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Chapter 7

Synthesis of *Schistosoma mansoni* glycan fragments*

Introduction

Schistosomiasis is an infection caused by schistosomes, a genus of parasitic helminths, and it is classified as a neglected tropical disease. Schistosomiasis affects an estimated 200 million people worldwide, mainly in (sub)tropical areas with poor hygienic standards.† *Schistosoma mansoni* is the major causative agent of schistosomiasis. This parasite has a complex life cycle, including an 'aquatic' phase and a human phase. Sporocysts in freshwater snails mature into cercariae, which can infect humans when they come in contact with infected water. The cercariae then mature in the host's intestine. A pair of worms reproduces sexually, laying up to 300 eggs per day. The eggs are excreted in the host's feces, thereby closing the cycle. The eggs can survive for a long time in the host and are deposited throughout the body. In severe cases, these eggs can cause liver and kidney failure.

† Hagen, B.; Harvey, M. R.; Kan, G. O.; Overkleeft, H. S.; Van der Marel, G. A.; Codée, J. D. C. were involved in the research described in this Chapter.
Current treatment of schistosomiasis consists of administration of Praziquantel. While effective, this drug does not prevent re-infection of the host. Additionally, depending on the severity of the infection, strong side-effects can occur, caused by release of cell contents of the parasites as they are killed. An alternative strategy, one that could lead to eradication of the disease, is vaccination. *S. mansoni* expresses a complex array of glycans that have been shown to be targeted by both the innate as well as the adaptive arm of the immune system. Most antibodies raised against *S. mansoni* upon infection are directed at glycan epitopes of the parasite. A prominent feature in many of the *S. mansoni* glycans is the presence of multi-fucosylated elements. These multi-fucosylated fragments have been shown to be a prime target for the generated antibodies. Scheme 1A depicts a heptasaccharide fragment 1, that is found in the larval stages of *S. mansoni*. This carbohydrate features a backbone consisting of N-acetylgalactosamine (GalNAc) and N-acetylgalactosamine (GlcNAc) units, decorated on the terminal GalNAc and GlcNAc units with a difucosyl chain. The fucosyl units are connected by α-(1→2)-glycosidic bonds, which are unique to *S. mansoni*.

Although it is clear that the multi-fucosylated structures are important in shaping the immune response against *S. mansoni*, it remains unclear which fragments are most effective as antigens. Synthetic chemistry can provide well-defined glycan fragments to study these for their antigenicity and for their ability to modulate the innate immune response. This Chapter describes preliminary studies towards the synthesis of *S. mansoni* glycan fragments. The research described can be applied in the synthesis of a library of *S. mansoni*-related glycan structures, to establish detailed structure-activity relationships for this class of complex glycans.

**Results & Discussion**

The target structures of four *S. mansoni* glycans are shown in Scheme 1B. The glycan consists of a ‘backbone’, comprising N-acetylgalactosamine (GlcNAc) and N-acetylgalactosamine (GalNAc) units, which are decorated with α-(1,2)-linked fucosyl chains. The synthesis of the GlcNAc-containing structures 2 and 3 have been reported by Van Roon, Aguilera *et al.* The authors’ approach was to use 3,4-iso-propyldiene protected fucosyl donors, with a 2-O-tert-butylidimethylsilyl (TBS) ether as a temporary, non-participating protecting group, which allows α-fucosylation. While this approach was effective in the synthesis of disaccharide 2, the yield dropped significantly as the fucosyl chain grew, possibly due to the large size of the TBS group. In addition, attempted deprotection of the *iso*-propyldiene group on larger fragments led to decomposition.
**Scheme 1:** A) Structure of *S. mansoni* heptasaccharide 1. B) Retrosynthetic analysis for glycan fragments 2-6.

Fucosyl donor 12 contains a non-participating 2- O-naphthylmethyl (Nap) ether, which can be selectively removed and is sterically less demanding than the TBS group. The remote 3- O and 4- O position are masked as pivaloyl esters. Additionally, the 2,2,2-trifluoro(N-phenyl)- acetimidoyl analogue 13 was also investigated as a donor. The GlcNAc donor 10 and GalNAc donors 11 N-acetyl groups are masked as trichloroacetyl groups during the synthesis, as the glycosylation of underivatized N-acetyl containing donors is often accompanied by formation of oxazoline byproducts. It is projected that these can be removed at the end of the synthesis, together with the pivaloyl esters, present on the fucosyl residues, by nucleophilic cleavage or concomitantly with the other protecting groups, the benzylidene acetal, the azide of the spacer and the Nap ether, through hydrogenation. Scheme 2 depicts the assembly of the required building blocks. The synthesis of the reducing end glucosamine unit 10 commenced with known glucosamine thioglycoside 14 (Scheme 2A). Introduction of a benzylidene acetal yielded building block 15 in 85% yield. Protection of the C-3-OH with a Nap group gave 16 in 82% yield. Purification of this building block proved to be challenging, due to the poor solubility of 16 in most organic solvents. For the same reason, the glycosylation of 16 with 6-azidohexanol, using NIS and a catalytic amount of TMSOTf, did not give any product 17. Due to the difference in reactivity
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between 6-azidohexan-1-ol and the C-3-OH of 15, the possibility to install the linker in the presence of the unprotected C-3-alcohol was explored. Fortunately, NIS/TMSOTf-mediated glycosylation of 15 with the spacer alcohol gave 10 in 76% yield. The synthesis of the analogously protected galactosamine unit 11 proceeded via the same sequence of events (Scheme 2B) from galactosamine thioglycoside 18. Introduction of the 4,6-benzylidene acetal gave 19 in 76% yield. The glycosylation of 3-O unprotected donor 19 with 6-azidohexan-1-ol, proved successful, giving 11 in 68% yield.

The synthesis of fucosyl building block 12 commenced from L-fucosyl thioglycoside 20 (Scheme 2C), following a known sequence to advanced intermediate 23. Thus, introduction of an iso-propylidene acetal over the C-3 and C-4-alcohols yielded 21 in 92% yield. The remaining C-2-OH was protected as a 2-O Nap ether, giving 22 in 89% yield. Acidic removal of the iso-propylidene group furnished the 3,4-diol 23 in 92% yield. Pivaloylation using pivaloyl anhydride in a Bi(OTf)_3-catalyzed protocol gave 12 in 87% yield. Next to thiofucoside 12, a imidate fucosyl donor was also generated. (N-phenyl)trifluoroacetimide 13 was synthesized in 2 steps from thioglycoside 12 by NBS-mediated hydrolysis, and subsequent introduction of the imidoyl group to give 13 in 69% over 2 steps.

Attention was directed next to the construction of the fucosylated glucosamine disaccharide 6 (Table 1). The use of imidate donor 13 in a glycosylation with 10 led to 6 in 61% yield, with complete α-selectivity (entry 1). Glycosylation of thioglycoside 12 with the Ph_3SO/Tf_2O pre-activation system, successfully employed in the synthesis of α-glycosidic linkages in the analogous 2-azidofucosyl (FucN_3) donors (see Chapters 3, 4 and 6) yielded disaccharide 6 in 15% yield (entry 2). The main product isolated was C-fucoside 27α (Scheme 3), which results from an electrophilic aromatic substitution on the naphthyl moiety. The conditions employed actually favor this intramolecular pathway, since the activation of the anomic phenylthio moiety occurs in the absence of an external nucleophile. Interestingly, only the α-isomer was isolated (δ: 5.55 ppm, J = 3.6 Hz), which implies the involvement of a transient oxocarbenium ion 26. Attack of the aromatic moiety likely occurs from the top (that is, α) face of the favored 3H_4 conformer 26, since this leads to a favored, chair-like transition state.
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**Scheme 2:** A) Synthesis of reducing end glucosamine acceptor 10; B) synthesis of reducing end galactosamine acceptor 11; C) synthesis of fucosyl donors 12 and 13.

**A**

![Chemical diagram showing synthetic pathways and reagents](image)

**B**

![Chemical diagram showing synthetic pathways and reagents](image)

**C**

![Chemical diagram showing synthetic pathways and reagents](image)

Reagents and conditions: a) PhCH(OMe)₂, TsOH (cat.), MeCN, 50 °C, 350 mbar (85% for 15, 76% for 19); b) NapBr, NaH (60% in oil), DMF, 0 °C (82% for 16, 89% for 22); c) 6-azidohecan-1-ol, NIS, TMSOTf (cat.), 3 Å MS, CH₂Cl₂ -20 to 0 °C (76% for 10, 68% for 11); d) (MeO)₂C(Me)₂, TsOH (cat.), MeCN, 50 °C, 350 mbar (92%); e) HCl (aq.), MeOH, 92%; f) Piv₂O, Bi(OTf)₃ (cat.), CH₂Cl₂ (87%); g) NBS, acetone, H₂O (90%); h) F₃CC(NPh)Cl, Cs₂CO₃, acetone (77%).

To prevent this intramolecular side reaction, glycosylation conditions that do not rely on a pre-activation protocol were explored. Fortunately, NIS/TMSOTf-mediated glycosylation of 12 yielded disaccharide 6 in 86% yield as a single anomer. Succinimidyl fucoside 28 was isolated as a side-product in minor amounts.
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Table 1: Synthesis of GlcNAc-Fuc disaccharide 6.

<table>
<thead>
<tr>
<th>entry</th>
<th>donor</th>
<th>activator</th>
<th>temperature (°C)</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>TfOH (cat.)</td>
<td>-40 → -20</td>
<td>61%</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>Ph₃SO, TTBP, Tf₂O</td>
<td>-80 → -60</td>
<td>15%</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>NIS, Me₂SiOTf (cat.)</td>
<td>-40 → -20</td>
<td>86%</td>
</tr>
</tbody>
</table>

Next, the fucosyl C-2-OH in disaccharide 6 was unmasked using oxidative conditions (Scheme 4). Using DDQ in a mixture of CH₂Cl₂ and water resulted in irreproducible results, providing the desired product 29 along with varying amounts of a side product in which the benzylidene acetal was removed. The oxidative cleavage of the Nap ether could be improved by carrying out the reaction in the presence an aqueous phosphate buffer (pH 7.2), giving 29 in 74% yield.¹⁹ The important Fuc-α-(1→2)Fuc linkage was introduced using the same NIS/TMSOTf-mediated glycosylation conditions used to synthesize disaccharide 6 (see Table 1). Unfortunately, the desired trisaccharide 7 was isolated in a moderate 33% yield.

Scheme 2: Byproducts arising from glycosylations with 12.

A

B

28

δ: 5.55 ppm
\( J = 3.6 \text{ Hz} \)

27α

27β
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Scheme 4: Synthesis of trisaccharide 7.

![Diagram of Scheme 4]

Reagents and conditions: a) DDQ, CH₂Cl₂, aqueous phosphate buffer (pH 7.2; 74%); b) NIS, TMSOTf (cat.), 3Å MS, CH₂Cl₂, -40 → -20 °C (33%).

The synthesis of the fucosylated galactosamine disaccharide 8 is shown in Scheme 5. Again using a NIS/TMSOTf-mediated glycosylation, fucosyl donor 12 and reducing end galactosamine acceptor 11 were unified to give disaccharide 8 in 68% yield. Removal of the Nap ether using the buffered oxidative conditions gave acceptor 30 in 83% yield. Trisaccharide 9 was constructed by NIS/TMSOTf-mediated glycosylation between donor 12 and 30 in 54% yield.

