Synthesis and application of glycans unique to S. mansoni

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*A novel approach to the synthesis of circulating anodic antigen**

Introduction

The circular anodic antigen (CAA) is a highly glycosylated protein excreted by the gut of *Schistosoma Mansoni* fluke worms. The CAA protein is decorated with long polysaccharides consisting of the 6-[GlcA-β-(1-3)-GalNAc-β-(1-] repeating unit (Figure 1).[1] It plays an important role in the survival of the schistoma worms in the hostile environment of the human host. The long negatively charged glycan chains on the CAA protein are one of the methods the worms employs to evade the hosts immune system. As the worms feed on blood their gut is subjected to all components of the immune system.[2] It has been reported that CAA interacts with the C1q protein complex of the complement system.[2], [3] As this protein is at the start of the classic pathway of the complement system, any complementary immune attack might get suppressed, thus ensuring its survival.

*Harvey, M. R., Amponsah, K. B., Hokke. C., Van der Marel, G. M., Codée, J. D. C. were involved in the research described in this chapter.

The CAA carbohydrate structure is unique to schistosoma worms and can therefore be used as a biomarker to monitor the degree of infection by schistosomes. Unlike the multi-fucosylated glycans discussed in previous chapters, CAA glycans are excreted by the host in urine, so analytic samples can be obtained without invasive methods.[4] In addition the excretion of CAA in the bloodstream doesn't fluctuate, thus greatly increasing analytical accuracy. [5]–[7]

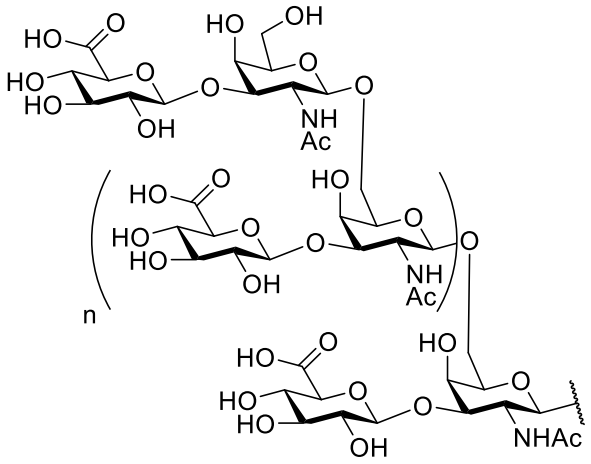


Figure 1: Structure of glycan present on CAA protein.

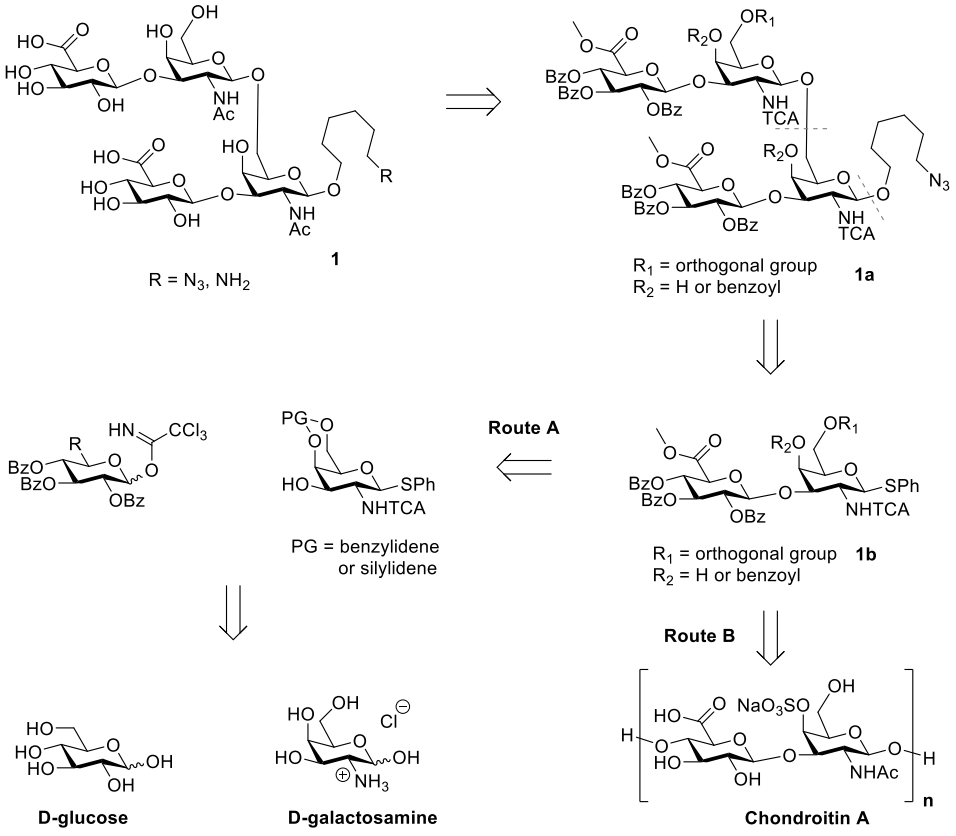
Besides being useful as a biomarker CAA may also be a target for a glycan based vaccine, as recognition of these antigens might help to target the hidden worms.[8] In order to make better diagnostics or a vaccine, well defined glycans are required, which cannot be obtained from biological sources. Vliegenthart and co-workers have previously described the synthesis of CAA oligosaccharides up to a pentasaccharide (see Chapter 1 for a more detailed description of their synthesis).[1], [3], [9]–[13] This chapter describes a feasible and efficient protocol to synthesize oligosaccharide fragments of CAA, that may ultimately lead to production of larger CAA oligomers.[14]

Results and discussion

Two routes (Route A and B) to synthesize CAA oligomers were envisioned and both are tested and evaluated in this chapter. In order to test the validity of these routes CAA tetrasaccharide **1** was selected as the target structure and the retrosynthesis towards this tetrasaccharide is depicted in Scheme 1. It was envisioned that tetrasaccharide **1** can be obtained from its protected precursor **1a**. The use of trichloroacetamide functions in combination with benzoyl and methyl esters should allow for a single step global deprotection, as all these groups can be removed through saponification. This would leave the azide in the spacer untouched and available for subsequent conjugation purposes. The tetrasaccharide can be built from GlcA-GalNAc-disaccharide building

blocks, wherein the galactosamine amine is protected as a trichloroacetamide to ensure 1,2-*trans* selective condensation reactions.[15]–[18] The galactosamine C4- and C6-hydroxyl functions may bear orthogonal protecting groups or the higher reactivity of the C6-OH over that of the C4-OH may be exploited in a regioselective glycosylation reaction.

Scheme 1: Retrosynthesis of selected target CAA tetrasaccharide.



The key disaccharide will be assembled as a thiophenyl glycoside as thioglycosides are stable to a wide range of conditions and the thiophenyl group can be readily activated to provide a glycosylating agent. Alternatively, it can be orthogonally removed or converted into another anomeric leaving group, such as a fluoride or an imidate.[19]

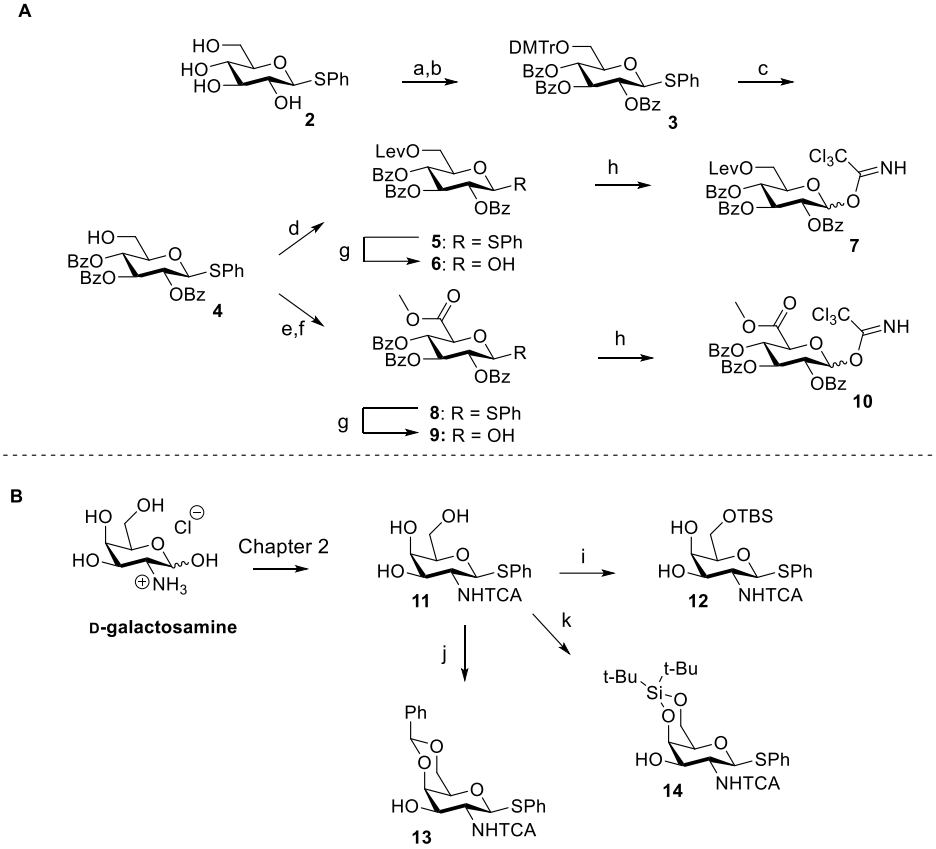
Disaccharide **1b** can be obtained through two different routes. The first, route A represents a flexible assembly route, as a diversity of D-glucose based donors and D-galactosamine based acceptors can be synthesized and evaluated, ensuring an optimization strategy for the synthesis of the core disaccharide. Optimization will include the timing of the oxidation of the glucose to the glucuronic acid and with this route it can

be determined whether it is more advantageous to oxidize the glucose monomer before glycosylation or to first generate a disaccharide and oxidize the primary glucose alcohol at a later stage. A downside of the flexibility is the number of steps required to obtain the disaccharide. Route B is based on the work of Jacquinet and co-workers, who described the assembly of well-defined chondroitin oligomers from GlcA-GalNAc dimer synthons, obtained from the acidic hydrolysis of chondroitin A, a cheap and readily available starting material.[20] As chondroitin and CAA share the same disaccharide motif this route presents a promising alternative to the *de novo* synthesis of route A. The main advantage of route B is the reduction in steps, as the core disaccharide can be obtained from chondroitin A, thus avoiding the glycosylation reaction. A downside in this route is a decrease in flexibility as the acidity of the C5-proton of the glucuronic acid prevents protective group manipulations that require a strong base, such as a benzylation.

Route A: Starting from D-galactosamine and D-glucose.

Scheme 2 depicts the monosaccharide synthons required for the assembly of key disaccharide **1b** following Route A. The synthesis of glucose donors **7** and **10** started from thioglycoside **2**, which was synthesized from D-glucose in three steps according to literature procedures (Scheme 2-A).[21] The primary alcohol of **2** could be selectively protected with a bulky 4,4'-di-methoxytrityl (DMT) group by treating it with DMT-Cl in pyridine at 80˚C.[22] After cooling to room temperature Bz-Cl was added and the mixture was left to stir overnight to provide the fully protected glucose **3**. Several methods were investigated to remove the DMT group. Initially $BF_3{\cdot}OEt_2$ was tested, but this resulted in partial benzoyl migration to the C6-OH.[23] When TFA was used together with TFAA, no benzoyl migration was observed but the reaction didn't go to completion resulting in a low yield. The use of TFA in conjunction with Et_3SiH as a scavenger for the released DMT cation, had none of the aforementioned side reactions and effectively liberated the C6-OH. The primary alcohol was either protected with a levuloyl group **5**, or oxidized to the acid, which in turn was protected as a methyl ester **8**.[24], [25] With these building blocks (**5** and **8**) in hand the imidate donors **7** and **10** were synthesized. The thiophenyl group was hydrolysed using N-Bromosuccinimide (NBS) in acetone/water in a near quantitative yield in both cases.[26] Lastly, the imidate was introduced using DBU and trichloroacetonitrile giving donors **7** and **10** in an overall yield of 26%, 40% respectively from D-glucose.[27]

*Scheme 2: Synthesis of the building blocks required for Route A. **A**) Synthesis of glucose donors **7** and **10**, **B**) Synthesis of galactosamine building blocks **12**, **13** and **14**.*



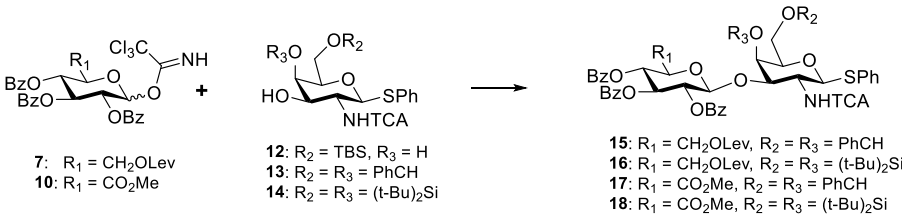
Reagents and conditions: **a**: DMTr-Cl, pyr, 80˚C, **b**: Bz-Cl, pyr, **c**: TFA, Et_3SiH, DCM, -40˚C, 78% (yield over three steps), **d**: Lev-OH, DMAP, EDC·HCl, DCM, 0˚C→RT, 65%, **e**: TEMPO (cat.), BAIB, DCM, 0˚C, **f**: MeI, K_2CO_3, DMF, 82% (over two steps), **g**: NBS, acetone, water, **6** quant., **9** 98%, **h**: Cl_3CCN, DBU, DCM, **9** 71%, **10** 88%, **i**: TBS-Cl, pyr, Et_3N, 70%, **j**: $PhCH(OMe)_2$, CSA (cat.), ACN, 50˚C, 330 mbar, 74%, **k**: $DTBS(OTf)_2$, DMF, -10˚C, 92%.

In order to synthesize the CAA disaccharide the following three acceptors **12**, **13**, and **14** were synthesized (Scheme 2-B). Diol **12** was synthesized to explore whether the reactivity difference between the C3-OH and the C4-OH is sufficient to be exploited in a regioselective glycosylation reaction.[28] Acceptors **13** and **14** are protected by either a benzylidene acetal or a silylidene ketal. The latter has been shown to have a beneficial effect on the reactivity of the C3-OH, however, it will have to be removed from the disaccharide as silylidene protected galactose-type donors react in a highly selective 1,2 *cis* fashion, even if C2-O/N protecting groups are present that are capable of neighbouring group participation.[29]–[32]

The synthesis of **11** from D-galactosamine is described in Chapter 2. Diol **12** was obtained by selective silylation of the primary alcohol using *tert*-butyldimethyl Chloride (TBS-Cl) with pyridine and Et_3N at -30˚C. Acceptors **13** and **14** could be synthesized from triol **11** by using either benzaldehyde dimethyl acetal and a catalytic amount of camphorsulfonic acid (CSA), or di-*tert*-butylsilylditriflate (DTBS$(OTf)_2$) in DMF.

