V. Demchenko, “Stereocontrolled 1,2-cis glycosylation as the driving force of progress in synthetic carbohydrate chemistry,” *Chem. Sci.*, vol. 6, no. 5, pp. 2687–2704, 2015.

[29] D. Lloyd, M. Bylsma, D. K. Bright, X. Chen, and C. S. Bennett, “Mild Method for 2-Naphthylmethyl Ether Protecting Group Removal Using a Combination of 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and β-Pinene,” *J. Org. Chem.*, vol. 82, no. 7, pp. 3926–3934, 2017.

[30] P. Palladino and D. A. Stetsenko, “New TFA-free cleavage and final deprotection in Fmoc solid-phase peptide synthesis: Dilute HCl in fluoro alcohol,” *Org. Lett.*, vol. 14, no. 24, pp. 6346–6349, 2012.

[31] W. A. Bubb, “NMR spectroscopy in the study of carbohydrates: Characterizing the structural complexity,” *Concepts Magn. Reson. Part A Bridg. Educ. Res.*, vol. 19, no. 1, pp. 1–19, 2003.

[32] J. D. C. Codée *et al.*, “Chemoselective glycosylations using sulfonium triflate activator systems,” *Tetrahedron*, vol. 60, no. 5, pp. 1057–1064, Jan. 2004.

[33] A. H. A. Chu, S. H. Nguyen, J. A. Sisel, A. Minciunescu, and C. S. Bennett, “Selective synthesis of 1,2- cis -α-glycosides without directing groups. Application to iterative oligosaccharide synthesis,” *Org. Lett.*, vol. 15, no. 10, pp. 2566–2569, 2013.

[34] L. Ban and M. Mrksich, “On-chip synthesis and label-free assays of oligosaccharide arrays,” *Angew. Chemie - Int. Ed.*, vol. 47, no. 18, pp. 3396–3399,

2008.

[35] S. P. Ali and N. K. Jalsa, “Order of reactivity of OH/NH groups of glucosamine hydrochloride and N -Acetyl glucosamine toward benzylation using NaH/BnBr in DMF,” *J. Carbohydr. Chem.*, vol. 33, no. 4, pp. 185–196, 2014.

[36] P. Fowler, B. Bernet, and A. Vasella, “A1H-NMR Spectroscopic Investigation of the Conformation of the Acetamido Group in Some Derivatives ofN-Acetyl-D-allosamine and -D-glucosamine,” *Helv. Chim. Acta*, vol. 79, no. 1, pp. 269–287, Feb. 1996.

[37] T. Kanaya, F. Schweizer, T. Takeda, F. Kiuchi, and N. Hada, “Synthetic studies on glycosphingolipids from protostomia phyla: Synthesis of glycosphingolipids and related carbohydrate moieties from the parasite Schistosoma mansoni,” *Carbohydr. Res.*, vol. 361, pp. 55–72, 2012.

[38] R. A. Jeanneret, C. E. Dalton, and J. M. Gardiner, “Synthesis of Heparan Sulfate-And Dermatan Sulfate-Related Oligosaccharides via Iterative Chemoselective Glycosylation Exploiting Conformationally Disarmed [2.2.2] l -Iduronic Lactone Thioglycosides,” *J. Org. Chem.*, vol. 84, no. 23, pp. 15063–15078, 2019.