Scheme 5: Synthesis of fucosylated galactosamine di- and trisaccharide 8 and 9.

![Diagram of Scheme 5]

Reagents and conditions: a) 11, NIS, TMSOTf (cat.), 3Å MS, CH₂Cl₂, -20 to 0 °C (68%); b) DDQ, CH₂Cl₂, aqueous phosphate buffer (pH 7, 83%); c) 12, NIS, TMSOTf (cat.), 3Å MS, CH₂Cl₂, -40 → -20 °C (54%).

The deprotection sequence for the disaccharides is shown in Scheme 6. Removal of the pivaloyl esters was initially attempted using a mixture of KOH and H₂O₂, since these conditions were successfully employed in the deprotection of Staphylococcus aureus trisaccharides (Chapters 4 and 6). However in this case the application of these conditions led to incomplete removal of the protecting groups. A mixture of aqueous KOH, THF and methanol proved to be effective for the removal of the pivaloyl esters giving diols 31 and 32 in 57% and 61% yield, respectively. In both cases, a minor byproduct was observed in which the amide was cleaved.
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Removal of the benzylidene acetal, the Nap ether, the conversion of the TCA into the acetyl group, and reduction of the azide was achieved in a one-pot operation by palladium-catalyzed hydrogenation. The use of an aqueous phosphate buffer prevented deactivation of the palladium catalyst. The disaccharides 2 and 4 were obtained in 34% and 67% yield, respectively. Curiously, employing a similar sequence on the trisaccharides 7 and 9 were fruitless. This, combined with the modest yields obtained in the installation of the terminal fucosyl unit, prompts a revision of the building blocks. In the synthesis of the trisaccharides, the bulky pivaloyl groups on the fucosyl units complicate approach of the incoming acceptor on the anomeric center of the donor. Additionally, the steric bulk of the groups may force the trisaccharide in unfavorable conformations, imposing an energetic penalty on glycosidic bond formation. In order to avoid the steric bulk and increase yield of the glycosylation reactions, the Piv groups can be replaced by benzyl ethers. The reactivity study of the analogous 2-azidofucosyl (FucN3) donors in Chapter 3 showed that benzyl ethers are generally more α-selective than benzyol-containing counterparts. An additional benefit is that by using benzyl ethers, the fully protected oligosaccharides can be deprotected in one step, using catalytic hydrogenation.

**Scheme 6**: Deprotection of disaccharides 6 and 8.

![Scheme 6](image)

*Reagents and conditions: a) KOH, THF, MeOH, H2O (57% for 31; 61% for 32); b) Pd/C, H2 (4 bar), MeOH, aqueous phosphate buffer (pH 7.0; 34% for 2, 67% for 4).*

**Conclusion**

The synthesis of fucosylated glycan fragments related to *Schistosoma mansoni* has been described. The synthesis of the GlcNAc- and GalNAc reducing end acceptors was achieved by efficient selective condensations of C-3-OH deprotected thioglycoside donors with the spacer alcohol. The success of the first fucosylations the depended on the activation conditions; a
NIS/TMSOTf-mediated protocol proved to be the most effective, while pre-activation conditions resulted mainly in an intramolecular annihilation involving the C-2-O naphthylmethyl ether. Removal of the Nap group, using DDQ, was more effective under buffered conditions. Synthesis of the two trisaccharides proceeded in moderate yields. The unprotected disaccharides were obtained after a saponification-hydrogenation sequence. The deprotection of the trisaccharides was unsuccessful. A revision of the fucosyl building blocks is suggested, in which the pivaloyl groups are replaced by benzyl ethers to reduce steric bulk, increase reactivity of the donor, and facilitate deprotection.

**Experimental**

**General procedures**

All reactions were carried out in oven-dried glassware (85 °C). Prior to reactions, traces of water and solvent were removed by co-evaporation with toluene where appropriate. Reactions sensitive to air or moisture were carried out under an atmosphere of argon (balloon). Solvents for reactions were of reagent grade and stored over 4Å molecular sieves (3Å for CH₂Cl₂, MeOH and MeCN), except pyridine and DMF. NET₃ was stored over KOH pellets. Tf₂O used in glycosylations was dried over P₂O₅ (~3 hours), followed by distillation, and stored in a Schlenk flask at -20 °C. All other chemicals were used as received. Reaction progress was monitored using aluminium-supported silica gel TLC plates (Merck, Kieselgel 60, with fluorescent indicator); visualization was carried out by irradiation with UV light (λ: 254 nm), followed by spraying with 20% H₂SO₄ in EtOH (w/v) or Hanessian’s stain ((NH₄)₆Mo₇O₂₄·4H₂O, 25 g/L; (NH₄)₄Ce(SO₄)₂·2H₂O, 10 g/L; in 10% aq. H₂SO₄). Column chromatography was carried out using silica gel (Screening Devices, 0.040-0.063 mm). Size-exclusion chromatography was carried out using Sephadex LH-20 (GE Healthcare). NMR spectra were recorded on Bruker AV-400, DMX-400 or AV-500 instruments. Chemical shifts (δ) are reported in ppm relative to Me₄Si (δ: 0.00 ppm) or residual solvent signals. NMR spectra were recorded at ambient temperature, and samples were prepared in CDCl₃ unless noted otherwise. ¹³C-APT spectra are ¹H decoupled. Structural assignment was achieved using HH-COSY and HSQC 2D experiments. Coupling constants of anomic carbon atoms (J_HH,CC) were determined using HMBC-GATED experiments. Infrared spectra were recorded with a Shimadzu FTIR 8300 instrument. Wavenumbers (ν) are reported in cm⁻¹. HRMS spectra were recorded on a Thermo Finnigan LCQ Orbitrap instrument.
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Phenyl 4,6-O-benzylidene-2-deoxy-2-trichloroacetamido-1-thio-β-D-glucopyranoside (15)

To a solution of 14 (10.4 g, 25.0 mmol, 1.0 eq.) in MeCN (150 mL, 0.15M) were added benzaldehyde dimethylacetal (60.0 mmol, 9.0 mL, 2.4 eq.) and p-TsOH (0.47 g, 2.5 mmol, 0.1 eq.). The solution was heated to 50 °C and stirred on a rotary evaporator at reduced pressure (350 mbar) until TLC analysis (toluene/ EtOAc, 4:1) indicated completed conversion of the starting material (~3 hours). The reaction was quenched by addition of NEt₃ until a basic pH was obtained, and the reaction mixture was poured onto a mixture of cold Et₂O/heptane (1:1). The brown solids were collected and purified by silica gel chromatography (PE:EtOAc, 9:1 → 7:3 v/v), to give the title product as a white solid in 87% yield. (11.0 g, 21.8 mmol). ¹H NMR (400 MHz, DMSO-d₆) δ: 7.73 (d, 1H, J = 9.2 Hz, NH); 7.50-7.31 (m, 10H, CH₃); 5.60 (s, 1H, PhCH); 5.07 (d, 1H, J = 10.4 Hz, H-1); 4.28 (dd, 1H, J = 4.8 Hz, 6.0 Hz, H-6); 3.92-3.80 (m, 2H, H-2, H-4); 3.76 (t, 1H, 10.0 Hz, H-6); 3.60-3.50 (m, 2H, H-3, H-5). ¹³C-APT NMR (100 MHz, DMSO-d₆) δ: 164.1 (CDCl₃); 138.7, 134.5 (C₃arom); 132.1, 129.9, 129.7, 129.5, 129.0, 128.7, 128.3, 127.0 (CH₃); 102.1 (PhCH); 87.6 (C-1); 81.6 (C-5); 72.6 (C-4); 71.3 (C-3); 68.9 (C-6); 57.9 (C-2).

Phenyl 4,6-O-benzylidene-2-deoxy-3-O-(2-naphthylmethyl)-2-trichloroacetamido-1-thio-β-D-glucopyranoside (16)

To a stirred solution of 15 (0.96 g, 1.90 mmol, 1.0 eq.) in DMF (10 mL, 0.2M) was added NaH (60% in oil, 0.23 g, 5.7 mmol, 3 eq.) portionwise over the course of ~10 minutes. The reaction mixture was left to stir until gas evolution ceased, at which point 2-(bromomethyl)naphthalene (0.46 g, 2.10 mmol, 1.1 eq.) was added. The reaction mixture was stirred at 0 °C until TLC analysis (toluene/ EtOAc, 4:1 v/v) indicated complete conversion of the starting material (~4 hours), after which the reaction was quenched by slow addition of MeOH. Added was H₂O (~100 mL). The resulting precipitate was collected and purified by column chromatography (toluene: EtOAc, 1:0 → 4:1 v/v), yielding the title compound in 82% yield (1.00 g, 1.55 mmol). ¹H NMR (400 MHz, acetone-d₆) δ: 8.59 (d, 1H, J = 8.4 Hz, NH); 7.87-7.76 (m, 4H, CH₃); 7.54-7.29 (m, 13H, CH₃); 5.78 (s, 1H, PhCH); 5.23 (d, 1H, J = 10.0 Hz, H-1); 5.05 (d, 1H, J = 12.0 Hz, PhCHH); 4.95 (d, 1H, J = 12.0 Hz, PhCHH); 4.33 (dd, 1H, J = 4.8 Hz, 10.4 Hz, H-6); 4.19-4.10 (m, 2H, H-2, H-3); 3.93-3.85 (m, 2H, H-4, H-6); 3.60 (dt, 1H, J = 4.8 Hz, 10.4 Hz, H-5). ¹³C-APT NMR (100 MHz, acetone-d₆) δ: 162.4 (CDCl₃); 138.9, 137.0, 134.5 (C₃arom); 132.6, 129.9, 129.6, 128.9, 128.7, 128.5, 128.5, 127.2, 127.1, 126.9, 126.8, 126.6 (CH₃); 101.8 (PhCH); 88.1 (C-1); 82.6 (C-3); 80.1 (C-4); 75.0 (PhCH₂); 190
71.3 (C-5); 69.0 (C-6); 56.8 (C-2). IR (thin film) ν: 2910, 1689, 1539, 1367, 1111, 1074, 1012, 964, 823, 748, 688, 661. HRMS: [M+NH₄]⁺ calculated for C₃₂H₃₂Cl₃N₂O₂S: 661.10920; found 661.11008.