The results of the glycosylation reactions of donors **7** and **10** and acceptors **12**-**14** are summarized below in Table 1. In all cases the reactions were performed in DCM at a concentration of 0.1M with freshly activated molecular sieves (3Å) and with TMSOTf as the activator.

Table 1: Optimization of the glycosylation reaction of disaccharide building blocks.



7: $R_1 = CH_2OLev$
10: $R_1 = CO_2Me$

12: R_2 = TBS, R_3 = H
13: $R_2 = R_3$ = PhCH
14: $R_2 = R_3 = (t\text{-}Bu)_2Si$

15: $R_1 = CH_2OLev$, $R_2 = R_3$ = PhCH
16: $R_1 = CH_2OLev$, $R_2 = R_3 = (t\text{-}Bu)_2Si$
17: $R_1 = CO_2Me$, $R_2 = R_3$ = PhCH
18: $R_1 = CO_2Me$, $R_2 = R_3 = (t\text{-}Bu)_2Si$

entry	donor	acceptor	TMSOTf	T (˚C)	product	yield (%)
1	**7**	**12**	0.1 (eq.)	-40˚C→ -10˚C	Complex mixture	-
2	**10**	**12**	0.1 (eq.)	-40˚C→ -10˚C	Complex mixture	-
3	**7**	**13**	0.1 (eq.)	-40˚C→ -20˚C	**15**	31
4	**10**	**13**	0.1-0.5 (eq.)[a]	-40˚C → RT	No reaction	-
5	**7**	**14**	0.1 (eq.)	-40˚C→ -20˚C	**16**	43[b]
6	**10**	**14**	0.1-0.5 (eq.)[a]	-20˚C→ RT	**18**	68[c]
7	**10**	**14**	0.3 (eq.)	RT	**18**	84

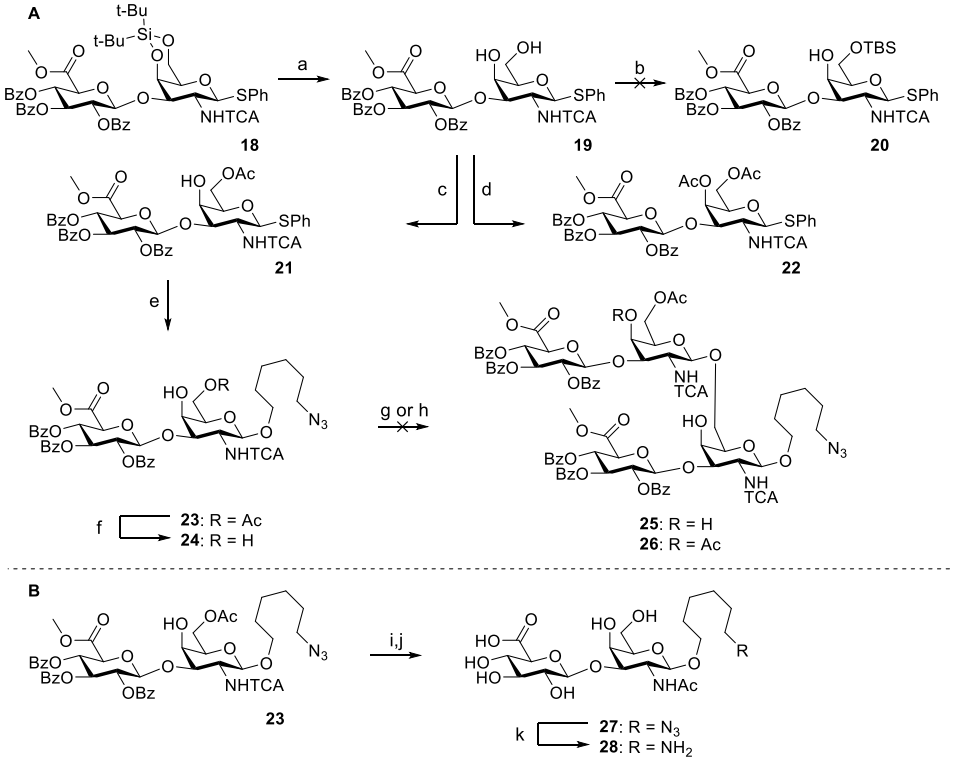
[a]five different experiments each with 0.1 eq. more of TMSOTf.
[b]yield determined after removal of silylidene
[c]This yield was obtained with 0.3 eq. of TMSOTf

Initially diol **12** was tested with donors **7** and **10** (entries 1 and 2). Unfortunately, this reaction led to a complex and inseparable mixture of C3-O and C4-O linked disaccharides. Although there are examples where excellent regioselectivity of the C3-OH over the C4-OH hydroxyl was observed, these building blocks provided poor regioselectivity.[33]–[38] Next benzylidene acceptor **13** was tested. When glucose donor **7** was used disaccharide **15** was formed in a modest yield of 31% (entry 3). Glucuronic acid donor **10** proved to be too unreactive as no reaction was observed even after 60 hours. Increasing the amount of activator did not solve this problem (entry 4). Lastly silylidene **14** was used as the acceptor. The condensation with Lev bearing donor **7** led to an inseparable mixture of disaccharide **16** and hydrolysed donor (entry 5). After removal of the silylidene with HF·pyridine the diol disaccharide **19** could be obtained in a yield of 43% over two steps.

The use of glucuronic acid donor **10** did not lead to this problem and after some optimization disaccharide **18** could be obtained in an excellent yield of 84% (entries 6 and 7).

Although it is known that silylidene donors are more reactive then benzylidene donors, the effect of this protecting group on the reactivity of the acceptor has not been investigated often.[39]–[41] There are examples showing that the silylidene ketal increases the reactivity of the neighbouring hydroxyl in comparison to the analogous benzylidene protected system, although the reason behind this phenomenon is not clear yet.[31] Del Bino *et al*. postulated that the increased flexibility of the silylidene ketal adds to the reactivity of the system.[30] Thollard *et al*. implied that the electron donating effect of the *t*-Bu groups increase the reactivity of the C3-OH.[29] With conditions established for the effective generation of the disaccharide, attention was focused next on the assembly of the tetrasaccharide (see Scheme 3).

*Scheme 3: **A**) Synthesis of tetrasaccharide **26**, **B**) deprotection of disaccharide **23**.*



Reagents and conditions: **a**: HF·pyridine, THF, pyr, 79%, **b**: TBS-Cl, pyr, -30˚C, 0%, **c**: Ac_2O, NaOAc, 50˚C, 92%, **d**: Ac_2O, NaOAc, 110˚C, 82%, **e**: 6-azidohexan-1-ol, NIS, TfOH (cat.), MS (3Å), DCM, 0˚C, 58%, **f**: Ac-Cl, MeOH, DCM, 4˚C, 88%, **g**: **21**, NIS, TfOH, MS (3Å), ACN/DCM, **h**: **22**, NIS, TfOH, MS (3Å), ACN/DCM, **i**: NaOH, dioxane, H_2O, **j**: Ac_2O, Et_3N, MeOH **k**: Pd/C, H_2, H_2O, 35% (over three steps).

In order to install the 6-azidohexan-1-ol spacer β-selectively, the silylidene ketal was

removed first as is it α-directing due its steric bulk. The removal of the silylidene was accomplished by treatment of **18** with HF·pyridine in good yield. Next the primary alcohol in **19** was selectively protected with an orthogonal protecting group. A variety of protective groups were tested and the results are shown in Table 2.

Initially it was attempted to introduce a TBS group on the primary alcohol of **19** (entry 1). The same conditions as used for the preparation of acceptor **12** were used, but these proved ineffective. At elevated temperatures the starting material was consumed, but the desired compound could not be obtained. Next the introduction of the Fmoc group was probed. Similar to the attempted introduction of the TBS protection group the starting material was consumed, but the desired product had not formed (entry 2). Since both the TBS and the Fmoc are quite bulky, a less sterically demanding acetyl group was tried (entry 3). Unfortunately treatment of **19** with Ac_2O in pyridine again resulted in a complex mixture. The common element in all these reactions was the use of pyridine as a solvent and it was reasoned that this basic solvent could be the cause of the complex reaction mixtures. When disaccharide **19** was dissolved in pyridine and left overnight, TLC analysis showed the appearance of multiple spots (entry 4), indicating that **19** was not stable in pyridine. Therefore, different solvents were used for the introduction of other protective groups. The introduction of a levulinoyl ester proceeded extremely sluggish taking 2 weeks to achieve 38% conversion (entry 5). Selective acylation using Taylor's catalyst **31** was successful for installing either an acetyl or a chloroacetyl (entries 6 and 7).[42] Lastly an acetyl was installed by using sodium acetate in acetic anhydride. When heated to 50˚C the primary alcohol could be selectively acetylated in an excellent yield of 92% (entry 8).

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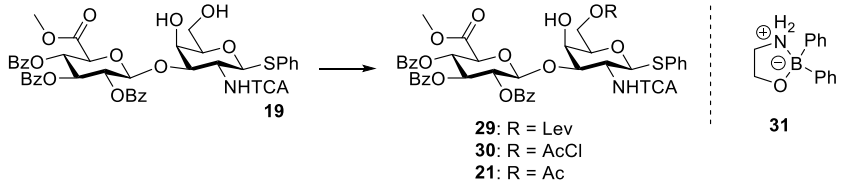
*Table 2: Selective protection of the primary alcohol of **19**.*



entry	reagents*	solvent	T (˚C)	yield
1	TBS-Cl	pyridine	-30 → 80	Complex mixture
2	Fmoc-Cl,	Pyridine	RT	Complex mixture
3	Ac_2O	pyridine	RT	Complex mixture
4	-	pyridine	RT	Complex mixture
5	Lev-OH, DMAP, EDC·HCl, pyr	DCM	RT	38%
6	ClAc-Cl, **31**, K_2CO_3, KI	ACN	RT	60%
7	Ac-Cl, **31**, DIPEA	ACN	RT	68%
8	NaOAc	Ac_2O	50	92%

*1.1 eq. of reagent was added in every reaction

Now that the primary alcohol of **21** was successfully protected, the 6-azidohexan-1-ol could be installed using N-iodosuccinimide (NIS) and triflic acid (TfOH) as the activator giving **23** in 58% yield (Scheme 3A). Subsequently, the acetyl ester was selectively removed with dry HCl in methanol to provide diol acceptor **23**. Since the primary alcohol of galactose is much more reactive than the 4-OH, it was reasoned that a regioselective glycosylation strategy could be employed to construct tetrasaccharide **25**, using disaccharide **24** as the acceptor. First the use of disaccharide donor **21** was explored. The glycosylation, however, proceeded very sluggishly as both the donor and the acceptor were poorly soluble in the mixture of acetonitrile and methylene chloride and the reaction mixture slowly turned into a gel. In order to increase the solubility of the donor, it was decided to synthesize the di-acetyl donor **22** by heating diol **19** to 110˚C in acetic anhydride with sodium acetate. Unfortunately using di-acetyl donor **22** did not proceed any better. Although in both glycosylation reactions the desired tetramer appeared to be the main product in the mixture, it was impossible to separate it from formed byproducts and therefore it was decided to abandon this synthetic route.

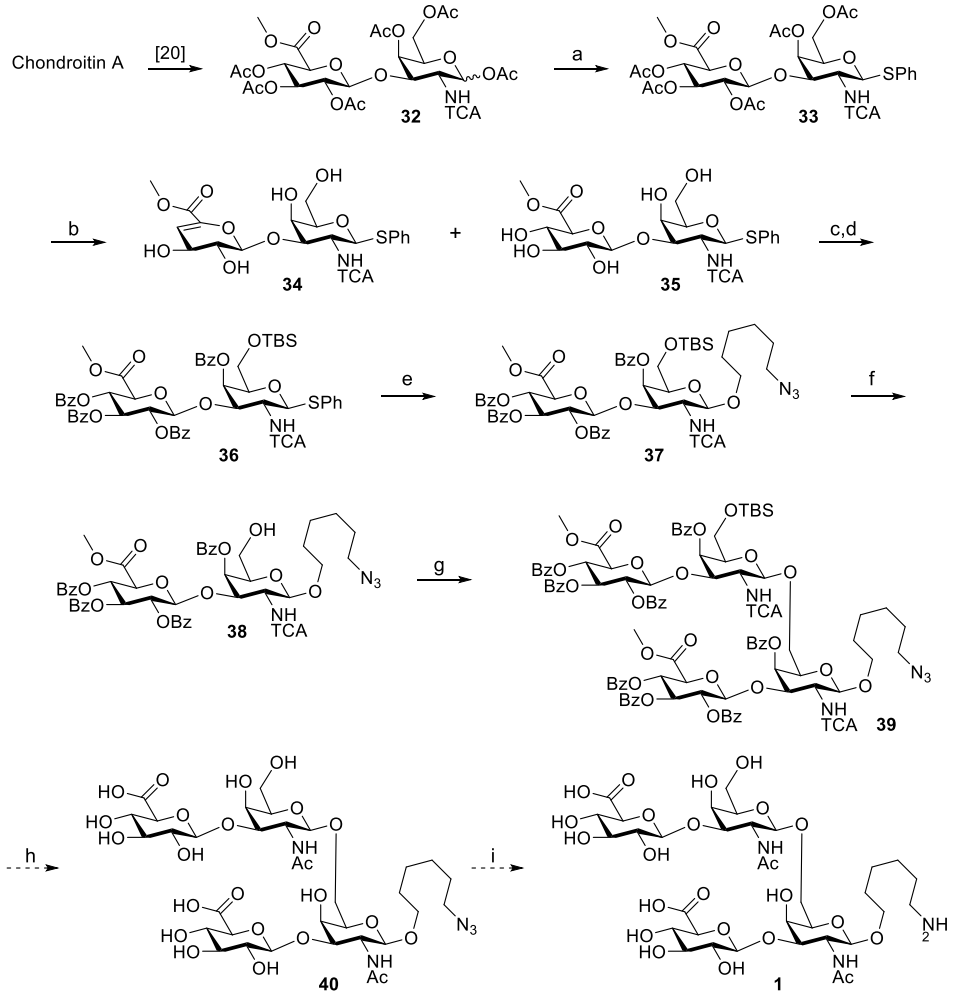
Disaccharide **23** was deprotected by hydrolysis of the esters and the trichloroacetamide using sodium hydroxide, after which the zwitterionic intermediate was purified over sephadex LH-20 size exclusion gel. The amine was then selectively acetylated under Schotten-Baumann conditions, resulting in disaccharide **27**. Finally, the spacer amine was liberated by catalytic hydrogenation of the azide giving rise to fully deprotected disaccharide **28** in 33% yield over three steps.

Route B: Starting from Chondroitin A.