6-azidohexyl 4,6-O-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (10)

To a solution of 15 (2.53 g, 5.0 mmol, 1.0 eq.) and 6-azido-hexan-1-ol (1.08 g, 7.5 mmol, 1.5 eq.) in CH₂Cl₂ (50 mL, 0.1M) were added flame-dried 3Å molecular sieves. After ~30 minutes, NIS (1.69 g, 7.5 mmol, 1.5 eq.) was added and the reaction mixture was cooled to -40 °C. TMSOTf (0.18 mL, 0.5 mmol, 0.1 eq.) was added and the reaction mixture was allowed to warm to -20 °C, and subsequently stirred at this temperature until TLC analysis (PE/EtOAc, 7:3 v/v) indicated complete conversion of the starting material (~2 hours). The reaction was quenched with NEt₃ and the mixture was diluted with EtOAc, washed with Na₂S₂O₅ (sat., aq., 1x), NaHCO₃ (sat., aq., 1x) and brine (1x), dried over MgSO₄, filtered and concentrated in vacuo. The title compound was obtained after column chromatography (PE/EtOAc, 9:1 → 7:3 v/v) in 57% yield (1.52 g, 2.84 mmol). 1H NMR (400 MHz) δ: 7.52-7.49 (m, 2H, CH₃arom); 7.43-7.29 (m, 3H, CH₃arom); 7.08 (d, 1H, J = 7.2 Hz, N=H); 5.55 (s, 1H, PhCH); 4.90 (d, 1H, J = 8.4 Hz, H-1); 4.37-4.30 (m, 2H, H-3, H-6); 3.90 (m, 1H, OCH₃hexyl); 3.79 (t, 1H, J = 10.0 Hz, H-6); 3.56-3.49 (m, 4H, H-2, H-4, H-5, OCHHhexyl); 3.27 (t, 2H, J = 4.8 Hz, N₃CH₂hexyl); 3.16 (s, 1H, 3-OH); 1.59-1.57 (m, 4H, CH₂hexyl); 1.27 -1.25 (m, 4H, CH₂hexyl). ¹³C-APT NMR (100 MHz) δ: 162.3 (C=OCA); 137.0 (C₃arom); 129.5, 128.5, 126.4 (CH₃arom); 101.9 (PhCH); 100.1 (C-1); 92.6 (CH₃); 81.7 (C-4); 70.3 (OCH₂hexyl); 69.6 (C-3); 68.6 (C-6); 66.2 (C-5); 59.6 (C-2); 51.4 (N₃CH₂hexyl); 29.5, 28.8, 26.6, 25.6 (CH₂hexyl). IR (thin film) ν: 3325, 2937, 2872, 2096, 1691, 1531, 1373, 1111, 1028, 823. HRMS: [M+H]⁺ calculated for C₂₁H₂₇Cl₃N₄O₆S: 537.10689; found 537.10681.

Phenyl 4,6-O-benzylidene-2-deoxy-2-trichloroacetamido-1-thio-β-D-galactopyranoside (19)

To a solution of 18 (6.60 g, 15.9 mmol, 1.0 eq.) in MeCN (120 mL, 0.15M) were added benzaldehyde dimethylacetal (2.63 mL, 17.6 mmol, 1.1 eq.) and p-TsOH (0.30 g, 1.6 mmol, 0.1 eq.). The solution was heated to 50 °C and stirred on a rotary evaporator under reduced pressure (350 mbar), until TLC analysis (PE/EtOAc, 7:3 v/v) indicated complete conversion of the starting
material (~2 hours). The reaction was quenched by addition of NEt₃ and the mixture was poured onto an ice-cold mixture of EtO/heptane (1:1 v/v). The solids were collected and purified by silica gel chromatography (PE: EtOAc, 9:1 → 7:3) to give the title compound as a white solid in 76 % yield. (6.08 g, 12.05 mmol). ¹H NMR (CDCl₃, 400 MHz) δ: 7.69-7.67 (m, 2H, CH₁-arom); 7.45-7.26 (m, 8H, CH₂-arom); 6.75 (d, 1H, J = 7.6, NH); 5.57 (s, 1H, PhCH); 5.10 (d, 1H, J = 10.0 Hz, H-1); 4.42 (dd, 1H, J = 1.6 Hz, 10.8 Hz, H-6); 4.26 (d, 1H, J = 2.8 Hz, H-4); 4.18 (dd, 1H, J = 3.2 Hz, 7.2 Hz, H-3); 4.06 (dd, 1H, J = 1.6 Hz, 11.6 Hz, H-6); 3.76 (dt, 1H, J = 7.6 Hz, 2.4 Hz, H-2); 3.61 (m, 1H, H-5); 2.60 (s, 1H, 3-OH). ¹³C-APT NMR (100 MHz) δ: 161.9 (CDCl₃); 139.4 (CH₁-arom); 132.6 (C₆-arom); 129.6, 129.2, 128.7, 128.0 (CH₂-arom); 127.3 (C₅-arom); 126.6 (CH₃-arom); 101.5 (PhCH); 86.4 (C-1); 75.1 (C-4); 70.6 (C-3); 70.3 (C-5); 69.4 (C-6).

6-azidohexyl 4,6-O-benzylidene-2-deoxy-2-trichloroacetamido-β-D-galactopyranoside (11)

To a solution of 19 (2.52 g, 5.0 mmol, 1.0 eq.) and 6-azidohexan-1-ol (1.08 g, 1.0 mmol, 1.5 eq.) in CH₂Cl₂ (40 mL, 0.13 M) were added flame-dried 3Å MS. After ~30 minutes, NIS was added (1.68 g, 7.50 mmol, 1.5 eq.) and the mixture was cooled to -40 °C. Added was TMSOTf (0.18 mL, 1 mmol, 0.2 eq.) and the mixture was allowed to warm to -20 °C, after which it was stirred until TLC analysis (PE/EtOAc, 1:1 v/v) indicated complete conversion of the starting material (~2 hours). The reaction was quenched by addition of NEt₃ and the mixture was washed with Na₂SO₄ (sat,aq), NaHCO₃ (sat, aq.) and brine, dried over MgSO₄ filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 9:1 → 2:3 v/v) furnished the title compound in 67% yield (1.79 g, 3.3 mmol). ¹H NMR (400 MHz) δ: 7.50-7.48 (m, 2H, CH₁-arom); 7.42-7.32 (m, 3H, CH₂-arom); 7.00 (d, 1H, J = 8.0 Hz, NH); 5.48 (s, 1H, PhCH); 4.60 (d, 1H, J = 8.4 Hz, H-1); 4.27 (d, J = 12.4 Hz, H-6); 4.15 (d, 1H, J = 3.6 Hz, H-4); 4.12-4.04 (m, 2H, H-3, H-6); 3.91-3.80 (m, 2H, H-2, OCH₃hexyl); 3.50-3.36 (m, 2H, H-5, OCH₃hexyl); 3.22 (t, 2H, J = 7.2 Hz, N₂CH₂); 2.94 (d, 1H, J = 9.6 Hz, OCH₃hexyl); 1.57-1.51 (m, 4H, CH₂hexyl); 1.42-1.26 (m, 4H, CH₂hexyl). ¹³C-APT NMR (100 MHz) δ: 162.6 (CDCl₃); 137.5 (C₆-arom); 129.3, 128.3, 126.4 (CH₁-arom); 101.1 (PhCH); 100.1 (C-1); 75.0 (C-4); 69.6 (OCH₂hexyl); 69.4 (C-3); 66.7 (C-6); 66.7 (C-5); 56.3 (C-2); 51.4 (N₂CH₂hexyl); 29.4, 28.8, 26.5, 25.6 (CH₂hexyl). IR (thin film) v: 3325, 2937, 2859, 2094, 1689, 1528, 1168, 1053, 819. HRMS: [M+Na]+ calculated for C₂₁H₂₇Cl₃N₄NaO₆: 559.08884; found 559.08849.
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**Phenyl 3,4-O-(2-propylidene)-1-thio-β-L-fucopyranoside (21)**

To a mixture of 20 (1.0 g, 5.8 mmol, 1.0 eq.) in 2,2- dimethoxypropane (20 mL, 0.3M) was added p-TsOH (0.05 g, 0.26 mmol, 0.05 eq.). The mixture was stirred until TLC analysis (PE/EtOAc, 4:1 v/v) indicated complete conversion of the starting material (~24 hours). The solution was neutralized by addition of NEt₃ and concentrated in vacuo. The residue was purified by column chromatography (PE:EtOAc, 7:3) to give the title compound in 88% yield (1.51 g, 5.1 mmol). ¹H NMR (400 MHz) δ: 7.56-7.54 (m, 2H, CH₆Δoring); 7.32-7.26 (m, 3H, CH₆Δoring); 4.42 (d, 1H, J = 10.2 Hz, H-1); 4.06-4.03 (m, 2H, H-3, H-4); 3.85 (dd, 1H, J = 2.1 Hz, 6.4 Hz, H-5); 3.54 (dd, 1H, J = 6.8 Hz, 10.2 Hz, H-2); 2.82 (s, 1H, OCH₂); 1.41 (s, 6H, C(CH₃)₂); 1.34 (d, 3H, J = 6.4 Hz, H-6). ¹³C-APT NMR (100 MHz) δ: 132.5 (C₉Δaring); 131.7, 128.5, 127.2 (CH₆Δoring); 109.3 (C(CH₃)₂); 86.8 (C-1); 79.1 (C-3); 75.8 (C-4); 72.0 (C-5); 70.7 (C-2); 27.7, 26.0 (C(CH₃)₂); 16.5 (C-6).

**Phenyl 2-O-(2-naphthylmethyl)-3,4-O-(2-propylidene)-1-thio-β-L-fucopyranoside (22)**

To a solution of 21 (0.9 g, 3.0 mmol, 1.0 eq.) in DMF (10 mL, 0.3M) was added, at 0 °C, NaH (60% in oil, 0.14 g, 3.6 mmol, 1.2 eq.) was slowly added and, after ~30 minutes, 2- (bromomethyl)naphthalene (3.6 mmol, 0.80 g, 1.2 eq.). After TLC analysis (toluene/EtOAc, 4:1 v/v) indicated complete conversion of the starting material (~5 hours). The reaction was quenched by addition of MeOH. The mixture was diluted with Et₂O (30 mL) and washed three times with H₂O, dried over MgSO₄ and concentrated in vacuo. The title compound was isolated after column chromatography (PE/EtOAc, 19:1 → 17:3 v/v) in 87% yield. (1.14 g, 2.6 mmol). ¹H NMR (400 MHz) δ: 7.83-7.79 (m, 4H, CH₆Δaring); 7.60-7.53 (m, 3H, CH₆Δaring); 7.48-7.44 (m, 2H, CH₆Δaring); 7.28-7.21 (m, 3H, CH₆Δaring); 4.97 (d, 1H, J= 11.6 Hz, PhCH₂H); 4.82 (d, 1H, J= 11.6 Hz, PhCH₂H); 4.60 (d, 1H, J= 9.6 Hz, H-1); 4.24 (t, 1H, J= 6.0 Hz, H-3); 4.02 (dd, 1H, J= 1.6 Hz, 5.6 Hz, H-4); 3.80 (q, 1H, J= 6.4 Hz, H-5); 3.54 (dd, 1H, J= 6.8 Hz, 10.0 Hz, H-2); 1.39-1.35 (m, 9H, H-6, C(CH₃)₂). ¹³C-APT NMR (100 MHz) δ: 135.5, 133.8, 133.3, 133.2 (C₉Δaring); 132.2, 128.9, 128.1, 128.0, 127.8, 127.5, 127.2, 126.5, 126.1, 125.9 (CH₆Δaring); 109.8 (C(CH₃)₂); 86.2 (C-1); 80.0 (C-4); 78.0 (C-5); 76.5 (C-2); 73.6 (PhCH₂); 72.5 (C-3); 28.0, 26.5 (C₉(CH₃)₂); 17.0 (C-6).
To a suspension of 22 in (1.70 g, 4.0 mmol, 1.0 eq.) in MeOH (20 mL, 0.2M) was added HCl (4M, 4.5 mL, aq.), turning the suspension into a clear solution. The reaction was stirred until TLC analysis (toluene/EtOAc, 7:3 v/v) indicated complete conversion of the starting material (~5 hours). The reaction was quenched with NEt3 (2 mL) and the mixture was concentrated in vacuo, during which a precipitate formed. The yellow mother liquor was purified using column chromatography (PE/EtOAc, 9:1 → 0:1). The combined purified fractions gave the title compound in 92% yield (1.44 g, 3.64 mmol, 92%). 1H NMR (400 MHz) δ: 7.80-7.74 (m, 4H, CH<sub>arom</sub>); 7.58-7.52 (m, 3H, CH<sub>arom</sub>); 7.48-7.44 (m, 2H, CH<sub>arom</sub>); 7.33-7.24 (m, 3H, CH<sub>arom</sub>); 5.06 (d, 1H, J = 11.2 Hz. PhCH<sub>2</sub>H); 4.84 (d, 1H, J = 11.2 Hz, PhCH<sub>H</sub>); 4.60 (d, 1H, J = 9.2 Hz, H-1); 3.62- 3.56 (m, 3H, H-2, H-3, H-4); 3.49 (q, 1H, J = 6.4 Hz, H-5); 2.81 (bs, 1H, OCH3); 2.03 (bs, 1H, OH); 1.27 (d, 3H, J = 6.4 Hz, H-6). <sup>13</sup>CAPT NMR (100 MHz) δ: 135.6, 134.2, 133.4, 133.2 (C<sub>arom</sub>); 131.7, 129.1, 128.5, 128.1, 127.8, 127.5, 127.2, 126.3, 126.2, 126.2 (CH<sub>arom</sub>); 87.5 (C-1); 78.0 (C-3); 75.3 (ArCH2); 75.2 (C-2); 74.4 (C-5); 71.8 (C-4); 16.7 (C-6).

Phenyl 2-O-(2-naphthylmethyl)-3,4-di-O-pivaloyl-1-thio-β-L-fucopyranoside (12)

To a solution of 23 (5.0 g, 12.6 mmol, 1.0 eq.) in DCM (40 mL, 0.3M) was added Piv<sub>2</sub>O (7.7 mL, 37.8 mmol, 3 eq.), followed by Bi(OTf)<sub>3</sub> (0.25 g, 0.38 mmol, 0.03 eq.) and the mixture was stirred until TLC analysis (PE/EtOAc, 4:1 v/v) indicated complete conversion of the starting material (~8 hours). The mixture was diluted with EtOAc and washed with NaHCO₃ (sat., aq., 2x) and brine (1x). The organic layers was filtered over Celite and dried over MgSO₄, filtered and the solvent was removed in vacuo. The residue was crystallized from iPrOH. The mother liquor was concentrated in vacuo and subjected to column chromatography (PE/EtO₂O, 9:1 → 7:3 v/v) to give the product in a combined yield of 87% yield (6.19 g, 11.0 mmol). <sup>1</sup>H NMR (400 MHz) δ: 7.82-7.78 (m, 3H, CH<sub>arom</sub>); 7.72 (s, 1H, CH<sub>arom</sub>); 7.65-7.63, (m, 2H, CH<sub>arom</sub>); 7.47-7.44 (m, 3H, CH<sub>arom</sub>); 7.32-7.29 (m, 3H, CH<sub>arom</sub>); 5.30 (d, 1H, J = 3.2 Hz, H-4); 5.13 (dd, 1H, J = 3.2, 9.8 Hz, H-3); 4.95 (d, 1H, J = 10.4 Hz, PhCH<sub>2</sub>); 4.73-4.70 (m, 2H, H-1, PhCH<sub>H</sub>); 3.88 (q, 1H, J = 6.4 Hz, H-5); 3.78 (t, 1H, J = 9.6 Hz, H-2); 1.25 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>); 1.22 (d, 3H, J = 6.4 Hz, H-6); 1.11 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>). <sup>13</sup>CAPT NMR (100 MHz) δ: 177.5 (CO<sub>Piv</sub>); 135.4, 133.4, 133.1, 132. (C<sub>arom</sub>); 132.5, 129.1, 128.2, 128.0, 127.8, 126.4, 126.2, 126.0, 125.7 (CH<sub>arom</sub>); 87.0 (C-1); 75.2 (C-3); 75.2 (PhCH<sub>2</sub>); 74.8 (C-2); 73.5 (C-5); 70.6 (C-4); 39.2, 38.9 (C(CH<sub>3</sub>)<sub>3</sub>); 27.3, 27.1 (C(CH<sub>3</sub>)<sub>3</sub>Piv); 16.5 (C-6). IR (thin film): 2976,
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1782, 1477, 1396, 1276, 1220, 1153, 1124, 1101, 1056, 1028, 900, 864, 812, 794, 769. HRMS: [M+H]+ calculated for C33H41O6S: 565.26184; found 565.26199.

\[ \text{N-phenyl 2,2,2-trifluoroacetimidoyl 2-O(2-naphthylmethyl)-3,4-di-O-pivaloyl-\alpha/\beta-l-fucopyranoside (13)} \]

To a solution of 12 (0.36 g, 0.64 mmol, 1.0 eq.) in acetone/water (4:1 v/v, 10 mL, 0.06 M) was added \( N \)-bromosuccinimide (0.32 g, 1.5 mmol, 3.0 eq.) and the solution was stirred until TLC analysis (PE/EtOAc, 4:1 v/v) indicated complete conversion of the starting material (~15 minutes). The reaction mixture was diluted with EtOAc and washed with \( \text{Na}_2\text{S}_2\text{O}_3 \) (sat., aq., 1x), \( \text{NaHCO}_3 \) (sat., aq., 1x) and brine (1x), dried over \( \text{MgSO}_4 \) filtered and concentrated \( \text{in vacuo} \). The residue was purified by column chromatography (PE/EtOAc, 4:1 \( \rightarrow 7:3 \) v/v) to give the title products (\( \alpha/\beta \) 5:4) in 93% yield (0.22 g, 0.47 mmol). \(^1\)H NMR (400 MHz) \( \delta \): 7.83-7.73 (m, 30H, \( \text{CH}_{\text{arom}} \)); 7.49-7.40 (m, 25H, \( \text{CH}_{\text{arom}} \)); 5.41 (dd, 5H, \( J = 3.2 \) Hz, 7.6 Hz, H-3\( \alpha \)); 5.27 (m, 10H, H-1\( \alpha \), H-4\( \alpha \)); 5.22 (d, 4H, \( J = 3.2 \) Hz, H-4\( \beta \)); 5.07-5.02 (m, 8H, H-3\( \beta \), Ph\( \text{CH}(\text{H}) \)); 4.87-4.76 (m, 18H, H-1\( \beta \), Ph\( \text{CH}(\text{H}) \)); 4.36 (q, 5H, \( J = 6.4 \) Hz, H-5\( \alpha \)); 3.90 (m, 9H, H-2\( \alpha \), OH\( \beta \)); 3.79 (q, 4H, \( J = 6.8 \) Hz, H-5\( \beta \)); 3.63 (dd, 4H, \( J = 2.8 \) Hz, 7.6 Hz, H-2\( \beta \)); 3.32 (bs, 5H, OH\( \alpha \)); 1.28 (s, 36H, C(\( \text{CH}(\text{H})_3\))_3\( \text{Piv}\)\( \beta \)); 1.24 (s, 45H, C(\( \text{CH}(\text{H})_3\))_3\( \text{Piv}\)\( \alpha \)); 1.20 (s, 45H, C(\( \text{CH}(\text{H})_3\))_3\( \text{Piv}\)\( \alpha \)); 1.14 (d, 12H, \( J = 6.8 \) Hz, H-6\( \beta \)); 1.08 (s, 36H, C(\( \text{CH}(\text{H})_3\))_3\( \text{Piv}\)\( \beta \)); 1.06 (d, 15H, \( J = 6.8 \) Hz, H-6\( \alpha \)). \(^{13}\)C-APT NMR (100 MHz, CDC\( \text{Cl}_3 \)) \( \delta \): 177.7, 177.5 (\( \text{CO}_{\text{Piv}} \)); 135.6, 134.9, 133.3, 133.2, 133.1 (\( \text{C}_{\text{arom}} \)); 128.5, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 126.5, 126.4, 126.3, 126.2, 126.0, 125.8 (\( \text{CH}_{\text{arom}} \)); 97.5 (C-1\( \beta \)); 91.8 (C-1\( \alpha \)); 77.7 (C-2\( \beta \)); 74.8 (Ar\( \text{CH} \)); 73.6 (C-2\( \alpha \)); 73.3 (Ph\( \text{CH}_2 \)); 73.0 (C-3\( \beta \)); 71.2 (C-4\( \alpha \)); 70.4 (C-4\( \beta \)); 70.3 (C-3\( \alpha \)); 69.1 (C-5\( \beta \)); 65.2 (C-5\( \alpha \)); 39.2 (\( \text{Qi}, \text{Piv} \alpha/\beta \)); 27.3 (Me, Piv \alpha/\beta); 16.2 (C-6\( \beta \)); 16.0 (C-6\( \alpha \)). To a solution of 24 (0.21 g, 0.45 mmol, 1.0 eq.) in acetone (5 mL, 0.1M) were added \( \text{Cs}_2\text{CO}_3 \) (0.18 g, 0.55 mmol, 1.25 eq.), and \( N \)-phenyl 2,2,2-trifluoroacetimidoyl chloride (0.14 mL, 0.90 mmol, 2.0 eq.) and the suspension was stirred until TLC analysis (PE/EtOAc, 9:1 v/v) indicated complete conversion of the starting material (~4 hours). The mixture was diluted with EtOAc and washed with \( \text{H}_2\text{O} \) (1x), brine (2x), dried over \( \text{MgSO}_4 \) filtered and concentrated \( \text{in vacuo} \). Purification by column chromatography (PE/EtOAc, 19:1 \( \rightarrow 17:3 \) v/v) furnished the title compounds (\( \alpha/\beta \) 3:2) in 77% yield (0.23 g, 0.35 mmol). \(^1\)H NMR for the \( \alpha \)-anomer (400 MHz) \( \delta \): 7.79-7.16 (m, 11H, \( \text{CH}_{\text{arom}} \)); 6.68 (d, 1H, \( J = 8.0 \) Hz, \( \text{CH}_{\text{arom}} \)); 6.52 (bs, 1H, H-1); 3.46 (dd, 1H, \( J = 3.2 \) Hz, 7.6 Hz, H-3); 5.36 (d, 1H, \( J = 2.0 \) Hz, H-4); 4.83 (d, 2H, \( J = 7.2 \) Hz, Ph\( \text{CH}(\text{H}) \)); 4.28 (q, 1H, \( J = 6.4 \) Hz, H-5); 4.06 (dd, 1H, \( J = 3.6 \) Hz, H-6).
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7.2 Hz, H-2); 1.28 (s, 9H, C(CH3)3,piv); 1.15 (s, 9H, C(CH3)3,piv); 1.10 (d, 3H, J = 6.8 Hz, H-6). 13C-
APT NMR (100 MHz) δ: 177.4, 177.2 (CO,piv); 143.8, 135.2 (Cq,arom); 128.5, 128.3, 127.8, 126.8,
126.7, 126.4, 126.2, 125.8, 124.4, 120.8, 119.5 (CH,arom); 94.2 (C-1); 73.5 (PhCH2); 73.1 (C-2); 72.9
(C-4); 70.6 (C-3); 68.2 (C-5); 38.9 (C(CH3)3,piv); 27.4 (C(CH3)3,piv); 16.0 (C-6). 1H NMR data for the
β-anomer (400 MHz, 323 K) δ: 7.82-7.77 (m, 3H, CH,arom); 7.73 (s, 1H, CH,arom); 7.47-7.45 (m, 2H,
CH,arom); 7.40 (m, 1H, arom); 7.28-7.24 (m, 2H, CH,arom); 7.09-7.07 (m, 2H, CH,arom); 6.81 (d, 1H, J =
8.0 Hz, CH,arom); 5.66 (bs, 1H, H-1); 5.23 (d, 1H, J = 2.4 Hz, H-4); 5.06 (bd, 1H, J = 8.8 Hz, H-3); 4.95
(d, 1H, J = 11.6 Hz, PhCH=H); 4.83 (d, 2H, J = 11.6, PhCH=H); 3.90 (t, 1H, J = 8.8 Hz, H-2); 3.71 (bs,
1H, H-5); 1.26 (s, 9H, C(CH3)3,piv); 1.16 (d, 3H, J = 6.4 Hz, H-6); 1.13 (s, 9H, C(CH3)3,piv). 13C-APT
NMR (100 MHz) δ: 189.5 (CN,Ph); 177.5 (CO,piv); 143.8, 135.2 (Cq,arom); 128.5, 128.3, 127.8, 126.8,
126.7, 126.4, 126.2, 125.8, 124.4, 120.8, 119.5 (CH,arom); 97.7 (C-1); 75.9 (C-2); 75.2 (PhCH2); 73.0
(C-3); 70.6 (C-5); 70.2 (C-4); 39.3 (C(CH3)3,piv); 38.9 (C(CH3)3,piv); 27.4 (C(CH3)3,piv); 27.3
(C(CH3)3,piv); 16.1 (C-6). IR (neat): 2974, 1734, 1598, 1479, 1458, 1323, 1282, 1207, 1138, 1120,
1029, 1001, 910, 694.