Scheme 4 depicts the assembly of tetrasaccharide **39** using disaccharide synthons obtained from chondroitin A. Thus, chondroitin A was treated according to the protocol of Jacquinet and co-workers to yield acetylated disaccharide **32** on a multi-gram scale.[20] The anomeric centre was functionalized with a thiophenyl group using thiophenol and $BF_3{\cdot}OEt_2$, delivering thioglycoside **33** in 62% yield. Side products formed in this reaction consisted of furanosides, present in the starting material and the α-S-phenyl product. Disaccharide **33** was deacetylated using Zemplén conditions, resulting in **35** as the major compound. Compound **34**, formed by the deprotonation of the C5' by a methoxide ion followed by the elimination of the C4 acetate, was isolated as a minor side product. The primary alcohol was selectively protected with a TBS group using TBSOTf and imidazole in DMF. The same reaction using TBS-Cl proceeded very sluggishly.[43] In route A (Scheme 3) the degradation of diol **19** was observed when pyridine was used as the solvent. Therefore, it was attempted to install benzoyl groups on the disaccharide using benzoic anhydride and sodium benzoate at elevated temperature (110˚C), analogous to the synthesis of compound **22**. Unfortunately, complete benzoylation could not be achieved using these conditions. Therefore, benzoyl chloride was used in the next attempt in combination with a minimal amount of pyridine, 1.5 eq. per free hydroxyl, this did result in less degradation but could not completely prevent it and donor **36** was obtained in a

yield of 44% over two steps. Thioglycoside **36** was condensed with 6-azidohexan-1-ol using the NIS/TMSOTf activator couple to give **37** in 56% yield. In order to prevent migration of the 4-O benzoyl to the primary alcohol, the removal of the TBS group was done using CSA in wet acetonitrile. Acceptor **38** was obtained in 97% yield without any benzoyl migration.

*Scheme 4: Synthesis of CAA tetrasaccharide **39**.*



Reagents and conditions: **a**: PhSH, $BF_3{\cdot}OEt_2$, DCM, 62%, **b**: NaOMe (cat.), MeOH, **35** 82%, **34** 9%, **c**: TBSOTf, imidazole, DMF, **d**: Bz-Cl, pyr, 44% (over 2 steps), **e**: 6-azidohexanol, NIS, TMSOTf (cat.), MS (3Å), DCM, -20˚C, 56%, **f**: CSA, H_2O, ACN, 97%, **g**: **37**, NIS, TMSOTf (cat.), MS (3Å), DCM, -20˚C, 42%, **h**: i) NaOH, 1,4 dioxane, H_2O, ii) Ac_2O, MeOH, Et_3N, **i**: Pd/C, H_2, H_2O.

Tetrasaccharide **39** was then synthesized by condensing donor **36** and acceptor **38** using NIS with catalytic TMSOTf as the activator couple. Although the reaction proceeded sluggishly, tetrasaccharide **39** could be obtained in a yield of 42%. A small quantity of **39** was obtained and the previously employed deprotection strategy was applied. Unfortunately, this was unsuccessful as removal of the esters and TCA groups led to a product that was poorly soluble, which hampered the purification by LH-20 gel permeation chromatography.

Conclusion

This Chapter has described a study to a novel approach of generating well-defined CAA-oligosaccharides. To this end, an assembly strategy was devised that hinges on the use of disaccharide GlcA-GalNAc building blocks. For the generation of the key disaccharide building blocks, two routes were designed. Route A started from D-glucose and D-galactosamine, which were turned into building blocks **10** and **14** using well-established protective group manipulations. Disaccharide **18** was synthesized by condensing these two building blocks in a yield of 84%. It was shown that a silylidene ketal bearing acceptor is more reactive than an acceptor bearing a benzylidene acetal. Further investigations showed that the diol **19**, formed by removal of the silylidene, was instable and therefore difficult to manipulate. The glycosylation reaction forming tetrasaccharide **1a** from the two disaccharide synthons proceeded problematically and therefore this route was ultimately abandoned. Route B started from chondroitin A, a cheap and readily available starting material, which could be hydrolysed to obtain the required [GlcA-β-(1-3)-GalNAc-β] disaccharide repeating unit of CAA. This reduced the total number of steps to get to tetrasaccharide **1a** from **15** (Route A) to only 6 steps. Also in this route, the base lability of the disaccharide intermediate was encountered but a fully protected building block could be obtained rapidly nonetheless. Importantly the crucial glycosylation in which two disaccharides were united to form tetrasaccharide **39** proceeded much better. An initial attempt to deprotect the tetrasaccharide unfortunately failed. However, the chemistry developed here will allow for the generation of sufficient amounts of building blocks to further optimize the glycosylation chemistry and provide sufficient material to develop a deprotection strategy. Eventually the optimized chemistry should lead to the generation of a set of well-defined CAA glycans to be used in diagnostics and perhaps open up possibilities for an anti-schistosome vaccine.

Experimental

General procedures

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.

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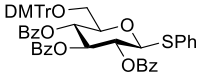
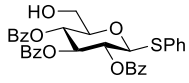
Phenyl 2,3,4-tri-*O*-benzoyl-6-*O*-(4,4'-dimethoxytrityl)-1-thio-β-D-glucopyranose (3)



Compound **2** (11.4 g, 42.0 mmol, 1.0 eq.) was dissolved in anhydrous pyridine (500 mL, 0.08M) and the solution was warmed to 80°C. DMTr-Cl (18.6 g, 55.0 mmol, 1.3 eq.) was slowly added and the reaction was stirred for one hour before increasing the temperature to 110°C. After 3 hours TLC analysis showed full consumption of the starting material. The mixture was cooled to room temperature and BzCl (30 mL, 258 mmol, 6.1 eq.) and DMAP (3.4 g, 27.4 mmol, 0.65 eq.) were added to the solution. After two days TLC analysis showed full conversion. The mixture was quenched by slow addition of water (100 mL) at 0˚C. The mixture was taken up in EtOAc and washed with sat. $CuSO_4$ (aq.), the layers were separated and the water layer was re-extracted with EtOA. The combined organic layers were then washed with sat. $NaHCO_3$ (aq.) until bubbling no longer occurred followed by brine. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to obtain the crude as a dark red oil. The crude was purified by silica gel column chromatography

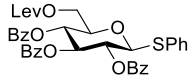
(PE:EtOAc, 9:1 → 1:1) to obtain the product as a yellow foam (25.7 g,28.9 mmol, 69%). ^{1}H NMR (CD_3CN, 400 MHz) δ: 8.22 – 8.18 (m, 2H, arom.), 7.97 (m, 4H, arom.), 7.90 – 7.84 (m, 2H, arom.), 7.73 – 7.68 (m, 2H, arom.), 7.63 – 7.26 (m, 41H, DMTrOH, arom.), 6.90 – 6.84 (m, 4H, arom.), 6.19 (t, 1H, *J*=9.4 Hz, H-3), 6.02 (t, 1H, *J*=9.8 Hz, H-4), 5.89 (t, 1H, *J*=9.7 Hz, H-2), 5.48 (d, 1H, *J*=10.0 Hz, H-1), 4.23 (d, 1H, *J*=10.2 Hz, H-5), 3.75 (3, 6H, OCH_3, DMTr), 3.65 (d, 1H, *J*=9.8 Hz, H-6), 3.41 (dd, 1H, *J*=10.7, 4.5 Hz, H-6) ppm. ^{13}C-APT NMR (CD_3CN, 101 MHz) δ: 166.6, 166.0, 165.7 (C=O, Bz), 159.6, 159.5, 146.1, 138.8, 136.8, 136.4, 134.5, 133.3, 131.0, 130.2, 130.2, 130.1, 129.9, 129.6, 129.2 (arom), 86.3 (C-1), 78.5 (C-5), 75.9 (C-3), 71.9 (C-2), 69.9 (C-4), 62.8 (C-6), 55.8 (OCH_3, DMTr) ppm. HRMS $[M+Na]^+$ calculated for $[C_{54}H_{46}O_{10}SNa]^+$: 909.27094, found 909.2718.

Phenyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranose (4)



Compound **3** (13.4 g, 15.1 mmol, 1.0 eq.) was dissolved in anhydrous DCM (150 mL, 0.1 M) and the round bottom flask purged with argon gas. The solution was cooled to -40°C. Et_3SiH (10.9 mL, 68.0 mmol, 4.5 eq.) and TFA (1.7 mL, 22.7 mmol, 1.5 eq.) were slowly added to the solution. The colour changed from a yellow solution to a bright red solution. The reaction was stirred for 4 hours at -40°C after which an additional 2.0 eq. of TFA was added. After one hour TLC analysis showed full consumption of the starting material. The mixture was quenched by adding solid $NaHCO_3$ until the evolution of gas ceased. The mixture was allowed to warm to room temperature before washing. The reaction mixture was transferred to a separatory funnel and washed once with water and once with brine. The organic layer was dried over $MgSO_4$, filtered and evaporated *in vacuo* to obtain the crude as a bright red oil. The crude was purified by silica gel column chromatography (PE:EtOAc, 9:1 → 3:7) to obtain the product as yellow foam in 78% yield (6.9 g, 11.8 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.04 – 7.78 (m, 6H, arom.), 7.59 – 7.17 (m, 15H, arom.), 5.98 (t, 1H, *J*=9.5 Hz, H-3), 5.51 (m, 2H, H-2, H-4), 5.10 (d, 1H, *J*=10.0 Hz, H-1), 3.96 – 3.82 (m, 2H, H-5, H-6), 3.75 (dd, 1H, *J*=13.2, 5.5 Hz, H-6), 2.82 (s, 1H, OH) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ: 165.9, 165.8, 165.1 (C=O, Bz), 133.7, 133.3, 132.9, 129.9, 129.1, 128.8, 128.6, 128.5, 128.3 (arom.), 86.2 (C-1), 78.9 (C-5), 74.1 (C-3), 70.6, 69.3 (C-2, C-4), 61.6 (C-6) ppm.

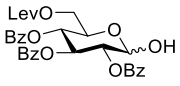
Phenyl 2,3,4-tri-*O*-benzoyl-6-*O*-levulinoyl-1-thio-β-D-glucopyranose (5)



Compound **4** (15.3 g, 26.2 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (250 mL, 0.1M) and cooled to 0°C. DMAP (3.8 g, 31,4 mmol, 1.2 eq.), EDC·HCl (6.8 g, 34.9 mmol, 1.3 eq.) and levulinic acid (3.2 mL, 31.4 mmol, 1.2 eq.) were added to the reaction and stirred for 2 days at room temperature under inert atmosphere. TLC analysis indicated full conversion and the reaction was quenched by adding sat. $NaHCO_3$ (aq.). The layers were separated and the organic layer washed with sat. $NaHCO_3$ (aq.), 1M HCl (aq.), and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to obtain the crude as an off-white solid. The crude was purified by silica gel column chromatography (PE:EtOAc, 19:1

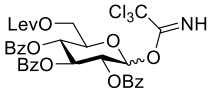
→ 1:4) to obtain the product as a white solid in 65% yield (11.5 g, 16.9 mmol). ^{1}H NMR ($CDCl_3$400 MHz) δ: 8.05 – 7.75 (m, 6H. arom.), 7.59 – 7.23 (m, 15H, arom.), 5.89 (t, 1H, *J*=9.5 Hz, H-3), 5.50 (m, 2H, H-2, H-4), 5.04 (d, 1H, *J*=10.0 Hz, H-1), 4.40 – 4.26 (m, 2H, H-6), 4.11 – 4.03 (m, 1H, H-5), 2.85 – 2.54 (m, 4H, CH_2, Lev), 2.18 (s, 3H, CH_3, Lev) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ: 172.4, 165.9, 165.3 (C=O, Bz, Lev), 133.2, 132.0, 130.0, 129.3, 129.1, 128.8, 128.6, 128.5, 128.5 (arom.), 86.28 (C-1), 76.3 (C-5), 74.2 (C-3), 70.6, 69.3 (C-2, C-4), 63.0 (C-6), 37.98, 27.92 (CH_2, Lev) ppm. HRMS: $[M+Na]^+$ calculated for $[C_{38}H_{34}O_{10}SNa]^+$: 705.1770, found 705.1782.

2,3,4-tri-*O*-benzoyl-6-*O*-levulinoyl-α/β-D-glucopyranose (6)



Thioglycoside **5** (0.7 g, 1.0 mmol, 1.0 eq.) was dissolved in a mixture of acetone and water (9:1, 10 mL, 0.1M). NBS (0.53 g, 3 mmol, 3.0 eq.) was added and the reaction was stirred under inert atmosphere at room temperature in the absence of light. After 2 hours an additional 2.0 eq. of NBS was added and the reaction stirred for an additional 1.5 hours. TLC analysis showed full consumption of the starting material and the mixture was diluted with EtOAc. The organic layer washed with sat. $Na_2S_2O_3$ (aq.) and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated *in vacuo* to obtain the crude as a yellow oil. The crude was purified by silica gel column chromatography (PE:EtOAc, 19:1 → 3:2) to obtain the product as a white foam in quantitative yield (0.6 g, 1.0 mmol). α/β ratio 9/1. ^{1}H NMR of α-anomer ($CDCl_3$, 400 MHz) δ: 8.02 – 7.92 (m, 5H, arom.), 7.90 – 7.85 (m, 2H), 7.51 – 7.30 (m, 8H, arom), 6.26 (t,, 1H, *J*=9.9 Hz, H-3), 5.78 (d, 1H, *J*=3.7 Hz, H-1), 5.60 (t, 1H, *J*=9.9 Hz, H-4), 5.33 (dd, 1H, *J*=10.2, 3.5 Hz, H-2), 5.13 (s, 1H, OH), 4.63 – 4.54 (m, 1H, H-5), 4.38 – 4.22 (m, 2H, H-6), 2.77 – 2.69 (m, 2H, CH_2, Lev), 2.62 – 2.53 (m, 2H, CH_2, Lev), 2.15 (s, 3H, CH_3, Lev) ppm.^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ: 172.5 (C=O, COMe), 165.8, 165.4, 165.3 (C=O, Bz, Lev), 133.5, 133.4, 133.3, 133.1, 130.0, 129.8, 129.7, 129.6, 129.1, 129.0, 128.8, 128.7, 128.4, 128.2, 95.7 (C-1), 72.3 (C-2), 70.3 (C-3), 69.4 (C-4), 67.2 (C-5), 62.7 (C-6), 37.9, (CH_2, lev), 29.7, (CH_3, lev), 27.9, (CH_2, lev) ppm.