6-azidoxyethyl 4,6-O-benzylidene-2-deoxy-3-O-(2-O-(2-naphthylmethyl)-3,4-di-O-pivaloyl-α-L-
fucopyranosyl)-2-trichloracetamido-β-D-glucopyranoside (6)

To a solution of acceptor 10 (0.16 g, 0.31 mmol, 1.0 eq.) and donor 12 (0.26 g, 0.46 mmol, 1.5 eq.)
in CH2Cl2 (5 mL, 0.06 M) were added flame-dried 3Å molecular sieves. After ~30 minutes, NIS
(0.14 g, 0.61 mmol, 2.4 eq.) was added and the mixture was cooled to -40 °C, after which TMSOTf
(6 μL, 0.03 mmol, 0.1 eq.) was added. The reaction mixture was allowed to warm to -20 °C and
stirred until TLC analysis (PE/EtOAc, 4:1 v/v) indicated complete conversion of the starting
material. The reaction was quenched by addition of NET3 (0.1 mL), the mixture was diluted with
EtOAc, washed with Na2S2O3 (sat,aq.), NaHCO3 (sat,aq.) and brine, dried over MgSO4, filtered and
concentrated in vacuo. After column chromatography (PE/EtOAc, 19:1 → 4:1 v/v), the title
product was obtained in 86% yield (0.28 g, 0.28 mmol). 1H NMR (400 MHz) δ: 7.83-7.79 (m, 3H,
CH,arom); 7.72 (s, 1H, CH,arom); 7.49-7.46 (m, 4H, CH,arom); 7.40-7.34 (m, 4H, CH,arom); 6.92 (d, 1H, J =
7.2 Hz, NH); 5.53 (s, 1H, PhCH=H); 5.44 (dd, 1H, J = 3.2 Hz, 10.8 Hz, H-3'); 5.16-5.14 (m, 2H, H-1', H-
4'); 5.06 (d, 1H, J = 8.4 Hz, H-1); 4.85 (d, 1H, J = 12.0 Hz, PhCH=H); 4.79 (d, 1H, J = 12.0 Hz, PhCH=H);
4.53 (t, 1H, J = 9.2 Hz, H-3); 4.40-4.32 (m, 2H, H-5', H-6); 3.91 (dd, 1H, J = 3.2 Hz, 10.4 Hz, H-2');
3.85-3.78 (m, 2H, H-6, OCH=H); 3.68 (t, 1H, J = 9.2 Hz, H-4); 3.59-3.57 (m, 1H, H-5); 3.47-3.43
(m, 2H, H-2, OCH$_3$CH$_2$); 3.20 (t, 2H, $J = 7.2$ Hz, N$_3$C$_3$H$_2$,OCH$_3$); 1.58 (m, 4H, CH$_2$CH$_2$); 1.32-1.26 (m, 4H, CH$_2$CH$_2$); 1.14 (s, 9H, C(CH$_3$)$_3$); 1.09 (s, 9H, C(CH$_3$)$_3$); 0.50 (d, 3H, 6.4 Hz, H-6). $^{13}$C-APT NMR (100 MHz) δ: 177.7, 177.5 ($\delta_{DO}$); 161.9 ($\delta_{DO}$); 137.1, 135.5, 133.3, 133.1 (C$_{arom}$); 129.5, 128.5, 128.0, 127.8, 126.6, 126.5, 126.2, 125.9, 125.4 (CH$_{arom}$); 102.4 (PhCH); 99.4 (C-1); 98.1 (C-1'); 80.6 (C-3); 74.1 (C-4); 73.9 (C-2'); 73.4 (PhCH$_2$); 71.3 (C-4'); 70.8 (C-3'); 70.5 (OCH$_2$CH$_2$); 68.9 (C-6); 66.3 (C-5); 65.5 (C-5'); 60.5 (C-2); 51.5 (N$_2$CH$_2$), 39.1, 38.9 (C(CH$_3$)$_3$); 29.5, 28.8, (CH$_2$CH$_2$); 27.3 (C(CH$_3$)$_3$), 27.1, 25.7 (CH$_2$CH$_2$), 15.1 (C-6'). IR (thin film) ν: 2972, 2934, 2870, 2093, 1730, 1521, 1479, 1283, 1163, 1092, 1028, 910, 820. HRMS: [M+NH$_4$]$^+$ calculated for C$_{48}$H$_{65}$Cl$_3$N$_5$O$_{12}$: 1010.36741; found 1010.36776.

Byproduct 27a

$^1$H NMR (400 MHz) δ: 8.39 (d, 1H, $J = 8.4$ Hz, CH$_{arom}$); 7.82 (d, 1H, $J = 7.6$ Hz, CH$_{arom}$); 7.78 (d, 1H, $J = 8.4$ Hz, CH$_{arom}$); 7.54 (t, 1H, $J = 1.6$ Hz, CH$_{arom}$); 7.50 (t, 1H, $J = 7.6$ Hz, CH$_{arom}$); 7.70 (d, 1H, $J = 8.4$ Hz, CH$_{arom}$); 5.55 (d, 1H, $J = 3.6$ Hz, H-1); 5.50 (dd, 1H, $J = 3.2$ Hz, 3.6 Hz, H-1); 3.56 (t, 1H, $J = 3.6$ Hz, H-4); 4.82 (d, 1H, $J = 16.0$ Hz, CH$_2$Nap); 4.20 (d, 1H, $J = 16.0$ Hz, CH$_2$Nap); 4.19 (dd, 2.8 Hz, 4.0 Hz, H-2); 4.00 (m, 1H, H-5); 1.40 (d, 3H, $J = 6.4$ Hz, H-6); 1.28 (s, 9H, C(CH$_3$)$_3$); 1.26 (s, 9H, C(CH$_3$)$_3$). $^{13}$C-APT NMR (100 MHz) δ: 177.6, 177.4 ($\delta_{DO}$); 133.9, 133.0, 132.2 (C$_{arom}$); 129.2, 129.2, 128.8, 128.4, 126.9, 126.2, 125.8, 125.4, 124.1, 122.2 (CH$_{arom}$); 72.5 (C-2); 69.0 (C-4); 68.7 (C-5); 68.6 (C-3); 66.0 (PhCH$_2$); 64.3 (C-1); 39.2 (C(CH$_3$)$_3$); 39.0 (C(CH$_3$)$_3$); 27.4 (C(CH$_3$)$_3$); 27.3 (C(CH$_3$)$_3$); 15.2 (C-6). IR (thin film) ν: 1734, 1598, 1282, 1207, 1120, 910, 694. HRMS: [M+H]$^+$ calculated for C$_{27}$H$_{35}$O$_6$: 455.24282; found 455.24254.

6-azidohexyl 4,6-O-benzylidene-2-deoxy-3-O-(3,4-di-O-pivaloyl-\(\alpha\)-l-fucopyranosyl)-2-trichloroacetamido-\(\beta\)-D-glucopyranoside (29)
Chapter 7

To a solution of disaccharide 6 (67 mg, 0.068 mmol, 1.0 eq.) in CH$_2$Cl$_2$ (0.8 mL, 0.1 M) was added an aqueous phosphate buffer (pH 7, 0.1 M, 0.2 mL). Under vigorous stirring, DDQ (36 mg, 0.16 mmol, 2.3 eq.) was added and the mixture was stirred until TLC analysis (toluene/EtOAc, 7:3 v/v) indicated complete conversion of the starting material (~3 hours). The reaction mixture was diluted with EtOAc, washed with Na$_2$S$_2$O$_3$ (sat., aq.) and a 1:1 mixture of NaHCO$_3$ (sat., aq.) and Na$_2$CO$_3$ (sat., aq.) until a clear aqueous phase was obtained. The organic phase was dried over MgSO$_4$ filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 4:1 → 3:2 v/v) yielded the title compound in 83% yield (48 mg, 0.056 mmol). $^1$H NMR (400 MHz) δ: 7.47-7.44 (m, 2H, CH$_{arom}$); 7.36-7.33 (m, 3H, CH$_{arom}$); 6.91 (d, 1H, $J$ = 8.0 Hz, NH); 5.50 (s, 1H, PhCHO); 5.16 (dd, 1H, $J$ = 3.2 Hz, 7.2 Hz, H-3’); 5.04 (d, 1H, $J$ = 2.0 Hz, H-4’); 4.98 (d, 1H, $J$ = 4.0 Hz, H-1’); 4.95 (d, 1H, $J$ = 8.4 Hz, H-1); 4.38 (dd, $J$ = 4.8 Hz, 6 Hz, H-6); 4.33 (t, 1H, $J$ = 9.2 Hz, H-4); 4.20 (q, 1H, $J$ = 7.2 Hz, H-5’); 3.89-3.85 (m, 2H, H-2’, OCH$_{hexyl}$); 3.81 (t, 1H, $J$ = 10.0 Hz, H-6’); 3.66-3.57 (m, 3H, H-2, H-3, H-5); 3.51-3.49 (m, 1H, OCH $H_{hexyl}$); 3.25 (t, 2H, $J$ = 6.8 Hz, N$_3$CH$_2$); 1.59-1.57 (m, 4H, CH$_2$hexyl); 1.37-1.35 (m, 4H, CH$_2$hexyl); 1.15, 1.13 (s, 9H, C(CH$_3$)$_3$); 0.41 (d, 3H, $J$ = 6.8 Hz, H-6’). $^{13}$C-APT NMR (100 MHz) δ: 178.7 177.6 (CO$_{pv}$); 162.2 (CO$_{TCA}$); 137.0 (C$_{arom}$); 129.6, 128.5, 126.6 (CH$_{arom}$), 102.7 (PhCH); 100.0 (C-1’); 99.8 (C-1); 80.2 (C-3); 75.5 (C-4); 71.1 (C-3’, C-4’); 70.4 (OCH$_2$hexyl); 68.8 (C-6); 67.6 (C-2’); 66.5 (C-5); 65.8 (C-5’); 59.8 (C-2); 51.5 (N$_3$CH$_2$hexyl); 39.2, 38.9 (C(CH$_3$)$_3$pv); 29.5, 28.8 (CH$_2$hexyl); 27.4, 27.2 (C(CH$_3$)$_3$pv); 26.6, 25.7 (CH$_2$hexyl); 15.0 (C-6’). IR (film) v: 3516, 3385, 2931, 2863, 2096, 1735, 1714, 1687, 1535, 1288, 1170, 1159, 1099, 1082, 1058. HRMS: [M+NH$_4$]$^+$ calculated for C$_{37}$H$_{57}$Cl$_3$N$_3$O$_{12}$: 870.30437; found 870.30486.

6-azidohexyl 4,6-O-benzylidene-2-deoxy-3-O-((2-O-(2-naphthylmethyl))-3,4-di-O-pivaloyl-α-L-fucopyranosyl)-3,4-di-O-pivaloyl-α-L-fucopyranoside (7)

![](image)

To a solution of acceptor 29 (77 mg, 0.090 mmol, 1.0 eq.) and donor 12 (68 mg, 0.120 mmol, 1.3 eq.) in CH$_2$Cl$_2$ (1 mL, 0.1M), were added flame-dried 3Å molecular sieves. After ~30 minutes, NIS (0.027 g, 0.130 mmol, 1.4 eq.) and, after cooling to ~40 °C, TMSOTf (1.8 µL, 0.01 mmol, 0.1 eq.) and the mixture was allowed warm to ~20 °C and stirred at this temperature (~6 hours). The reaction was quenched by addition of NEt$_3$ (0.15 mL), the mixture diluted with EtOAc (20 mL), washed with Na$_2$S$_2$O$_3$ (sat., aq.), NaHCO$_3$ (sat., aq.) and brine, dried over MgSO$_4$, filtered and concentrated
in vacuo. The residue was purified by column chromatography (PE/EtOAc, 19:1 → 4:1) to afford the title compound in 33% yield (39 mg, 0.029 mmol). \(^1\)H NMR (400 MHz, 333 K) \(\delta\): 7.82-7.32 (m, 13H, \(CH_{arom}\) \(N\)\(H\)); 5.54 (s, 1H, Ph\(CH\)); 5.50 (dd, 1H, \(J = 3.2 \text{ Hz}, 7.6 \text{ Hz}, \text{ H}-3\)’’); 5.47 (d, 1H, \(J = 2.8 \text{ Hz}, \text{ H}-1\)’); 5.21 (dd, 1H, \(J = 3.2 \text{ Hz}, 7.2 \text{ Hz}, \text{ H}-3\)’’); 5.19-5.17 (m, 2H, \(H\)-4’, \(H\)-4’’); 4.81 (d, 1H, \(J = 12.0 \text{ Hz}, \text{ PhCH}_2\)\(H\)); 4.78 (d, 1H, \(J = 3.2 \text{ Hz}, \text{ H}-1\)’’); 4.62 (d, 1H, \(J = 12.0 \text{ Hz}, \text{ PhCH}_2\)\(H\)); 4.54-4.48 (m, 2H, \(H\)-1, H-3); 4.37 (q, 1H, \(J = 6.8 \text{ Hz}, \text{ H}-5\)’); 4.30-4.27 (m, 2H, \(H\)-5”, H-6); 3.96 (dd, 1H, \(J = 3.6 \text{ Hz}, 6.8 \text{ Hz}, \text{ H}-2\)’); 3.90 (dd, 1H, \(J = 3.2 \text{ Hz}, 7.2 \text{ Hz}, \text{ H}-2\)”); 3.73–3.69 (m, 3H, H-2, H-6, O\(CH\)\(_{hexyl}\)); 3.60 (t, 1H, \(J = 9.2 \text{ Hz}, \text{ H}-4\)); 3.38-3.35 (m, 1H, H-5); 3.26-3.24 (m, 3H, O\(CH\)\(_{hexyl}\), N\(_3\)\(CH\)_2\(hexyl\)); 1.58-1.54 (m, 4H, \(CH\)_2\(hexyl\)); 1.35-1.32 (m, 4H, \(CH\)_2\(hexyl\)); 1.14 (s, 18H, C\((CH\)_3\)\(_{3}\)\(_{Piv}\)); 1.12 (s, 9H, C\((CH\)_3\)\(_{3}\)\(_{Piv}\)); 1.02 (s, 9H, C\((CH\)_3\)\(_{3}\)\(_{Piv}\)); 0.98 (d, 3H, \(J = 6.4 \text{ Hz}, \text{ H}-6\)”); 0.78 (d, 3H, \(J = 6.0 \text{ Hz}, \text{ H}-6\)”’. \(^{13}\)C-APT NMR (100 MHz, 333 K) \(\delta\): 177.9, 177.4, 177.3, 177.2 (\(\alpha\)\(O\)\(_{Piv}\)); 162.6 (\(\alpha\)\(O\)\(_{TCA}\)); 137.4, 135.0, 133.3, 129.2 (\(C_{arom}\)); 128.9, 128.4, 128.0, 127.9, 127.2, 126.7, 126.5, 126.4, 125.7 (\(\alpha\)\(CH\)\(_{arom}\)); 101.8 (Ph\(CH\)); 100.6 (C-1); 97.2 (C-1”); 96.3 (C-1’); 92.7 (\(C\)\(_{Cl}\)); 81.4 (C-4); 74.1 (C-2’, C-3); 73.8 (Ph\(CH\)_2); 73.0 (C-2’); 71.5 (C-4”); 71.2 (C-4’); 70.2 (O\(CH\)_2\(hexyl\)); 69.8 (C-3’, C-3’’); 68.8 (C-6); 66.0 (C-5, C-5’’); 65.4 (C-5’); 56.5 (C-2); 51.5 (N\(_3\)\(CH\)_2); 39.2, 39.1, 39.0, 38.8 (C\((CH\)_3\)\(_3\)); 29.8, 29.6 (\(CH\)_2\(hexyl\)); 28.8 (C\((CH\)_3\)\(_{3}\)\(_{Piv}\)); 27.4, 27.3 (\(CH\)_2\(hexyl\)); 15.7 (C-6’, C-6’’). IR (thin film) \(\nu\): 2974, 2933, 2872, 2094, 1734, 1479, 1367, 1280, 1161, 1128, 1055, 964, 910. HRMS: [M+\(NH\)_4]’ calculated for C\(_{56}\)H\(_{91}\)Cl\(_3\)N\(_{5}\)O\(_{18}\): 1324.54114; found 1324.54131.

6-azidohexyl 4,6-O-benzylidene-2-deoxy-3-O-(2-O-(2-naphthylmethyl)-3,4-di-O-pivaloyl-\(\alpha\)-l-fucopyranosyl)-2-trichloroacetamido-\(\beta\)-D-galactopyranoside (8)

![Structural formula of 8](image)

To a solution of acceptor 11 (0.16 g, 0.3 mmol, 1.0 eq.), donor 12 (0.20 g, 0.36 mmol, 1.2 eq.) in CH\(_2\)Cl\(_2\) (3 mL, 0.1 M) were added 3Å molecular sieves. After ~30 minutes, NIS (90 mg, 0.39 mmol, 1.3 eq.) was added and the mixture was cooled to -40 °C. TMSOTf (5\(\mu\)L, 0.03 mmol, 0.1 eq.) was added and the reaction mixture was allowed to warm to -20 °C, and was stirred at this temperature until TLC analysis (PE/EtOAc, 7:3 v/v) indicated complete conversion of the starting material (~3 hours). The reaction was quenched by addition of \(\text{NEt}_3\), the mixture was diluted with EtOAc, washed with Na\(_2\)S\(_2\)O\(_3\) (sat., aq.), NaHCO\(_3\) (sat., aq.) and brine, dried over MgSO\(_4\), filtered and concentrated \(\text{in vacuo}\). Purification by column chromatography (PE/EtOAc, 9:1 → 3:1 v/v) furnished the title compound in 68% yield (0.20 g, 0.20 mmol). \(^1\)H NMR (400 MHz, \(\delta\)): 7.84-7.80
(m, 3H, C<sub>H<sub>arom</sub></sub>; 7.72 (s, 1H, C<sub>H<sub>arom</sub></sub>; 7.50-7.47 (m, 4H, C<sub>H<sub>arom</sub></sub>; 7.39-7.35 (m, 3H, C<sub>H<sub>arom</sub></sub>; 7.08 (d, 1H, J = 6.8 Hz, NH); 5.48 (s, 1H, PhC<sub>H</sub>); 5.37 (dd, 1H, J = 2.8 Hz, 10.8 Hz, H-3′); 5.15-5.13 (m, 2H, H-1, H-4′); 4.87 (d, 1H, J = 3.6 Hz, H-1′); 4.80 (d, 1H, J = 12.4 Hz, PhCH<sub>H</sub>); 4.70 (d, 1H, J = 12.4 Hz, PhCH<sub>H</sub>); 4.53 (dd, 1H, J = 3.6 Hz, 11.2 Hz, H-3); 4.35-4.30 (m, 3H, H-4, H-5′, H-6); 4.04 (d, 1H, J = 11.2 Hz, H-6); 3.96-3.92 (m, 1H, OC<sub>H</sub>H<sub>ε</sub>); 3.83-3.76 (m, 2H, H-2, H-2′); 3.51-3.48 (m, 2H, H-5, OCH<sub>H</sub>H<sub>ε</sub>); 3.24 (d, 2H, J = 6.8 Hz, N<sub>η</sub>C<sub>H</sub>); 1.61-1.56 (m, 4H, C<sub>H</sub>ε<sub>N</sub>B<sub>ε</sub>H<sub>ε</sub>); 1.38-1.14 (m, 22H, C<sub>H</sub>ε<sub>N</sub>B<sub>ε</sub>H<sub>ε</sub>B<sub>ε</sub>C<sub>(C<sub>H</sub>)<sub>3</sub></sub>); 0.79 (d, 3H, J = 6.4 Hz, H-6′). 13<sup>C</sup>-APT NMR (100 MHz) δ: 177.6, 177.3 (C<sub>ε</sub>N<sub>Na</sub>); 162.2 (C<sub>ε</sub>N<sub>Na</sub>); 137.5, 135.5, 133.2, 133.2 (C<sub>ε</sub>N<sub>Na</sub>); 129.3, 128.5, 128.4, 127.9, 127.8, 127.3, 126.8, 126.4, 126.2 (C<sub>ε</sub>N<sub>Na</sub>); 101.3 (PhCH); 100.2 (C-1′); 98.6 (C-1); 92.7 (C<sub>ε</sub>N<sub>Na</sub>); 76.8 (C-3); 75.1 (C-4); 73.1 (PhCH<sub>H</sub>); 72.2 (C-2′); 71.1 (C-4′); 70.6 (C-3′); 69.9 (OCH<sub>H</sub>H<sub>ε</sub>); 69.4 (C-6); 66.4, 66.0 (C-5, C-5′); 55.4 (C-2); 51.5 (N<sub>η</sub>C<sub>H</sub>); 39.1, 38.9 (C<sub>ε</sub>N<sub>Na</sub>)<sub>(Piv)</sub>; 29.5, 28.9 (CH<sub>H</sub>H<sub>ε</sub>); 27.3, 27.2 (C<sub>ε</sub>N<sub>Na</sub>)<sub>(Piv)</sub>; 26.6, 25.7 (CH<sub>H</sub>H<sub>ε</sub>); 16.0 (C-6′). IR (thin film) v: 2972, 2936, 2870, 2093, 1732, 1695, 1531, 1479, 1368, 1283, 1161, 1128, 1088, 1051, 908, 822. HRMS: [M+Na]<sup>+</sup> calculated for C<sub>48</sub>H<sub>61</sub>C<sub>13</sub>N<sub>4</sub>NaO<sub>12</sub>: 1015.32280; found 1015.32229.