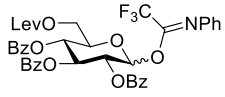
2,3,4-tri-*O*-benzoyl-6-*O*-levulinoyl-1-*O*-(2,2,2-trichloroacetimidoyl)-α/β-D-glucopyranose (7)



Compound **6** (0.6 g, 1.0 mmol, 1.0 eq.) was dissolved in anhydrous DCM (10 mL, 0.1 M) and the round-bottom flask purged with N_2-gas. K_2CO_3 (0.6 g, 4.0 mmol, 4.0 eq.) was added and the mixture cooled to 0°C. Trichloroacetonitrile (0.6 mL, 6.0 mmol, 6.0 eq.) was added slowly to the mixture and the reaction was stirred overnight at room temperature under N_2-atmosphere. TLC analysis showed full conversion and the reaction was diluted in EtOAc. The organic layer was washed with sat. $NaHCO_3$ (aq.) and brine followed by drying over $MgSO_4$. The organic layer was filtered and the volatiles were removed *in vacuo* to obtain crude immidate donor **7** as a yellow oil. The crude was purified by silica gel column chromatography (PE:EtOAc:Et_3N, 90:9:1 → 50:49:1) to obtain the product as a yellow oil in 71% yield (0.52 g, 0.71 mmol). First eluted was the α-anomer: ^{1}H NMR (CD_3CN 300

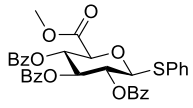
MHz) δ: 9.10 (s, 1H, NH), 7.97 – 7.77 (m, 6H, arom.), 7.62 – 7.31 (m, 9H, arom.), 6.77 (d, 1H, *J*=3.6 Hz, H-1), 6.14 (t, 1H, *J*=9.9 Hz, , H-3), 5.80 – 5.63 (m, 2H, H-2, H-4), 4.60 – 4.49 (m, 1H, H-5), 4.37 – 4.19 (m, 2H, H-6), 2.72 (t, 1H, 2H, CH_2, Lev), 2.50 (t, 2H, *J*=6.8, 5.7 Hz, CH_2, Lev), 2.12 (s, 3H, CH_3, Lev) ppm. ^{13}C-APT NMR (CD_3CN, 75 MHz) δ: 173.1(C=O, COMe), 166.5, 166.0 (C=O, Bz), 160.7 (C=O, NH), 134.8, 134.6, 130.5, 130.3, 129.9, 129.6 (arom.), 93.9 (C-1), 71.6, 71.3 (C-2, C-3, C-4), 69.3 (C-5), 62.6 (C-6), 38.4, 28.7 (CH_2, Lev). Next eluted was the β-anomer. ^{1}H NMR (CD_3CN, 300 MHz): δ:=8.05 (s, 1H, NH), 6.95 – 6.55 (m, 7H, arom.), 6.49 – 6.16 (m, 12H, arom.), 5.17 (d, 1H, *J*=8.2 Hz, H-1), 4.86 (t, 1H, *J*=9.4 Hz, H-3), 4.71 – 4.38 (m, 2H, H-3, H-4), 3.34 – 2.88 (m, 3H, H-5, H-6), 1.53 (t, 2H, *J*=6.3 Hz, CH_2, Lev), 1.33 (td, 2H, *J*=6.8, 3.0 Hz, CH_2, Lev), 0.92 (s, 3H, CH_3, Lev) ppm.

2,3,4-tri-*O*-benzoyl-6-*O*-levulinoyl-1-*O*-(*N*-phenyl-2,2,2-trifluoroacetimidoyl)-α/β-D-glucopyranose (7b)



Compound **6** (0.6 g, 1.0 mmol, 1.0 eq.) and Cs_2CO_3 (1.0 g, 3.0 mmol, 3.0 eq.) were dissolved in anhydrous CH_2Cl_2 (10 mL, 0.1 M). $CF_3C(N=Ph)Cl$ (0.3 mL, 2 mmol, 2.0 eq.) was added and the mixture stirred overnight at room temperature under inert atmosphere. TLC analysis showed complete consumption of the starting material. The mixture was filtered over Celite and the filtrate was concentrated to obtain the crude as a yellow oil. The crude was purified by silica gel column chromatography (PE:EtOAc, 19:1 → 1:1) to obtain the product as a white foam in a 62% yield (0.47 g, 0.62 mmol). ^{1}H NMR (CD_3CN, 400 MHz, 325 K) δ: 9.12 – 8.78 (m, 6H, arom.), 8.76 – 8.11 (m, 14H, arom), 7.34 (s, 1H, H-1), 7.05 (t, 1H, *J*=9.3 Hz, H-3), 6.86 – 6.65 (m, 2H, H-2, H-4), 5.45 – 5.19 (m, 3H, H-5, H-6), 3.80 – 3.70 (m, 2H, CH_2, Lev), 3.63 – 3.50 (m, 2H, CH_2, Lev), 3.16 (3H, CH_3, Lev) ppm. ^{13}C-APT NMR (CD_3CN, 101 MHz) δ: 173.2, 171.4, 166.5, 166.2 (C=O, Bz, Lev), 134.8, 130.2, 130.0, 129.9, 125.8, 120.3 (arom.), 96.3 (C-1), 74.1 , 74.0 (C-3, C-5), 72.4, 70.0 (C-2, C-4), 63.0 (C-6), 38.6 (CH_2, Lev), 28.9 (CH_2, Lev) ppm.

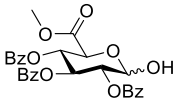
Methyl (phenyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranosyl uronate) (8)



Compound **4** (2.7 g, 4.9 mmol, 1.0 eq.) was dissolved in a mixture of CH_2Cl_2 and THF (1:2, 50 mL, 0.1 M) and cooled to 0°C. TEMPO (0.15 g, 1.0 mmol, 0.2 eq.) was added and stirred 10 minutes before adding BAIB (1.6 g, 4.9 mmol, 1.0 eq.) and water (5 mL). The reaction was stirred 2 hours before an additional 0.8 eq. of BAIB was added. After an additional 2 hours TLC analysis showed full conversion. The reaction mixture was acidified to pH 1 using 3M aq. HCl. Brine was added to the mixture and the layers were separated. The aqueous layer was extracted thrice with $CHCl_3$ and the organic layers were collected, dried over $MgSO_4$ and evaporated in vacuo. The crude was obtained as a yellow oil and used without further purification. The crude (0.59 g, 0.1 mmol, 1.0 eq.) was dissolved in anhydrous DMF (1 mL, 0.1 M). K_2CO_3 (0.016 g, 0.12 mmol, 1.2 eq.) and iodomethane (0.03 mL, 0.5 mmol, 5.0 eq.) were added sequentially and the reaction was left to stir overnight under inert atmosphere. TLC analysis showed full consumption of the starting material and the

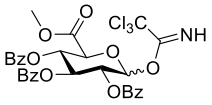
reaction was partitioned between EtOAc and water. The layers were separated and the organic layer was washed with water, sat. $NaHCO_3$(aq.), and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated *in vacuo* to obtain the crude as a yellow oil. The crude was purified over silica gel column chromatography (PE:EtOAc 9:1 → 3:2) to obtain the product obtained as a yellow oil in 82% over 2 steps (0.05 g, 0.082 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.01 – 7.89 (m, 4H, arom.), 7.84 – 7.79 (m, 2H, arom.), 7.58 – 7.24 (m, 14H, arom.), 5.92 (t, 1H, *J*=9.5 Hz, H-3), 5.64 (t, 1H, *J*=9.7 Hz, H-4), 5.49 (t, 1H, *J*=9.6 Hz, H-2), 5.05 (d, 1H, *J*=9.9 Hz, H-1), 4.36 (d, 1H, *J*=9.8 Hz, H-5), 3.71 (s, 3H, OCH_3) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ: 169.4 (C=O, CO_2Me), 166.6, 166.3, 166.1 (C=O, Bz), 133.7, 133.6, 133.5, 133.5, 130.0, 129.9, 129.2, 128.8, 128.6, 128.4, (arom.), 86.7 (C-1), 76.6 (C-5), 73.5 (C-3), 70.2 (C-2, C-4), 53.1 (OCH_3) ppm. HRMS: $[M+Na]^+$ calculated for $[C_{34}H_{28}O_9SNa]^+$: 635.1352, found 635.1358.

Methyl 2,3,4-tri-*O*-benzoyl-α/β-D-glucopyranosyl uronate (9)



Thioglycoside **8** (1.0 mmol, 0.6 g, 1.0 eq.) was dissolved in a mixture of acetone and water (7:3, 10 ml, 0.1 M) and the mixture was cooled to 0°C. NBS (1.8 g, 5.0 mmol, 5.0 eq.) was added to the reaction. The white suspension was stirred in the absence of light for 45 minutes before the reaction was quenched by adding sat. $Na_2S_2O_3$ (aq.). The mixture was diluted in EtOAc and the layers separated. The organic layer was washed once with $Na_2S_2O_3$ (aq.) and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated.The crude was obtained as a yellow oil and purified by silica gel column chromatography (PE/EtOAc (9:1 → 1:1) to obtain the product as a white solid in 98% yield (0.51 g, 0.98 mmol). α/β ratio 5/1. ^{1}H NMR ($CDCl_3$, 400 MHz): δ:=8.01 – 7.83 (m, 7H, arom.), 7.53 – 7.26 (m, 11H, arom.), 6.30 (t, 1H, *J*=9.7 Hz, H-3α), 5.98 (t, 0.2H, *J*=9.5 Hz, H-3β), 5.89 (d, 1H, *J*=2.7 Hz, H-1α), 5.75 – 5.62 (m, 1.2H, H-4α, H-4β), 5.48 (dd, 0.2H, *J*=9.5, 7.5 Hz, H-2β), 5.36 (dd, 1H, *J*=10.0, 3.5 Hz, H-2α), 5.15 (d, 0.2H, *J*=7.4 Hz, H-1β), 4.91 (d, 1H, *J*=9.9 Hz, H-5α), 4.84 (s, 1H, OH), 4.42 (d, 0.2H, *J*=9.6 Hz, H-5β), 3.64 (s, 0.6H, OCH_3α), 3.61 (s, 3H, OCH_3β) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MH) δ: 169.4 (C=O, CO_2Me), 166.6, 166.3, 166.1 (C=O, Bz), 134.7, 134.6, 134.6, 130.4, 130.4, 130.3, 130.3, 130.3, 130.1, 130.0, 129.7, 129.6 (arom.), 95.7 (C-1β), 91.0 (C-1α), 73.9 (C-2β), 73.6 (C-5β), 73.1 (C-3β), 72.6(C-2α), 71.3 (C-4β), 71.1 (C-4α), 71.0 (C-3α), 69.2 (C-5α), 53.3 (OCH_3α, OCH_3β) ppm.

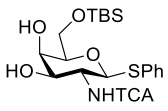
Methyl 2,3,4-tri-*O*-benzoyl-1-*O*-(2,2,2-trichloroacetimidoyl)-α/β-D-glucopyranosyl uronate (10)



Anomeric alcohol **9** (1.1 g, 1.8 mmol, 1.0 eq.) was dissolved in anhydrous DCM (18 mL, 0.1 M). Trichloroacetonitrile (1.8 mL, 18 mmol, 10 eq.) was added and the mixture was cooled to 0°C before slow addition of DBU (80 µL, 0.54 mmol, 0.3 eq.). The reaction was stirred under N_2-atmosphere while slowly warming to room temperature turning it into a dark brown solution. After 30 minutes TLC analysis showed complete consumption of the starting material. The reaction was concentrated *in vacuo* to obtain the crude as a

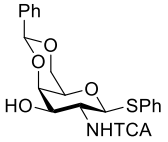
dark brown oil. The crude was purified by silica gel column chromatography (DCM:Et_2O, 9:1 → 1:1) to obtain the product as a yellow foam in 88% yield (1.1 g, 1.6 mmol). α/β ratio 29/1 ^{1}H NMR of the α-product (CD_3CN, 400 MHz) δ: 9.15 (s, 1H, $NHCCl_3$), 7.99 – 7.81 (m, 6H, arom.), 7.63 – 7.31 (m, 9H, arom.), 6.84 (d, 1H, *J*=3.8Hz, H-1), 6.20 (t, 1H, *J*=9.8 Hz, H-3), 5.83 (t, 1H, *J*=9.8, 1.7 Hz, H-4), 5.75 (dd, 1H, *J*=10.1, 3.5, 1.6 Hz, H-2), 4.80 (d, 1H, H-5), 3.61 (s, 3H, OCH_3) ppm. ^{13}C-APT NMR (CD_3CN, 101 MHz) δ: 168.2 (C=O, CO_2Me), 166.4, 166.0 (C=O, Bz), 160.5 (C=NH), 134.8, 130.4, 129.8, 129.7, 129.6 (arom.), 93.7 (C-1), 71.6 (C-5), 70.8 (C-3), 70.3 (C-2, C-4), 53.6 (OCH_3) ppm.

Phenyl 2-deoxy-6-*O*-(*tert*-butyldimethylsilyl)-1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranose (12)



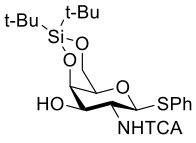
Triol **11** (0.2 g, 0.5 mmol, 1.0 eq.) was dissolved in anhydrous pyridine (5 mL, 0.1 M). TBS-Cl (50%wt in toluene, 1.5 mL, 0.8 mmol, 1.6 eq.) was added slowly to the reaction and the mixture was cooled to -30°C. Et_3N (0.8 mL, 0.6 mmol, 1.1 eq.) was added slowly over the course of 5 minutes. The reaction was allowed to warm to room temperature and stirred overnight under N_2-atmosphere. TLC analysis showed full conversion and the reaction mixture was diluted in methylene chloride. The mixture was poured into ice-cold water and the layers were separated. The aqueous layer was extracted four times with CH_2Cl_2. The organic layers were combined, filtered over Celite® and washed with sat. $NaHCO_3$ (aq.) and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was obtained as a brown oil and purified by silica gel column chromatography (PE:EtOAc, 1:1 → 0:1) to obtain the product as a white solid (0.19 g, 0.35 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 – 7.45 (m, 2H, arom.), 7.35 – 7.24 (m, 3H, arom.), 7.20 (d, 1H, *J*=7.6 Hz, NH), 4.94 (d, 1H, *J*=9.6 Hz, H-1), 4.09 (s, 1H, H-5), 4.01 – 3.82 (m, 5H, H-2, H-3, H-4, H-6), 3.73 (s, 1H, OH), 3.56 (t, 1H, OH), 0.91 (s, 9H, *t*-Bu, TBS), 0.10 (s, 3H, CH_3, TBS), 0.9 (s, 3H, CH_3, TBS) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ: 162.8 (C=O, TCA), 132.9, 132.5, 129.1, 128.06 (arom.), 92.5 (CCl3, TCA), 86.2 (C-1), 78.2 (C-3), 72.2 (C-4), 69.6 (C-5), 63.8 (C-6), 54.3 (C-2), 26.0 (*t*-Bu, TBS), 18.3 (C_q, TBS), -5.3 (CH_3, TBS) ppm.

Phenyl 4,6-*O*-benzylidene-2-deoxy-1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranose. (13)



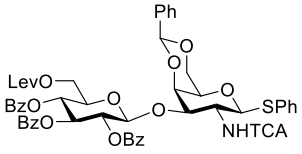
The synthesis and characterization of this compound are described in Chapter 2 compound **3**.