6-azidohexyl 4,6-O-benzylidene-2-deoxy-3-O-(3,4-di-O-pivaloyl-α-L-fucopyranosyl)-2-trichloroacetamido-β-D-galactopyranoside (30)

To a solution of 8 (90 mg, 0.091 mmol, 1.0 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (0.8 mL, 0.1 M) was added aqueous phosphate buffer (pH 7, 0.1 M, 0.2 mL). Under vigorous stirring, DDQ (62 mg, 0.27 mmol, 3.0 eq.) was added and the mixture was stirred until TLC analysis (PE/EtOAc, 7:3 v/v) indicated complete conversion of the starting material (~2.5 hours). The reaction mixture was diluted with EtOAc and washed with Na<sub>2</sub>SO<sub>4</sub> (sat.,aq.) and Na<sub>2</sub>CO<sub>3</sub> (sat.,aq.) until the water layer had become clear, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 9:1 → 7:3 v/v) furnished the title compound in 81% yield (62 mg, 0.073 mmol). 1H NMR (400 MHz) δ: 7.49-4.48 (m, 2H, C<sub>H</sub>arom); 7.39-7.37 (m, 3H, C<sub>H</sub>arom); 7.06 (d, 1H, J = 6.8 Hz, NH); 5.53 (s, 1H, PhC<sub>H</sub>); 5.18-5.03 (m, 4H, H-1, H-1′, H-3′, H-4′); 4.59 (dd, 1H, J = 3.2 Hz, 8.0 Hz, H-3); 4.42 (d, 1H, J = 3.2 Hz, H-4); 4.36-4.31 (m, 2H, H-5′, H-6); 4.09 (d, 1H, J = 12.0 Hz, H-6); 3.97-3.81 (m, 3H, H-2, H-2′, OCH<sub>H</sub>H<sub>ε</sub>); 3.54-3.47 (m, 2H, H-5, OCH<sub>H</sub>H<sub>ε</sub>); 3.25 (t, 2H, J = 6.8 Hz, N<sub>η</sub>C<sub>H</sub>); 1.92 (d, 1H, J = 11.2 Hz, O<sub>H</sub>); 1.60-1.56 (m, 4H, C<sub>H</sub>ε<sub>N</sub>B<sub>ε</sub>H<sub>ε</sub>); 1.43-1.14 (m, 22H, C<sub>H</sub>ε<sub>N</sub>B<sub>ε</sub>H<sub>ε</sub>B<sub>ε</sub>C<sub>(C<sub>H</sub>)<sub>3</sub></sub>); 0.97 (d, 3H, J = 6.4 Hz, H-6′). 13<sup>C</sup>-APT NMR (100 MHz) δ: 178.6, 177.5 (C<sub>ε</sub>N<sub>Na</sub>); 162.3
Synthesis of Schistosoma mansoni glycans

(\text{CO}_{\text{TCA}}); 137.4 (C_{\text{arom}}); 129.4, 128.7, 128.5, 126.2 (CH_{\text{arom}}); 101.8 (C-1'); 101.4 (PhCH); 98.7 (C-1); 92.4 (\text{CO}_{\text{3,TCA}}); 77.0 (C-3); 75.3 (C-4); 71.0, 70.8 (C-3', C-4'); 69.9 (OCH_{\text{2,hexyl}}); 69.4 (C-6); 68.0 (C-2'); 66.4, 66.3 (C-5, C-5'); 55.4 (C-2'); 51.5 (N_{3}CH_{\text{2,hexyl}}); 39.2, 38.9 (C(CH_{3})_{3,\text{Py}}); 29.8, 29.5 (CH_{2,hexyl}); 27.4, 27.2 (C(CH_{3})_{3,\text{Py}}); 26.6, 25.7 (CH_{2,hexyl}); 16.2 (C-6'). IR (thin film) ν: 3524, 3329, 3236, 2936, 2920, 2852, 1761, 1712, 1694, 1539, 1479, 1369, 1287, 1157, 1126, 1086, 1059, 1009, 822. HRMS: [M+NH_{4}]^+ calculated for C_{37}H_{57}Cl_{3}N_{3}O_{12}: 870.30415; found 870.30471.

\[6\text{-azidohexyl } 4,6\text{-O-benzylidene-2-deoxy-3-O-}((2-O-(2-naphthylmethyl)-3,4\text{-di-O-pivaloyl-\text{\textalpha-L-fucopyranosyl}})-3,4\text{-di-O-pivaloyl-\text{\textalpha-L-fucopyranosyl}})-2\text{-trichloroacetamido-\textbeta-D-galactopyranoside (9)}\]

To a solution of acceptor 30 (40 mg, 0.047 mmol, 1.0 eq.), donor 12 (53 mg, 0.093 mmol, 2.0 eq.) in CH_{2}Cl_{2}(0.25 mL, 0.2 M) were added flame-dried 3Å molecular sieves. After ~30 minutes, NIS (23 mg, 0.10 mmol, 2.2 eq.) were added and the mixture was cooled to -40 °C. TMSOTf (1.7 μL, 0.009 mmol, 0.2 eq.) was added and the mixture was allowed to warm to -20 °C and kept at this temperature (~5.5 hours). The reaction was quenched with NEt_{3} (0.1 mL), diluted with EtOAc, washed with Na_{2}S_{2}O_{3} (sat,aq), NaHCO_{3} (sat, aq) and brine, dried over MgSO_{4}, filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 19:1 → 3:1 v/v) furnished the title trisaccharide in 54% yield (33 mg, 0.025 mmol). 1H NMR (400 MHz) δ: 7.91-7.84 (m, 3H, CH_{arom}); 7.76-7.73 (m, 2H, CH_{arom}); 7.60-7.57 (m, 2H, CH_{arom}); 7.42-7.40 (m, 3H, CH_{arom}); 7.29-7.28 (m, 3H, NH, CH_{arom}); 5.63 (dd, 1H, J = 3.2 Hz, 10.4 Hz, H-3'''); 5.24-5.16 (m, 4H, H-1', H-3', H-4', H-4''); 5.03 (s, 2H, H-1'', PhCH); 4.78-4.70 (m, 2H, PhCH_{2}); 4.48-4.41 (m, 2H, H-1, H-2); 4.32 (q, 1H, J = 6.4 Hz, H-5''); 4.23 (q, 1H, J = 6.8 Hz, H-5'''); 3.93 (dd, 1H, J = 2.8 Hz, 10.4 Hz, H-2''); 3.88-3.81 (m, 3H, H-2', H-6, OC\text{H}H_{\text{hexyl}}); 3.64 (dd, 1H, J = 2.8 Hz, 10.4 Hz, H-3); 3.42-3.40 (m, 1H, OCHH_{\text{hexyl}}); 3.29 (d, 1H, J = 2.4 Hz, H-4); 3.22 (t, 2H, J = 6.8 Hz, N_{3}CH_{\text{2,hexyl}}); 2.99 (d, 1H, J = 11.2 Hz, H-6); 2.37 (s, 1H, H-5'); 1.58-1.53 (m, 4H, CH_{2,hexyl}); 1.37-1.11 (m, 40H, CH_{2,hexyl}C(CH_{3})_{3,\text{hexyl}}); 1.05 (d, 3H, J = 6.8 Hz, H-6'''); 0.54 (d, 3H, J = 6.4 Hz, H-6'). 13C-APT NMR (100 MHz) δ: 178.6, 177.3, 177.1, 176.7 (\text{CO}_{\text{Py}}); 162.2 (\text{CO}_{\text{TCA}}); 137.7, 134.3, 133.3, 133.2 (C_{\text{arom}}); 129.1, 128.8, 128.2, 128.1, 127.9, 127.9, 127.1, 126.4, 126.4 (CH_{\text{arom}}); 101.7 (C-1’’); 101.1 (C-1); 100.9
(PhCH); 96.9 (C-1’); 93.1 (C3, C3a); 79.1 (C-2’); 78.1 (C-3); 76.0 (C-2’’); 74.3 (PhCH2); 73.1 (C-4); 71.6, 71.5 (C-4’, C-4’’); 69.9 (C-3’); 69.2 (C-3’); 68.9 (C-6, OCH2,hexyl); 66.7 (C-5’); 66.2 (C-5); 65.6 (C-5’); 51.8 (C-2); 51.5 (N2CH2,hexyl); 39.3, 39.2, 39.2, 38.7 (CH3,3,5,PD); 29.5, 28.9 (CH2,hexyl); 27.5, 27.4, 27.4, 27.2 (C(CH3)3,5,PD); 26.6, 25.7 (CH2,hexyl); 15.9, 15.5 (C-6’, C-6’’). IR (thin film) ν: 3366, 2974, 2935, 2096, 1736, 1283, 1163, 1129, 1076, 1054, 822. HRMS: [M+NH4]+ calculated for C64H91Cl3N5O16C: 1324.54114; found 1324.54132.