Phenyl 2-deoxy-4,6-*O*-(di-*tert*-butylsilyl)-1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranose (14)



Galactopyranose **11** (5.0 g, 12.0 mmol, 1.0 eq.) was co-evaporate twice with anhydrous toluene and dissolved in anhydrous DMF (100 mL, 0.12 M). Activated molecular sieves (4Å) were added and the mixture was stirred one hour under argon gas while cooling to -10°C. Di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (6.0 mL, 18 mmol, 1.5 eq.) was added and the mixture stirred for 3 hours at -10°C under argon gas before TLC analysis indicated full conversion and the reaction was quenched by addition of water (50 mL). The reaction was diluted in Et_2O and the layers separated. The organic layer was washed with twice with water and five times with brine. The organic layer was dried over $MgSO_4$ and filtered before evaporation *in vacuo* to obtain crude silylidene as an orange oil. The crude was purified by silica gel column chromatography (DCM:Et_2O, 99:1 → 7:3) to obtain the product as a white foam in 92% yield (6.2 g, 11.0 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49 – 7.42 (m, 2H, arom.), 7.29 – 7.23 (m, 3H, arom.), 7.10 (d, 1H, *J*=8.9 Hz, NHTCA), 4.88 (d, 1H, *J*=10.5 Hz, H-1), 4.43 (d, 1H, *J*=3.3 Hz, H-4), 4.23 (s, 2H, H-6), 4.09 (q, 1H, *J*=10.0 Hz, H-2), 3.84 (t, 1H, *J*=10.6, 3.2 Hz, H-3), 3.49 (t, 1H, *J*=1.5 Hz, H-5), 2.95 (d, 1H, *J*=11.1 Hz, OH), 1.08 (s, 9H, *t*-Bu, DTBS) 1.04 (s, 9H, *t*-Bu, DTBS) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ: 162.4 (C=O, TCA), 133.6, 132.2, 129.0, 127.8 (arom.), 92.6 (CCl_3, TCA), 86.7 (C-1), 75.0 (C-5), 72.1 (C-3, C-4), 67.0 (C-6), 54.3 (C-2), 27.5 (*t*-Bu, DTBS), 23.3 (C_q, DTBS), 20.7 (C_q, DTBS) ppm.

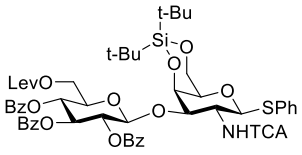
Phenyl 4,6-*O*-benzylidene-3-*O*-(2,3,4-tri-*O*-benzoyl-6-*O*-levulinoyl-β-D-glucopyranose)-2-deoxy-1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranose (15)



Acceptor **13** (0.051 g, 0.10 mmol, 1.0 eq.) and donor **7** (0.080 g, 0.15 mmol, 1.5 eq.) were co-evaporated thrice with anhydrous toluene before dissolving in anhydrous DCM (1 mL, 0.1 M). Activated molecular sieves (4Å) were added and the reaction stirred 1 hour under inert atmosphere at room temperature. The reaction was cooled to 0˚C and TMSOTf (0.1 M solution in dry DCM, 0.1 mL, 0.01 mmol, 0.1 eq.) was added. The reaction was stirred as an orange solution at 0°C under N_2 atmosphere. After 5 hours TLC analysis and TLC-MS analysis showed consumption of the starting material and the reaction was quenched by adding Et_3N (0.1 mL) to the solution. The mixture was diluted in EtOAc and the organic layer was washed with sat. $NaHCO_3$ (aq.) and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to obtain the crude as a colourless oil. The crude was purified by size exclusion chromatography (DCM:MeOH, 1:1) to obtain the product as a colourless oil in 31% yield (0.031 g, 0.031 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 – 7.73 (m, 10H, arom.), 7.64 – 7.60 (m, 2H, arom.), 7.54 – 7.21 (m, 21H, arom, NH), 5.74 (t, 1H, *J*=9.6 Hz, H-3'), 5.61 – 5.42 (m, 3H, H-2', H-4', PhCH), 5.28 (d, 1H, *J*=10.1 Hz, H-1), 5.19 (d, 1H, *J*=7.9 Hz, H-1'), 4.81 (dd, 1H, *J*=10.8, 3.3 Hz, H-3), 4.64 (dd, 1H, *J*=12.2, 2.1 Hz, H-6), 4.52 (d, 1H, *J*=3.3 Hz, H-4), 4.38 – 4.30 (m, 2H, H-5', H-6'), 4.12 – 3.95

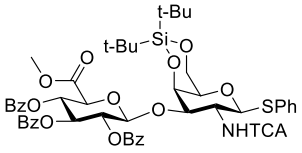
(m, 3H, H-2, H-6, H-6'), 3.62 (s, 1H, H-5), 2.95 – 2.49 (m, 4H, CH_2, Lev), 2.25 (s, 3H, CH_3, Lev) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ: 172.3 (C=O, COMe), 165.7, 165.5, 165.3 (C=O, Bz, Lev), 161.8 (C=O, TCA), 138.0, 137.9, 132.1, 129.9, 129.2, 129.0, 128.8, 128.7, 128.6, 128.5, 128.5, 128.4, 128.4, 126.4 (arom.), 100.8 (PhCH), 99.7 (C-1'), 84.6 (C-1), 75.7 (C-4), 73.7 (C-3), 73.1 (C-3'), 72.7 (C-5'), 71.6 (C-2'), 70.3 (C-5) , 69.4 (C-6'), 68.7 (C-4'), 62.2 (C-6), 52.2 (C-2), 38.3 (CH_2, Lev), 29.9 (CH_3 Lev), 28.5 (CH_2, Lev) ppm.

Phenyl 2-deoxy-3-*O*-(2,3,4-tri-*O*-benzoyl-6-*O*-levulinoyl-β-D-glucopyranose)-4,6-*O*-(di-*tert*-butylsilyl)-1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranose (16)



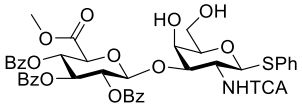
Acceptor **14** (0.056 g, 0.1 mmol, 1.0 eq.) and donor **7** (0.11 g, 0.15 mmol, 1.5 eq.) were co-evaporated thrice with anhydrous toluene before dissolving in anhydrous DCM (1 mL, 0.1 M). Freshly activated molecular sieves (3Å) were added and the reaction stirred for 1 hour under inert atmosphere at room temperature. The reaction was cooled to 0˚C and TMSOTf (0.1 M solution in anhydrous CH_2Cl_2, 0.1 mL, 0.01 mmol, 0.1 eq.) was added after 20 min. The reaction was stirred as an orange solution at 0°C under argon atmosphere. After 35 minutes TLC analysis and TLC-MS showed consumption of acceptor **14** and the reaction was quenched by addition of sat. $NaHCO_3$ (aq.) to the solution. The mixture was diluted in EtOAc and the organic layer was washed with sat. $NaHCO_3$ (aq.) and brine. The organic layer was dried over $MgSO_4$ filtered and the organic layer was evaporated *in vacuo* to obtain the crude as a colourless oil. The crude was purified by size exclusion chromatography (DCM/MeOH, 1/1, v/v) to obtain the product as a colourless oil in 58% yield (0.066 g, 0.058 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 – 7.89 (m, 4H, arom.), 7.78 – 7.75 (m, 2H, arom.), 7.61 – 7.33 (m, 7H, arom.), 7.28 – 7.23 (m, 7H, arom.), 5.75 (t, 1H, *J*=9.7 Hz, H-3'), 5.55 (t, 1H, *J*=9.7, Hz, H-2'), 5.47 – 5.37 (m, 2H, H-1', H-4'), 5.24 (d, 1H, *J*=10.3 Hz, H-1), 4.69 (d, 1H, *J*=2.6 Hz, H-4), 4.63 – 4.54 (m, 2H, H-3, H-6'), 4.30 – 4.18 (m, 3H, H-2, H-6), 4.12 (dd, 1H, *J*=12.1, 6.6 Hz, H-6'), 4.02 (ddd, 1H, *J*=9.0, 6.6, 2.1 Hz, H-5), 3.49 (d, *J*=5.3 Hz, 1H, H-5'), 2.84 – 2.79 (m, 2H, CH_2, Lev), 2.64 – 2.47 (m, 2H, CH_2, Lev), 2.18 (s, 3H, CH_3, Lev), 1.10 (s, 9H, *t*-Bu, DTBS), 0.99 (s, 9H, *t*-Bu, DTBS) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ: 172.4 (C=O, C=OMe), 165.7, 165.5, 165.4, 161.9 (C=O, Bz, Lev, TCA), 134.4, 133.8, 133.4, 132.7, 130.2, 130.1, 130.0, 129.8, 129.1, 129.0, 128.8, 128.7, 128.6, 128.4, 127.8 (arom.), 99.6 (C-1'), 87.0 (C-1), 75.2 (C-5), 75.0 (C-3), 73.5 (C-4), 73.1 (C-3'), 72.7 (C-5'), 71.7 (C-2'), 69.3 (C-4'), 67.4 (C-6), 63.0 (C-6'), 52.9 (C-2), 38.2 (CH_2, Lev), 29.9 (CH_3, Lev), 28.3 (CH_2, Lev), 27.8 (*t*-Bu, DTBS), 27.6 (*t*-Bu, DTBS), 23.4 (C_q, DTBS), 20.8 (C_q, DTBS) ppm.

Phenyl 2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl uronate)-4,6-*O*-(di-*tert*-butylsilyl)-2-(2,2,2-trichloroacetamido)-1-thio-β-D-galactopyranose (18)



Acceptor **14** (0.56 g, 1.0 mmol, 1.0 eq.) and donor **10** (1.0 g, 1.5 mmol, 1.5 eq.) were co-evaporated thrice with anhydrous toluene before dissolving in anhydrous DCM (10 mL, 0.1 M). Activated molecular sieves (3Å) were added and the mixture stirred 1 hour under inert atmosphere. TMSOTf (0.1M in anhydrous DCM, 3.0 mL, 0.3 mmol, 0.3 eq.) was added and the mixture stirred for 30 minutes before TLC analysis indicated full consumption of the acceptor. The reaction was quenched by adding sat. aq. $NaHCO_3$ (aq.) to the reaction mixture. The mixture was diluted with EtOAc and the layers were separated. The organic layer washed with sat. $NaHCO_3$ (aq.) and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to obtain crude **18** as a yellow oil. The crude was purified by silica gel column chromatography (toluene/acetone, 19:1 → 1:1) and size exclusion chromatography (MeOH:DCM, 1:1) to obtain the product as a pale yellow solid in 84% yield (0.84 mmol, 0.89 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 – 7.89 (m, 4H, arom.), 7.85 – 7.79 (m, 2H, arom.), 7.63 – 7.21 (m, 14H, arom.), 5.83 (t, 1H, *J*=9.2 Hz, H-3'), 5.62 (t, 1H, *J*=9.5 Hz, H-4'), 5.58 – 5.48 (m, 2H, H-1', H-2'), 5.43 (d, 1H, *J*=10.2 Hz, H-1), 4.76 (d, 1H, *J*=2.7 Hz, H-4), 4.57 (dd, 1H, *J*=10.7, 2.7 Hz, H-3), 4.28 (d, 1H, *J*=9.7 Hz, H-5'), 4.21 (s, 2H, H-6), 3.99 (q, 1H, *J*=10.5, 6.9 Hz, 1H, H-2), 3.68 (s, 3H, OCH_3), 3.46 (s, 1H, H-5), 1.11 (s, 9H, *t*-Bu, DTBS), 1.03 (s, 9H, *t*-Bu, DTBS) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ: 167.2 (C=O, CO_2Me), 165.7, 165.4, 165.1 (C=O, Bz), 162.1 (C=O, TCA), 133.5, 133.4, 133.1, 130.1, 129.9, 128.8, 128.7, 128.5, 128.1 (arom.), 100.1 (C-1'), 85.6 (C-1), 75.9 (C-3), 75.3 (C-5), 73.6 (C-4), 72.6 (C-3'), 72.5 (C-5'), 71.9 (C-2'), 70.0 (C-4'), 67.4 (C-6), 53.9 (C-2), 53.2 (OCH_3), 27.8 (*t*-Bu, DTBS), 23.4 (C_q, DTBS), 20.8 (C_q, DTBS) ppm.

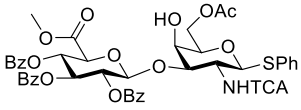
Phenyl 2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl uronate)-2-(2,2,2-trichloroacetamido)-1-thio-β-D-galactopyranose (19)



Disaccharide **18** (6.5 mmol, 6.9 g, 1.0 eq.) was dissolved in THF (65 mL, 0.1 M). HF·pyridine (26.1 mmol, 2.4 mL, 4.0 eq.) was slowly added and the solution was stirred for 4 hours at which point TLC analysis showed full consumption of the starting material. The reaction mixture was diluted in EtOAc and treated with $CaCO_3$ (36 mmol, 3.6 g, 6.0 eq.) until the evolution of gas ceased. The organic layer was washed with 10% NaCl (aq.), dried over $MgSO_4$, filtered and evaporated *in vacuo* to obtain crude **19** as a yellow solid. The crude was purified by silica gel column chromatography (toluene: acetone 9:1 → 1:1) to obtain the product as a white solid in 75% yield (4.9 mmol, 4.5 g). ^{1}H NMR (400 MHz, CD_3CN) δ: 7.92 – 7.85 (m, 4H), 7.78 – 7.73 (m, 2H), 7.63 – 7.23 (m, 14H), 5.93 (t, 1H, *J*=9.4 Hz, H-3'), 5.62 (t, 1H, *J*=10Hz, H-4'), 5.53 (dd, 1H, *J*=9.4, 7.7 Hz, H-2'), 5.25 (d, 1H, *J*=7.7 Hz, H-1'), 4.96 (d, 1H, *J*=10.3 Hz, H-1), 4.58 (d, 1H, *J*=9.9 Hz, H-5'), 4.26 (t, 1H, *J*=3.3 Hz, H-4), 4.16 (dd, 1H, *J*=10.4, 3.0 Hz, H-3), 4.05 (m, 1H, H-2), 3.79 – 3.67 (m, 2H, H-6), 3.65 – 3.58 (m, 4H, H-5', OCH_3), 3.47 (d, 1H, *J*=3.9,

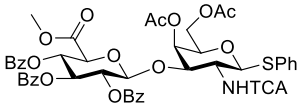
1.1 Hz, 4-OH), 3.05 (t, 1H, *J*=6.0 Hz, 6-OH) ppm. ^{13}C-APT NMR (CD_3CN, 101 MHz) δ: 168.6 (C=O, CO_2Me), 166.2, 166.1, 165.8 (C=O, Bz), 162.6 (C=O, TCA), 135.0, 134.8, 132.0, 130.7, 130.2, 130.0, 130.0, 129.8, 129.5, 129.4, 128.3 (arom.), 101.2 (C-1'), 87.4 (C-1), 80.9 (C-3), 79.6 (C-5), 73.7 (C-3'), 72.7 (C-2'), 72.6 (C-5'), 70.9 (C-4'), 68.7 (C-4), 62.4 (C-6), 53.5 (OCH_3), 52.5 (C-2) ppm. HRMS: $[M+Na]^+$ calculated for $[C_{42}H_{38}Cl_3NO_{14}SNa]^+$: 940.0976, found 940.0992.