6-aminohexyl 2-deoxy-3-O-(α-L-fucopyranosyl)-2-acetamido-β-D-glucopyranoside (2)

![Structure of 6-aminohexyl 2-deoxy-3-O-(α-L-fucopyranosyl)-2-acetamido-β-D-glucopyranoside (2)](image)

To a solution of disaccharide 6 (82 mg, 0.082 mmol, 1.0 eq.) in THF (1 mL, 0.1 M) was added KOH (1 M, aq., 1.2 mL) and the mixture was stirred until TLC analysis (toluene/ETOAc, 4:1 v/v) indicated complete consumption of the starting material (~2 days). The mixture was neutralized by addition of HCl (1 M, aq.), washed with NaHCO3 (sat, aq.) and brine, dried over MgSO4, filtered and concentrated in vacuo. Purification by column chromatography (toluene/ETOAc, 4:1 → 3:2 v/v) yielded the saponified intermediate 31 in 57% yield (39 mg, 0.046 mmol). 1H NMR (400 MHz) δ: 7.85-7.78 (m, 4H, CHarom); 7.51-7.40 (m, 5H, CHarom); 7.36-7.35 (m, 3H, CHarom); 6.84 (d, 1H, J = 8.0 Hz, NH); 5.53 (s, 1H, PhCH); 5.30 (d, 1H, J = 3.6 Hz, H-1’); 4.86 (d, 1H, J = 12.0 Hz, PhCH2); 4.74 (d, J = 11.6 Hz, PhCH2); 4.68 (d, 1H, J = 8.0 Hz, H-1); 4.38-4.23 (m, 2H, H-4, H-6); 4.20 (q, 1H, J = 6.4 Hz, H-5’); 4.00 (dd, 1H, J = 2.8 Hz, 6.8 Hz, H-3’); 3.86-3.67 (m, 5H, H-2, H-3, H-6, H-2’, OCH2,hexyl); 3.63 (1H, d, J = 2.4 Hz, H-4’); 3.50-3.44 (m, 1H, H-5’); 3.42-3.38 (m, 1H, OCH2,hexyl); 3.22 (t, 2H, J = 6.8 Hz, N3CH2,hexyl); 2.34 (s, 1H, OCH); 2.19 (s, 1H, OCH); 1.55-1.52 (m, 4H, CH2,hexyl); 1.33-1.30 (m, 4H, CH2,hexyl); 0.92 (d, 3H, J = 6.8 Hz, H-6’). 13C-APT NMR (100 MHz) δ: 161.9 (C(Tail)); 137.2, 135.4, 133.3, 133.2, 129.4, 128.8, 128.1, 127.9, 127.0, 126.4, 126.4, 126.2, 125.8 (CHarom); 101.9 (PhCH); 100.7 (C-1); 96.6 (C-1’); 92.6 (Cl2); 80.7 (C-3); 77.1 (C-2’); 73.6 (C-4); 73.3 PhCH2); 71.8 (C-4’); 70.4 (OCH2,hexyl); 69.5 (C-3’); 68.8 (C-6); 66.5 (C-5); 68.8 (C-5’); 59.3 (C-2’); 51.5 (N3CH2,hexyl); 29.5, 28.8, 26.6, 25.7 (CH2,hexyl) 15.8 (C-6’). To a mixture of 31 (34 mg, 0.041 mmol, 1.0 eq.) in MeOH (4 mL, 0.01M) was added an aqueous phosphate buffer (pH 7, 0.1 M, 0.2 mL). The mixture was degassed with argon before addition of palladium on carbon (10% w/w Pd, 0.017 g). The black suspension was shaken for 24h in a Parr apparatus under H2 atmosphere (4 bar). The solution was filtered over a Whatman filter to remove the catalyst, and subsequently purified by gel-filtration (Sephadex LH-20, eluted with H2O). After lyophilization, the title compound was obtained in 34% yield (8.2 mg, 0.014 mmol). 1H NMR (850 MHz, D2O) δ:
4.97 (d, 1H, J = 4.3 Hz, H-1'); 4.49 (d, 1H, J = 8.5 Hz, H-1); 4.30 (q, 1H, J = 6.8 Hz, H-5'); 3.91 (dd, 1H, J = 1.7 Hz, 10.2 Hz, H-6); 3.88 (dt, 1H, J = 5.6 Hz, 4.3 Hz, 1.7 Hz, OC\(\text{H}_{2\text{hexyl}}\)); 3.79 (m, 3H, H-2, H-3', H-4'); 3.73 (dd, 1H, J = 5.9 Hz, H-6); 3.67, (dd, 1H, J = 3.4 Hz, 6.8 Hz, H-2'); 3.61 (t, 1H, J = 9.4 Hz, H-3); 3.56 (dt, 1H, J = 5.6 Hz, 4.3 Hz, 1.7 Hz, OCH\(\text{H}_{2\text{hexyl}}\)); 3.49 (t, 1H, J = 10.2 Hz, H-4); 3.44 (m, 1H, H-5); 2.97 (t, 2H, J = 7.7 Hz, NCH\(_2\text{hexyl}\)); 2.0 (s, 3H, CH\(_3\text{NHAc}\)); 1.63 (m, 2H, CH\(_2\text{hexyl}\)); 1.55 (m, 2H, CH\(_2\text{hexyl}\)); 1.35 (m, 4H, CH\(_2\text{hexyl}\)); 1.14 (d, 3H, J = 5.9 Hz, H-6'). 13C-APT NMR (D\(_2\text{O}, 212\) MHz) δ: 175.4 (CO\(\text{NHAc}\)); 101.9 (C-1); 100.9 (C-1'); 81.3 (C-3); 76.8 (C-5); 72.8 (C-4'); 71.4 (OC\(\text{H}_{2\text{hexyl}}\)); 70.5 (C-3'); 69.5 (C-4); 68.9 (C-2'); 67.8 (C-5'); 61.7 (C-2); 29.3, 27.6, 26.2, 25.6 (CH\(_2\text{hexyl}\)); 23.2 (CH\(_3\text{Ac}\)); 16.1 (C-6'). HRMS: [M+H]+ calculated for C\(_{29}\)H\(_{39}\)N\(_2\)O\(_{10}\): 467.25992; found 467.25987.

![Chemical structure](image)

6-aminohexyl 2-deoxy-3-O-(\(\alpha\)-L-fucopyranosyl)-2-acetamido-\(\beta\)-D-galactopyranoside (4)

To a solution of 8 (0.112 g, 0.114 mmol, 1.0 eq.) in THF (0.7 mL, 0.15 M) was added KOH (1M, aq., 0.3 mL) and the mixture was stirred until TLC analysis (toluene/EtOAc, 7:3 v/v) indicated complete conversion of the starting material (~18 hours). The reaction was neutralized with HCl (1M, aq.), the mixture was diluted with EtOAc, washed with Na\(_2\)CO\(_3\) (sat., aq.) and brine, dried over MgSO\(_4\), filtered and concentrated in vacuo. Purification by column chromatography (toluene/EtOAc, 7:3 → 1:1 v/v) furnished the saponified intermediate 32 in 61% yield (57 mg, 0.069 mmol). 1H NMR (400 MHz) δ: 7.85-7.81 (m, 3H, CH\(_{arom}\)); 7.75 (s, 1H, CH\(_{arom}\)); 7.51-7.44 (m, 5H, CH\(_{arom}\)); 7.38-7.34 (m, 3H, CH\(_{arom}\)); 7.05 (d, 1H, J = 6.8 Hz, NH); 5.52 (s, 1H, PhCH); 5.05 (d, 1H, J = 3.6 Hz, H-1'); 4.98 (d, 1H, J = 8.4 Hz, H-1); 4.88 (d, 1H, J = 12.8 Hz, PhCHH); 4.64 (d, 1H, J = 12.8 Hz, PhCHH); 4.41-4.30 (m, 3H, H-3, H-4, H-6); 4.17 (q, 1H, J = 6.8 Hz, H-5'); 4.06 (d, 1H, J = 11.6 Hz, H-6); 4.00-3.80 (m, 3H, H-2, H-3', OCH\(_{H_{\text{hexyl}}}\)); 3.66-3.63 (m, 2H, H-2', H-4'); 3.53-3.45 (m, H-5, OCH\(_{H_{\text{hexyl}}}\)); 3.24 (t, 2H, N\(_3\)CH\(_2\text{hexyl}\)); 2.38 (bs, 1H, OH); 2.23 (bs, 1H, OH); 1.59-1.56 (m, 4H, CH\(_2\text{hexyl}\)); 1.38-1.31 (m, 4H, CH\(_2\text{hexyl}\)); 1.10 (d, 3H, J = 6.4 Hz, H-6'). 13C-APT NMR (100 MHz) δ: 162.2 (CO\(\text{TCA}\)); 137.8, 135.4, 133.3, 133.2 (C\(_{arom}\)); 129.2, 128.8, 128.7, 128.4, 128.1, 127.9, 127.3, 126.6, 126.4, 126.2, 125.9 (CH\(_{arom}\)); 101.1 (PhCH); 99.2 (C-1'); 98.9 (C-1); 92.7 (C\(_{\text{Cl}_{3}TCA}\)); 76.9 (C-3); 75.6 (C-2'); 75.2 (C-4); 72.8 (PhCH\(_2\)); 71.5 (C-4'); 69.9 (OC\(\text{H}_{2\text{hexyl}}\)); 69.4 (C-6); 69.4 (C-3'); 66.5, 66.4 (C-5, C-5'); 55.2 (C-2); 51.5 (N\(_3\)CH\(_2\text{hexyl}\)); 29.5, 28.9, 26.7, 25.7 (CH\(_2\text{hexyl}\)); 16.4 (C-6'). To a solution of 32 (57 mg, 0.069 mmol, 1.0 eq.) in THF and tBuOH (3:1 v/v, 0.4 mL) was added an aqueous phosphate buffer (pH 7, 0.1 M, 0.3 mL). The mixture was degassed by sparging with argon before addition of palladium on carbon (10% w/w Pd, 0.11 g). The mixture was purged with H\(_2\).
and subsequently stirred under a H₂ atmosphere at 4 bar for 2 days in a Parr apparatus, after which it was filtered over a Whatmann filter and concentrated in vacuo. The residue was purified by gel filtration (Sephadex LH-20, MeOH/H₂O 9:1 v/v) and lyophilized to furnish the disaccharide in 67% yield (12.7 mg, 0.046 mmol). ¹H NMR (600 MHz, D₂O) δ: 4.95 (d, 1H, J = 4.2 Hz, H-1'); 4.46 (d, 1H, J = 8.4 Hz, H-1); 4.09 (q, 1H, J = 6.6 Hz, H-5'); 3.97-3.85 (m, 4H, H-2, H-4', H-5, OCH₃hexyl); 3.78-3.70 (m, 4H, H-3, H-4', H-6); 3.66-3.64 (m, 2H, H-2', H-5); 3.59-3.55 (1H, OCH₃hexyl); 2.95 (t, 2H, J = 7.8 Hz, NCCH₂hexyl); 1.98 (s, 3H, CH₃NH₂); 1.64-1.52 (m, 4H, CH₂hexyl); 1.38-1.24 (m, 4H, CH₂hexyl); 1.16 (d, 3H, J = 6.6 Hz, H-6'). ¹³C-APT NMR (151 MHz) δ: 175.8 (t, CH₂NH₂); 102.4, 102.3 (C-1, C-1'); 79.6 (C-3); 75.9 (C-2' or C-4); 72.6 (C-4'); 71.3 (OCH₂hexyl); 70.3 (C-3'); 69.1 (C-2' or C-4); 68.9 (C-5); 68.1 (C-5'); 52.5 (C-2); 40.3 (NCCH₂hexyl); 30.5, 27.7, 26.3, 25.5 (CH₂hexyl); 23.2 (CH₃NH₂); 16.2 (C-6'). IR (thin film) ν: 3363, 2939, 1651, 1542, 1512, 1072, 1033, 917. HRMS: [M+Na]⁺ calculated for C₂₀H₃₄N₃NaO₁₀: 489.24187; found 489.24180.
References