Phenyl 6-*O*-acetyl-2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl uronate)-1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranose (21)



Diol **19** (0.92 g, 1.0 mmol, 1.0 eq.) and NaOAc (0.05 g, 0.6 mmol, 0.6 eq.) were suspended in Ac_2O (10 mL, 0.1 M) and the white suspension was warmed to 50°C. After 1.5 hours TLC analysis showed full consumption of the starting material. The reaction was quenched by adding solid $NaHCO_3$ and the mixture was diluted in EtOAc and washed with sat. $NaHCO_3$ (aq.) followed by brine. The crude was obtained as a yellow oil and purified by silica gel column chromatography (toluene:MeCN, 9:1 → 4:1). The product was obtained as a white solid in 92% yield (0.88 g, 0.92 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 – 7.77 (m, 6H, arom.), 7.67 – 7.33 (m, 9H, arom.), 7.31 – 7.27 (m, 5H, arom.), 6.92 (d, 1H, *J*=7.3 Hz, NH), 5.85 (t, 1H, *J*=8.9 Hz, H-3'), 5.69 (t, 1H, *J*=9.1 Hz, H-4'), 5.53 (dd, 1H, *J*=8.8, 6.8 Hz, H-2'), 5.31 (d, 1H, *J*=12.5 Hz, H-1), 5.11 (d, 1H, *J*=6.9 Hz, H-1'), 4.61 (dd, 1H, *J*=10.3, 3.0 Hz, H-3), 4.39 (m, 3H, H-5', H-6), 4.29 (d, 1H, *J*=2.9 Hz, H-4), 3.83 (t, 1H, *J*=6.3 Hz, H-5), 3.80 – 3.70 (m, 1H, H-2), 3.66 (s, 3H, OCH_3), 3.47 (s, 1H, OH), 2.07 (s, 3H, CH_3, Ac) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ: 171.0, 167.6, 165.6, 165.3, 165.2, 162.0 (C=O, Ac, Bz, CO_2Me, TCA), 133.7, 132.8, 132.5, 130.1, 129.9, 129.1, 128.7, 128.5 (arom.), 100.9 (C-1'), 84.3 (C-1), 78.4 (C-3), 76.0 (C-5), 72.5 (C-5'), 71.7 (C-4'), 71.6 (C-3'), 69.5 (C-2'), 68.1 (C-4), 63.8 (C-6), 53.2 (C-2, OCH_3, Me), 21.0 (CH_3, Ac) ppm.

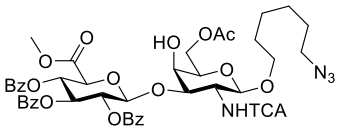
Phenyl 4,6-di-*O*-acetyl-2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl uronate)-1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranose (22)



Diol **19** (0.09 g, 0.1 mmol, 1.0 eq.) and NaOAc (0.025 g, 0.3 mmol, 0.3 eq.) were dissolved in Ac_2O (1 mL, 0.1 M) and the solution warmed to 50°C. After two hours to mixture was warmed to 110°C. After one additional hour TLC analysis indicated full conversion and the reaction was quenched with sat. $NaHCO_3$ (aq.). The mixture was diluted in EtOAc and the layers separated. The organic layer was washed three times with sat. $NaHCO_3$ (aq.) and twice with brine. The organic layer was dried over $MgSO_4$ evaporated *in vacuo* to obtain the crude as a yellow oil. The crude was purified silica gel column chromatography (tol:MeCN, 9:1 → 3:2) to obtain the product as a white solid in 82% yield (0.082 g, 0.082 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 – 7.77 (m, 6H, arom.), 7.56 – 7.25 (m, 16H, arom.), 6.80 (d, 1H, *J*=7.2 Hz, NH), 5.79 (t, 1H, *J*=9.4 Hz, H-3'), 5.67 (t, 1H, *J*=9.6 Hz, H-4'), 5.59 (d, 1H, *J*=3.3 Hz, 1H, H-4), 5.45 (dd, 1H, *J*=9.4, 7.5 Hz,

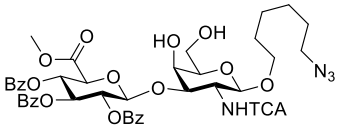
H-2), 5.31 (d, 1H, *J*=10.4 Hz, H-1), 4.99 (d, 1H, *J*=7.5 Hz, H-1'), 4.76 (dd, 1H, *J*=10.4, 3.3 Hz, H-3), 4.29 (d, 1H, *J*=9.7 Hz, H-5'), 4.23 – 4.04 (m, 2H, H-6), 3.95 (dd, 1H, *J*=7.3, 6.2 Hz, H-5), 3.70 (s, 3H, OCH_3), 3.64 (q, 1H, *J*=10.4, 7.1 Hz, H-2), 2.13 (s, 3H, CH_3, Ac), 2.07 (s, 3H, CH_3, Ac) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ: 172.6, 171.6 (C=O, Ac) 169.9, 166.9, 165.6 (C=O, Bz, CO_2Me), 162.0 (C=O, TCA), 133.6, 133.5, 133.1, 132.0, 130.0, 129.9, 129.9, 129.9, 129.1, 129.0, 128.7, 128.6, 128.4 (arom.), 100.4 (C-1'), 84.4 (C-1), 75.4 (C-5), 74.2 (C-3), 72.9 (C-5'), 72.2 (C-3'), 71.8 (C-2'), 69.9 (C-4'), 69.0 (C-4), 62.7 (C-6), 54.2 (C-2), 53.0 (OCH_3), 20.9 (CH_3, Ac), 20.8 (CH_3, Ac) ppm.

6-azidohexyl 6-*O*-acetyl-2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl uronate)-2-(2,2,2-trichloroacetamido)-β-D-galactopyranose (23)



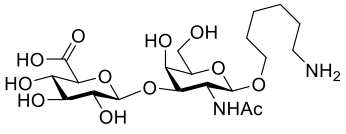
Donor **21** (0.35 g, 0.36 mmol, 1.0 eq.) and 6-azidohexan-1-ol (0.06 g, 0.4 mmol, 1.1 eq.) were co-evaporated with anhydrous toluene thrice and dissolved in anhydrous DCM (3.6 mL, 0.1 M). Activated molecular sieves (3Å) were added and the mixture was stirred for 1 hour at room temperature under inert atmosphere. NIS (0.08 g, 0.36 mmol, 1.0 eq.) was added and the reaction was cooled to -40°C and stirred for an additional 30 min. TfOH (0.1 M in anhydrous DCM, 0.3 mL, 0.03 mmol, 0.08 eq.) was added and the reaction was left to stir as a dark red solution at -40°C. After 30 minutes TLC analysis indicated that the starting material was completely consumed. The reaction was quenched by addition of sat. $NaHCO_3$ (aq.) and diluting the mixture in EtOAc. The organic layer was washed with sat. $Na_2S_2O_3$ (aq.), sat. $NaHCO_3$ (aq.) and brine. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to obtain crude **23** as a dark yellow oil. The crude was purified by size exclusion chromatography (DCM:MeOH, 1:1) to obtain the product as a colourless oil in 56% yield (0.2 g, 0.2 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ:=7.92 (ddd, 3H, *J*=10.8, 8.4, 1.4 Hz, arom), 7.84 – 7.78 (m, 2H, arom.), 7.59 – 7.21 (m, 10H, arom.), 6.95 (d, 1H, *J*=6.8 Hz, NH), 5.87 (t, 1H, *J*=9.1 Hz, H-3'), 5.70 (t, 1H, *J*=9.3 Hz, H-4'), 5.57 (dd, 1H, *J*=9.0, 7.1 Hz, H-2'), 5.11 (d, 1H, *J*=7.1 Hz, H-1'), 4.95 (d, 1H, *J*=8.3 Hz, H-1), 4.66 (dd, 1H, *J*=10.7, 3.2 Hz, H-3), 4.45 – 4.36 (m, 3H, H-6, H-5'), 4.25 (d, 1H, *J*=3.3 Hz, H-4), 3.86 (qd, 1H, *J*=6.3, 3.1 Hz, OCH_2), 3.79 (t, 1H, *J*=6.4 Hz, H-5), 3.74 – 3.64 (m, 4H, OCH_3, OH), 3.58 (ddd, 1H, *J*=10.7, 8.2, 6.7 Hz, H-2), 3.52 – 3.40 (m, 1H, OCH_2), 3.22 (t, 2H, *J*=6.9 Hz, CH_2N_3), 2.09 (s, 3H, CH_3, Ac), 1.60 – 1.46 (m, 4H, CH_2-hexyl), 1.36 – 1.28 (m, 4H, CH_2-Hexyl) ppm. ^{13}C-APT NMR (101 MHz, $CDCl_3$) δ: 171.0 (C=O, CO_2Me), 167.5 (C=O, Ac), 165.6, 165.3, 165.1 (C=O, Bz), 162.3 (C=O, TCA), 133.7, 133.6, 130.1, 129.9, 129.8, 128.6, 128.6, 128.5, 128.4 (arom.), 101.0 (C-1'), 98.4 (C-1), 92.1 (C_q, TCA), 77.2 (C-3), 72.4 (C-5'), 71.8 (C-5), 71.7 (C-3'), 71.6 (C-2'), 69.9 (OCH_2), 69.7 (C-4'), 68.0 (C-4), 63.3 (C-6), 55.6 (C-2), 53.2 (OCH_3), 51.4 (CH_2N_3), 29.5, 28.8, 26.5, 25.6 (CH_2, hexyl), 20.9 (CH_3, Ac) ppm.

6-azidohexyl 2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl uronate)-2-(2,2,2-trichloroacetamido)-β-D-galactopyranose (24)



Disaccharide **23** (0.2 g, 0.2 mmol, 1.0 eq.) was dissolved in anhydrous DCM (2 mL, 0.1 M) and the mixture was cooled to 0°C. Acetyl chloride (0.1 M in anhydrous MeOH, 2 mL, 0.2 mmol, 1.0 eq.) was added and the reaction was stirred under inert atmosphere at 4°C for 6 days until TLC analysis showed full conversion of the starting material. The mixture was concentrated *in vacuo* and adsorbed on silica. The crude was purified by silica gel column chromatography (DCM:MeOH, 99:1 → 0:1) and recrystallized from EtOH to obtain **24** as colourless solid in 88% yield (0.16 g, 0.18 mmol). ^{1}H NMR (CD_3CN, 500 MHz): δ:=7.93 (ddd, 1H, *J*=8.5, 5.2, 1.3 Hz, arom.), 7.90 – 7.86 (m, 2H, arom.), 7.86 – 7.82 (m, 2H, arom), 7.76 – 7.71 (m, 2H, arom), 7.65 – 7.27 (m, 10H, arom., NH), 5.89 (t, 1H, *J*=9.4 Hz, H-3'), 5.60 (t, 1H, *J*=9.7 Hz, H-4'), 5.49 (dd, 1H, *J*=9.4, 7.7 Hz, H-2'), 5.21 (d, 1H, *J*=7.7 Hz, H-1'), 4.55 (d, 1H, *J*=9.9 Hz, H-5'), 4.48 (d, 1H, *J*=8.4 Hz, H-1), 4.20 – 4.14 (m, 1H, H-4), 4.07 (dd, 1H, *J*=10.9, 3.1 Hz, H-3), 3.85 (dt, 1H, *J*=11.1, 9.0 Hz, H-2), 3.75 (dt, 1H, *J*=9.7, 6.3 Hz, OCH_2), 3.73 – 3.63 (m, 2H, H-6), 3.59 (s, 3H, OCH_3), 3.49 (ddd, 1H, *J*=6.5, 5.2, 1.2 Hz, H-5), 3.40 (dt, 1H, *J*=9.9, 6.5 Hz, OCH_2), 3.31 (s, 1H, OH), 3.21 (t, 2H, *J*=6.9 Hz, CH_2N_3), 1.54 – 1.40 (m, 4H, CH_2-hexyl), 1.32 – 1.19 (m, 4H, CH_2-hexyl) ppm. ^{13}C-APT NMR (CD_3CN, 101 MHz) δ: 168.5 (C=O, CO_2Me), 166.2, 166.1, 165.8 (C=O, Bz), 162.8 (C=O, TCA), 134.7, 134.6, 134.4, 134.0, 130.8, 130.7, 130.4, 130.3, 130.2, 130.1, 130.0, 129.8, 129.7, 129.6, 129.5, 129.5, 129.4 (arom.), 101.5 (C-1'), 101.1 (C-1), 93.4 (C_q, TCA), 80.1 (C-3), 75.4 (C-5), 73.7 (C-3'), 72.6 (C-5'), 72.5 (C-2'), 70.8 (C-4'), 70.0 (OCH_2), 68.5 (C-4), 62.2 (C-6), 54.1 (C-2), 53.4 (OCH_3), 52.0 (CH_2N_3), 30.1, 29.3, 27.1, 26.2 (CH_2, hexyl) ppm.

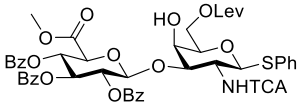
6-aminohexyl 2-acetamido-2-deoxy-3-*O*-(β-D-glucopyrano iduronic acid)-β-D-galactopyranose (28)



Compound **23** (14.2 mg, 15 µmol) was dissolved in a mixture of water and 1,4-dioxane (1:1, 2 mL, 0.01 M) and 1M NaOH (aq.) was added to the mixture until pH 13 was reached. The solution was stirred for 3 days under inert atmosphere at room temperature until LCMS analysis indicated full consumption of the starting material. The mixture was diluted in MeOH (1 mL) and quenched by slow addition of solid CO_2 until pH 7 was reached. The solvents were evaporated *in vacuo* to obtain the crude as a white solid. The crude was purified by size exclusion chromatography (MeOH:H_2O, 9:1) LCMS: $[M+H]^+$ calculated for $[C_{18}H_{32}N_4O_{11}H]^+$: 481.21, found 481.07. The deprotected disaccharide was dissolved in anhydrous MeOH (1.0 mL) and Ac_2O (0.1 mL) was added. The mixture was stirred for 3 hours until LCMS indicated full consumption of the starting material. The solvents were evaporated *in vacuo* and the crude **27** was dissolved in 0.1M NaOH (aq.) (10 mL) and stirred at room temperature. After 30 minutes the solvents were evaporated *in vacuo* and the product was co-evaporated (2x) with D_2O. ^{1}H NMR (D_2O, 400 MHz) δ: 4.51 (2x d,

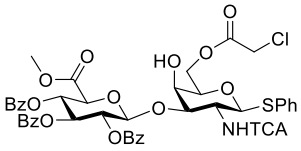
2H, *J*=11.4, 8.2 Hz, H-1, H-1'), 4.18 (d, 1H, *J*=3.2 Hz, H-4), 4.06 – 3.56 (m, 8H, H-2, H-2', H-3, H-3', H-4, H-5', H-6), 3.50 (t, 2H, *J*=8.8 Hz, OCH_2), 3.34 (t, 3H, *J*=6.9 Hz, H-5, CH_2N_3), 2.04 (s, 3H, CH_3, Ac), 1.68 – 1.53 (m, 4H, CH_2-hexyl), 1.39 – 1.36 (m, 6H, CH_2-hexyl). ESI-MS: $[M+H]^+$ calculated for $[C_{20}H_{34}N_4O_{12}H]^+$: 523.23, found 523.00. Compound **27** was dissolved in water (1.0 mL) and the round-bottom flask was purged with N_2-gas. Pd/C (5 mg) was added and the round-bottom flask purged with H_2-gas. Glacial AcOH (0.05 mL) was added and the reaction stirred one hour before LCMS and IR-spectroscopy confirmed full conversion. The round-bottom flask was purged with N_2-gas and the black suspension filtered over Celite® with milliQ water. The crude was purified by size exclusion chromatography (HW-40 gel, H_2O with NH_4HCO_3) and the product was lyophilized to obtain the product as a white solid in 33% yield over 3 steps (5 µmol, 2.7 mg). ^{1}H NMR (D_2O, 400 MHz) δ: 4.54 (dd, *J*=12.7, 8.2 Hz, 2H, H-1, H-1'), 4.21 (d, *J*=3.1 Hz, 1H, H-4), 4.08 – 3.46 (m, 11H, H-2, H-2', H-3, H-3', H-4, H-5, H-5', H-6, OH), 3.37 (td, *J*=7.4, 2.5 Hz, 1H, OCH_2), 3.05 – 2.98 (m, 2H, CH_2N_3), 2.11 (s, 3H, CH_3, Ac), 1.74 – 1.57 (m, 4H, CH_2, hexyl), 1.41 (t, *J*=3.6 Hz, 5H, C*H*$_2$, hexyl) ppm. ESI-MS: $[M+H]^+$ calculated for $[C_{20}H_{36}N_2O_{12}H]^+$: 497.23, found 497.17.

Phenyl 2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl uronate)-6-*O*-levulinoyl-1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranose (29)



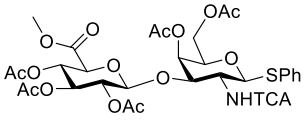
Diol **19** (0.92 g, 1 mmol, 1.0 eq.) was dissolved in a mixture of anhydrous DCM/ACN (10 mL, 9/1, 0.1M) and cooled to 0°C. DMAP (0.15 g, 1.2 mmol, 1.2 eq.), EDC·HCl (0.25 g, 1.3 mmol, 1.3 eq.) and levulinic acid (0.11 mL, 1.1 mmol, 1.1 eq.) were added. The reaction was stirred for 48 hours and stopped by addition of sat. $NaHCO_3$ (aq.). The mixture was diluted in DCM and washed with sat. $NaHCO_3$ (aq.), 1M HCl (aq.) and brine. The organic layer was dried over $MgSO_4$ filtered and the solvents evaporated *in vacuo* to obtain the crude as dark brown oil. The crude was purified by silica gel column chromatography (tol:DCM:Et_2O:CH_3CN, 3:5:1:1) to obtain the product as a yellow oil in 38% yield (0.039 g, 0.38 mmol). ^{1}H NMR (CD_3CN, 400 MHz) δ: 7.92 – 7.73 (m, 6H, arom.), 7.62 – 7.27 (m, 14H, arom.), 5.95 (t, 1H, *J*=9.4 Hz, H-3'), 5.63 (t, 1H, *J*=9.5 Hz, H-4'), 5.59 – 5.53 (m, 1H, H-2'), 5.27 (d, 1H, *J*=7.7 Hz, H-1'), 4.98 (dd, 1H, *J*=10.5, 2.9 Hz, H-1), 4.60 (d, 1H, *J*=9.9 Hz, H-5'), 4.28 (m, 2H, H-6), 4.23 – 3.92 (m, 2H, H-2, H-3), 3.87 – 3.77 (m, 1H, H-5), 3.56 (s, 3H, OCH_3), 3.54 – 3.47 (m, 1H, OH), 2.73 (m 2H, CH_2, Lev), 2.50 (m, 2H, CH_2, Lev), 2.11 (s, 3H, CH_3, Lev). ^{13}C-APT NMR (CD_3CN, 101 MHz) δ: 173.4 (C=O, CO_2Me), 168.5, 165.9, 165.8, 162.7 (C=O, Bz, CO_2Me, Lev), 134.9, 134.4, 130.7, 130.3, 130.2, 130.0, 129.8, 129.7, 129.5 (arom.), 101.1 (C-1'), 87.2 (C-1), 80.5 (C-3), 76.8 (C-5), 73.7 (C-3'), 72.6, 72.5 (C-2', C-5'), 70.8 (C-4'), 68.4 (C-4), 64.5 (C-6), 53.5 (OCH_3), 52.3 (C-2), 38.4 (CH_2, Lev), 29.9 (CH_3, Lev), 28.6 (CH_2, Lev) ppm. HRMS: $[M+Na]^+$ calculated for $[C_{47}H_{44}Cl_3NO_{16}SNa]^+$: 1038.1344, found 1038.1350.

Phenyl 6-*O*-(2-chloroacetyl)-2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyluronate)- 1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranose (30)



Compound **19** (0.092 g, 0.1 mmol, 1.0 eq.) was dissolved in a mixture of anhydrous 1,2-dichloroethane and anhydrous pyridine (9:1, 1.0 mL, 0.1M). Chloroacetyl chloride (0.01 mL, 0.12 mmol, 1.2 eq.) was added and the reaction stirred under inert atmosphere. After two hours additional chloroacetyl chloride (6 µL, 0.8 mmol, 0.8 eq.) was added and stirred for an additional 1.5 hours before the reaction was diluted in EtOAc. The organic layer was washed with 1M HCl (aq.), sat. $NaHCO_3$ (aq.), and brine. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to obtain the crude as yellow oil. The crude was purified by silica gel column chromatography (toluene:CH_3CN, 99:1 → 3:1) to obtain the product as a yellow oil in 48% yield (0.48 g, 0.048 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.03 – 7.81 (m, 6H, arom.), 7.59 – 7.30 (m, 14H, arom.), 6.94 (d, 1H, *J*=7.1 Hz, NH 5.88 (t, 1H, *J*=8.9 Hz, H-3'), 5.71 (t, 1H, *J*=9.1 Hz, H-4'), 5.55 (dd, 1H, *J*=8.7, 6.8 Hz, H-2'), 5.35 (d, 1H, *J*=10.3 Hz, H-1), 5.12 (d, 1H, *J*=6.9 Hz, H-1'), 4.64 (dd, 1H, *J*=10.2, 3.1 Hz, H-3), 4.60 – 4.46 (m, 2H, H-6), 4.43 (d, 1H, *J*=9.2 Hz, H-5'), 4.33 (d, 1H, *J*=1.9 Hz, H-4), 4.10 (s, 2H, CH_2Cl), 3.93 – 3.85 (m, 1H, H-5), 3.77 (q, 1H, *J*=10.2, 7.0 Hz, H-2), 3.69 (s, 3H, OCH_3) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ: 167.7, 167.3, 165.6, 165.4, 165.2 (C=O, Bz, CO_2Me, $COCH_2Cl$), 162.1 (C=O, TCA), 132.9, 132.3, 130.2, 129.2, 128.7, 128.7, 128.7, 128.6 (arom.), 100.9 (C-1'), 84.3 (C-1), 78.3 (C-3), 75.7 (C-5), 72.5 (C-5'), 71.7 (C-4'), 71.6 (C-3'), 69.5 (C-2'), 68.1 (C-4), 65.2 (C-6), 53.3 (C-2, OCH_3), 40.9 (CH_2Cl) ppm.

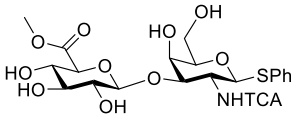
Phenyl 4,6-di-*O*-acetyl-2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyl uronate)-1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranose (33)



Disaccharide **32** (1.25 g, 1.62 mmol, 1.0 eq.) was dissolved in dry DCM (16 mL, 0.1M) and cooled to 0˚C. Thiophenol (0.18 mL, 1.78 mmol, 1.1 eq.) and $BF_3{\cdot}OEt_2$ (0.40 mL, 3.25 mmol, 2.0 eq.) were added consecutively and the mixture was stirred for 4 hours while letting the temperature increase to RT. The mixture was then diluted in EtOAc and washed with sat. $NaHCO_3$ (aq.) thrice followed by 1M NaOH (aq.) and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The dark yellow oil was purified by silicagel chromatography (PE:EtOAc, 4:1 → 1:1) to give the title compound in a 62% yield (0.82 g, 1.01 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ:=7.57 – 7.47 (m, 2H, Ph), 7.35 – 7.27 (m, 3H, Ph), 7.24 (d, 1H, *J*=8.2 Hz, NH), 5.46 (d, 1H, *J*=3.2 Hz, H-4), 5.22 – 5.06 (m, 3H, H-1, H-3', H-4'), 4.93 (t, 1H, *J*=7.9, Hz, H-2'), 4.77 (d, 1H, *J*=7.7 Hz, H-1'), 4.47 (dd, 1H, *J*=10.4, 3.3 Hz, H-3), 4.20 – 4.06 (m, 2H, H-6), 4.06 – 3.89 (m, 3H, H-2, H-5, H-5'), 3.72 (s, 3H, OCH_3), 2.09 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.03 (s, 3H, Ac), 1.99 (s, 3H, Ac), 1.98 (s, 3H, Ac) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ: 170.6, 170.0, 170.0, 169.4, 169.3, 166.9 (C=O, Ac), 161.8 (C=O, TCA), 132.6, 132.4, 129.0, 128.3 (arom.), 99.7 (C-1'), 92.4, CCl_3, TCA), 85.5 (C-1), 75.1 (C-5'), 75.0 (C-3), 72.3 (C-5), 72.0 (C-3'), 70.8 (C-

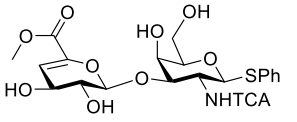
2'), 69.1 (C-4'), 68.5 (C-4), 62.5 (C-6), 53.1 (C-2), 53.0 (OCH_3), 20.8, 20.7, 20.6, 20.5, 20.5 (CH_3, Ac) ppm. HRMS $[M+Na]^+$ calcd for $C_{31}H_{36}Cl_3NO_{16}SNa$: 838.07181, found 838.07126.

Phenyl 2-deoxy-3-*O*-(methyl β-D-glucopyranosyl uronate)-1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranose (35)



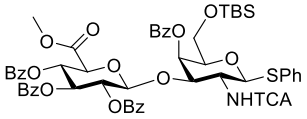
Thioglycoside **33** (0.80 g, 1.0 mmol, 1.0 eq.) was suspended in dry MeOH (10 mL, 0.1M) and NaOMe (11 mg, 0.2 mmol, 0.2 eq.) was added. After 3 hours TLC analysis showed full conversion and the mixture was neutralized by addition of AcOH (0.2 mmol, 0.2 eq.). The neutralized mixture was concentrated *in vacuo*, redissolved in a mixture of $CHCl_3$:*iso*-propanol (4:1) and washed with water twice followed by brine. The organic layer was dried over $MgSO_4$, filtered and concentrated, giving the title compound as an amorphous solid (0.82 mmol, 82%). ^{1}H NMR (MeOD, 400 MHz): δ:=7.61 – 7.46 (m, 2H, Ph), 7.40 – 7.20 (m, 3H, Ph), 5.00 (d, 1H, *J*=10.5 Hz, H-1), 4.54 (d, 1H, *J*=7.3 Hz, H-1'), 4.23 (t, 1H, *J*=10.4 Hz, H-2), 4.12 (d, 1H, *J*=3.0 Hz, H-4), 4.02 (dd, 1H, *J*=10.3, 3.1 Hz, H-3), 3.87 (d, 1H, *J*=9.8 Hz, H-5'), 3.85 – 3.71 (m, 5H, H-6, OCH_3), 3.62 (t, 1H, *J*=6.6, 5.5 Hz, H-5), 3.54 (t, 1H, *J*=9.2 Hz, H-4'), 3.40 – 3.28 (m, 2H, H-2', H-3') ppm. ^{13}C-APT NMR (MeOD, 101 MHz) δ: 171.4(C=O, CO_2Me), 164.0 (C=O, TCA), 135.6, 132.6, 129.9, 128.5 (arom), 105.6 (C-1'), 94.1 (CCl_3), 88.4 (C-1), 80.8 (C-3), 80.5 (C-5), 76.9 (C-3'), 76.7 (C-5'), 74.4 (C-2'), 73.1 (C-4'), 69.5 (C-4), 62.5 (C-6), 53.4 (C-2), 52.9 (OCH_3) ppm. HRMS $[M+Na]^+$ calcd for $C_{21}H_{26}Cl_3NO_{11}SNa$: 628.01898, found 628.01844.

Phenyl 2-deoxy-3-*O*-(methyl 4,5-anhydro-β-D-glucopyranosyl uronate)-1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranose (34)



^{1}H NMR (MeOD, 400 MHz): δ:=7.58 – 7.51 (m, 2H, Ph), 7.37 – 7.24 (m, 3H, Ph), 6.20 (d, 1H, *J*=4.4 Hz, H-4'), 5.27 (d, 1H, *J*=3.1 Hz, H-1'), 4.96 (d, 1H, *J*=10.5 Hz, H-1), 4.25 (t, 1H, *J*=10.2 Hz, H-2), 4.10 – 4.00 (m, 2H, H-3, H-4), 3.97 – 3.90 (m, 1H, H-3'), 3.85 (td, 1H, *J*=3.0, 1.2 Hz, H-2'), 3.82 (s, 3H, OCH_3), 3.81 – 3.75 (m, 1H, H-6), 3.71 (dd, 1H, *J*=11.5, 5.1 Hz, H-6), 3.63 (t, 1H, *J*=6.0 Hz, H-5) ppm.^{13}C-APT NMR (MeOD, 101 MHz) δ: 164.6 (C=O, CO_2Me), 164.0 (C=O, TCA), 141.1, 135.4, 132.7, 130.0, 128.5 (arom), 113.2 (C-4'), 102.8 (C-1'), 88.4 (C-1), 82.1 (C-3), 80.6 (C-5), 70.8 (C-2'), 69.4 (C-4), 66.4 (C-3'), 62.5 (C-6), 53.2 (C-2) , 53.0 (OCH_3) ppm. HRMS $[M+Na]^+$ calcd for

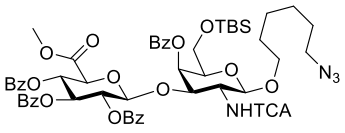
Phenyl 4-*O*-benzoyl-2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl uronate)-6-*O*-*tert*-butyldimethylsilyl-1-thio-2-(2,2,2-trichloroacetamido)-β-D-galactopyranose (36)



Compound **35** (0.20 g, 0.33 mmol, 1.0 eq.) was dissolved in dry DMF (1.0 mL, 0.3M) and cooled to 0˚C, before addition of TBSOTf (84 µL, 0.36 mmol, 1.1 eq.). After 5 min. of stirring imidazole (0.067 g, 0.99 mmol, 3.0 eq.) was added. TLC indicated full conversion after 2 hours and benzoyl chloride (0.31 mL, 2.64

mmol, 8 eq.) and pyridine (1 mL, 0.15 M) were added. The mixture was left stirring overnight at RT. MeOH was added to quench any remaining benzoyl chloride and the mixture was diluted in EtOAc and washed twice with brine, twice with 1M HCl (aq.), twice with sat. $NaHCO_3$ (aq.) and finally once more with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The orange oil was purified using silicagel chromatography (PE:EtOAc 9:1 → 4:1) to obtain the title compound as a white foam (0.164 g, 0.14 mmol, 44%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ:=7.97 – 7.85 (m, 4H, arom.), 7.80 – 7.72 (m, 4H, arom.), 7.64 – 7.54 (m, 3H, arom.), 7.54 – 7.47 (m, 2H, arom.), 7.47 – 7.28 (m, 11H, arom.), 7.28 – 7.18 (m, 4H, arom.), 6.82 (d, 1H, *J*=7.2 Hz, NH), 5.87 (d, 1H, *J*=3.2 Hz, H-4), 5.74 (t, 1H, *J*=9.3 Hz, H-3'), 5.65 (t, 1H, *J*=9.5 Hz, H-4'), 5.43 – 5.31 (m, 2H, H-1, H-2'), 5.05 (d, 1H, *J*=7.4 Hz, H-1'), 4.88 (dd, 1H, *J*=10.4, 3.2 Hz, H-3), 4.29 (d, 1H, *J*=9.5 Hz, H-5'), 3.89 (t, 1H, *J*=6.1 Hz, H-5), 3.78 – 3.67 (m, 3H, H-2, H-6), 3.64 (s, 3H, OCH_3), 0.87 (s, 9H, *t*-Bu, TBS), 0.01 (s, 6H, CH_3, TBS) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ: 167.0 (C=O, CO_2Me), 165.6 (C=O, Bz), 165.1 (C=O, Bz), 164.8 (C=O, Bz), 161.9 (C=O, TCA), 133.5, 133.4, 133.4, 133.1, 131.7, 130.1, 130.0, 129.9, 129.9, 129.2, 129.1, 128.9, 128.7, 128.5, 128.4, 128.4 (arom.), 99.9 (C-1'), 83.8 (C-1), 79.1 (C-5), 74.5 (C-3), 73.1 (C-5'), 72.3 (C-3'), 72.0 (C-2'), 69.8 (C-4'), 69.5 (C-4), 62.2 (C-6), 54.5 (C-2), 53.0 (OCH_3), 26.0 (*t*-Bu, TBS), 18.4 ($C(CH_3)_3$, TBS), -5.3 (CH_3, TBS) ppm. HRMS $[M+Na]^+$ $C_{55}H_{56}Cl_3NO_{15}SSiNa$: 1158.21032, found 1158.20977.

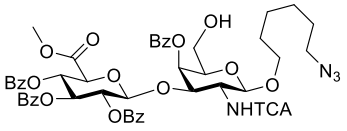
6-azidohexyl 4-*O*-benzoyl-2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl uronate)-6-*O*-*tert*-butyldimethylsilyl-2-(2,2,2-trichloroacetamido)-β-D-galactopyranose (37)



Thiodonor **36** (0.10 g, 0.088 mmol, 1.0 eq.) and azidohexan-1-ol (0.015 g, 0.11 mmol, 1.2 eq.) were co-evaporated together thrice with dry toluene, before being dissolved in dry DCM (0.9 mL, 0.1 M). Freshly activated molecular sieves (3Å) were added followed by NIS (0.029 g, 0.13 mmol, 1.5 eq.) and the solution was left to stir for 1 hour at -20˚C. At this point TMSOTf (88 µL of a 0.1M solution in DCM, 0.1eq.) was added and the cooling bath was removed. After 30 min. TLC indicated full conversion of the starting material and the reaction was quenched by addition of pyridine (0.1 mL). Next the reaction was diluted in EtOAc and washed once with sat. $Na_2S_2O_3$ (aq.) and once with brine. After drying the organic layer over $MgSO_4$, it was filtered and concentrated. The light brown oil was purified using silicagel chromatography (PE:EtOAc 9:1 → 4:1) to obtain the title compound as white solid (0.058 g, 0.050 mmol, 56%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ:=8.08 – 8.02 (m, 2H, arom.), 7.93 – 7.88 (m, 2H, arom.), 7.82 – 7.73 (m, 4H, arom.), 7.61 – 7.30 (m, 10H, arom.), 7.28 – 7.20 (m, 2H, arom.), 6.92 (d, 1H, *J*=7.0 Hz, NH), 5.81 (d, 1H, *J*=3.4 Hz, H-4), 5.77 (t, 1H, *J*=9.4 Hz, H-3'), 5.67 (t, 1H, *J*=9.5 Hz, H-4'), 5.40 (dd, 1H, *J*=9.3, 7.5 Hz, H-2'), 5.08 – 4.98 (m, 2H, H-1, H-1'), 4.89 (dd, 1H, *J*=10.9, 3.5 Hz, H-3), 4.31 (d, 1H, *J*=9.6 Hz, H-5'), 3.92 (dt, 1H, *J*=9.7, 6.2 Hz, OCH_2), 3.88 – 3.75 (m, 2H, H-5, H-6), 3.75 – 3.62 (m, 5H, H-2, H-6, OCH_3), 3.49 (dt, 1H, *J*=9.7, 6.7 Hz, OCH_2), 3.23 (t, 2H, *J*=6.9 Hz, CH_2N_3), 1.64 – 1.50 (m, 4H, CH_2-

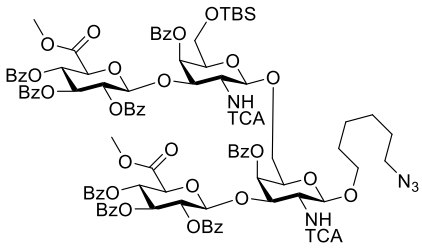
hexyl), 1.43 – 1.29 (m, 4H, CH_2-hexyl), 0.87 (s, 9H, *t*-Bu, TBS), 0.01 (s, 3H, CH_3, TBS), -0.00 (s, 3H, CH_3, TBS) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ: 167.0 (C=O, CO_2Me), 165.6, 165.4, 165.1, 164.7 (C=O, Bz), 162.2 (C=O, TCA), 133.5, 133.4, 133.0, 130.1, 130.0, 130.0, 129.9, 129.8, 129.1, 128.9, 128.7, 128.5, 128.4, 128.4 (arom.), 100.3 (C-1'), 98.8 (C-1), 92.3 (CCl_3, TCA), 75.0 (C-5), 73.5 (C-3), 73.1 (C-5'), 72.3 (C-3'), 71.8 (C-2'), 70.2 (OCH_2), 69.9 (C-4'), 69.7 (C-4), 62.1 (C-6), 56.9 (C-2), 53.0 (OCH_3), 51.4 (CH_2N_3), 29.5, 28.8, 26.6 (CH_2, hexyl), 25.9 (*t*-Bu, TBS), 25.7 (CH_2, hexyl), 18.3 ($C(CH_3)_3$, TBS), -5.3 (CH_3, TBS), -5.4 (CH_3, TBS) ppm. HRMS $[M+NH_4]^+$ calcd for $C_{55}H_{63}Cl_3N_4O_{16}SiNH_4$: 1186.34176, found 1186.34122.

6-Azidohexyl 4-*O*-benzoyl-2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl urinate)-2-(2,2,2-trichloroacetamido)-β-D-galactopyranose (38)



Disaccharide **37** (0.050 g, 0.043 mmol, 1.0 eq.) was dissolved in a mixture of H_2O in acetonitrile (1/9, v/v, 4 mL, 0.01M). CSA (0.035 g, 0.150 mmol, 3.5 eq.) was added to pH 2. TLC analysis showed full conversion of the starting material in a lower running spot. The mixture was concentrated to approximately 1 mL at RT and subsequently diluted with EtOAc. The organic layer was washed once with sat. $NaHCO_3$ (aq.) followed by brine. The organic layer was dried over $MgSO_4$ filtered and concentrated. The yellow oil was purified using silicagel chromatography (PE:EtOAc 4:1 → 2:3) to obtain the title compound as colourless oil (0.044 g, 0.042 mmol, 97%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ:=8.13 – 8.06 (m, 2H, arom.), 7.93 – 7.85 (m, 4H, arom.), 7.77 – 7.70 (m, 2H, arom.), 7.64 (t, 1H, *J*=7.4 Hz, arom.), 7.50 (td, 4H, *J*=7.7, 1.9 Hz, arom.), 7.43 – 7.31 (m, 5H, arom), 7.23 (m, 2H, arom.), 6.93 (d, 1H, *J*=6.8 Hz, NH), 5.79 (t, 1H, *J*=9.5 Hz, H-3'), 5.72 (d, 1H, *J*=2.7 Hz, H-4), 5.59 (t, 1H, *J*=9.5 Hz, H-4'), 5.42 (dd, 1H, *J*=9.6, 7.6 Hz, H-2'), 5.11 – 5.01 (m, 2H, H-1, H-1'), 4.92 (dd, 1H, *J*=9.3, 2.4 Hz, H-3), 4.32 (d, 1H, *J*=9.7 Hz, H-5'), 3.94 – 3.82 (m, 2H, H-5, OCH_2), 3.69 (m, 5H, H-2, H-6, OCH_3), 3.60 – 3.40 (m, 3H, H-6, OCH_2, OH), 3.22 (t, 2H, *J*=6.9 Hz, CH_2N_3), 1.61 – 1.47 (m, 4H, CH_2-hexyl), 1.38 – 1.28 (m, 3H, CH_2-hexyl) ppm. ^{13}C-APT NMR ($CDCl_3$, 101 MHz) δ: 168.0 (C=O, CO_2Me), 166.6, 165.5, 165.0, 164.8 (C=O, Bz), 162.3 (C=O, TCA), 133.7, 133.5, 133.5, 133.3, 130.3, 130.0, 129.8, 129.7, 129.3, 128.8, 128.7, 128.5, 128.4, 128.3 (arom.), 101.0 (C-1'), 98.7 (C-1), 92.0 (CCl_3, TCA), 74.4 (C-3), 73.5 (C-5), 72.9 (C-5'), 72.1 (C-3'), 71.5 (C-2'), 70.7 (C-4), 70.3 (OCH_2), 69.7 (C-4'), 60.0 (C-6), 56.7 (C-2), 53.0 (OCH_3), 51.3 (CH_2N_3), 29.4, 28.7, 26.5, 25.6 (CH_2, hexyl) ppm. HRMS $[M+Na]^+$ calcd for $C_{49}H_{49}Cl_3N_4O_{16}Na$: 1077.21068, found 1077.21014.

6-azidohexyl [4-*O*-benzoyl-2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl uronate)-6-*O*-*tert*-butyldimethylsilyl-2-(2,2,2-trichloroacetamido)-β-D-galactopyranose] (1→6) 4-*O*-benzoyl-2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl uronate)-2-(2,2,2-trichloroacetamido)-β-D-galactopyranose (39)



Disaccharide acceptor **38** (0.037 g, 0.035 mmol, 1.0 eq.) and disaccharide donor **36** (0.058 g, 0.051 mmol, 1.4 eq.) were co-evaporated together thrice and afterwards solved in dry DCM (0.35 mL, 0.1M). Freshly dried molecular sieves (3Å) were added and the mixture was stirred at RT. After 30 min. NIS (0.013 g, 0.060 mmol, 1.7 eq.) was added and the mixture was cooled to -20˚C and stirred at this temperature for another 30 min. TMSOTf (35 µL of a 0.1M solution in DCM, 0.1 eq.) was added and the reaction was allowed to warm to 0˚C. After 6 hours the reaction was quenched by addition of pyridine (0.05 mL). The mixture was taking up in EtOAc and washed with once with sat. $Na_2S_2O_3$ (aq.) and once with brine. After drying the organic layer over $MgSO_4$, it was filtered and concentrated. The light brown oil was purified using silicagel chromatography (tol:ACN 1:0 → 9:1), followed by size exclusion of LH-20 (DCM/MeOH, 1/1, v/v) to obtain the title compound as pale white solid (0.028 g, 0.015 mmol, 42%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ:=8.10 – 8.03 (m, 2H, arom.), 8.02 – 7.97 (m, 2H, arom.), 7.96 – 7.84 (m, 5H, arom.), 7.84 – 7.72 (m, 7H, arom.), 7.62 – 7.18 (m, 25H, NH, arom.), 6.85 (d, 1H, *J*=7.0 Hz, NH), 5.81 (d, 1H, *J*=3.4 Hz, H-4''), 5.78 (d, 1H, *J*=2.5 Hz, H-4), 5.77 – 5.73 (m, 2H, H-3'. H-3'''), 5.70 – 5.61 (m, 2H, H-4', H-4'''), 5.45 – 5.35 (m, 2H, H-2', H-2'''), 5.11 – 4.99 (m, 3H, H-1, H-1', H-1'''), 4.98 – 4.93 (m, 2H, H-1'', H-3''), 4.81 (dd, 1H, *J*=10.9, 3.4 Hz, H-3), 4.37 – 4.23 (m, 2H, H-5', H-5'''), 3.99 (dd, 1H, *J*=10.7, 5.0 Hz, H-6), 3.96 – 3.86 (m, 2H, H-5, OCH_2), 3.81 – 3.74 (m, 1H, 5''), 3.71 – 3.60 (m, 9H, H-2, H-6, H-2'', OCH_3', OCH_3'''), 3.60 – 3.56 (m, 1H, H-6''), 3.56 – 3.50 (m, 1H, H-6''), 3.45 (dt, 1H, *J*=9.8, 6.6 Hz, OCH_3), 3.23 (t, 2H, *J*=6.9 Hz, CH_2N_3), 1.62 – 1.48 (m, 4H, CH_2-hexyl), 1.41 – 1.26 (m, 4H, CH_2-hexyl), 0.81 (s, 9H, *t*-Bu, TBS), -0.07 (s, 3H, CH_3, TBS), -0.09 (s, 3H, CH_3, TBS) ppm. ^{13}C-APT NMR ($CDCl_3$, 126 MHz) δ: 167.1, 167.0 (CO_2Me), 165.7, 165.6, 165.4, 165.2, 165.1, 165.1, 164.8, 164.7 (C=O, Bz), 162.4, 162.2 (C=O, TCA), 133.6, 133.5, 133.4, 133.3, 133.3, 133.1, 133.0, 130.2, 130.1, 130.0, 129.9, 129.9, 129.9, 129.8, 129.1, 129.0, 129.0, 128.8, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.4, 128.4, 128.3 (arom.), 100.3 (C-1'), 100.2 (C-1'''), 98.7 (C-1''), 98.0 (C-1), 92.2 (CCl_3, TCA), 74.8 (C-5''), 73.4 (C-5), 73.3 (C-3), 73.1 (C-3''), 73.0 (C-5', C-5'''), 72.4 (C-3'), 72.2 (C-3'''), 71.8 (C-2'), 71.6 (C-2'''), 70.2 (OCH_2), 70.0 (C-4'), 69.9 (C-4), 69.9 (C-4'''), 69.4 (C-4''), 67.1 (C-6), 61.6 (C-6'), 56.7 (C-2, C-2''), 53.1 (OCH_3), 53.0 (OCH_3), 51.4 (CH_2N_3), 29.5, 28.8, 26.6 (CH_2, hexyl), 25.9 (*t*-Bu, TBS), 25.7 (CH_2, hexyl), 18.3 ($C(CH_3)_3$, TBS), -5.5 (CH_3, TBS) ppm. HRMS $[M+Na+H]^{2+}$ calcd for Chemical Formula: C98H99Cl6N5O31SiNaH: 1051.71002, found 1051.70947.

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