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A New Reactivity-Based One-Pot Synthesis of *N*-Acetyllactosamine Oligomers

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Poly-*N*-acetyllactosamine oligomer is a type-2 glycan core from which a number of important bioactive glycoconjugates are assembled in vivo. Development of an effective synthesis of *N*-acetyllactosamine oligomers will therefore provide a new chemoenzymatic entry to this class of complex saccharides. This paper describes the design and synthesis of thioglycoside building blocks, determination of their relative reactivity values, and demonstration of their use in the programmable one-pot synthesis of various *N*-acetyllactosamine oligomers. Through a combination of segment condensation, the strategy allows for the preparation of larger oligosaccharides with minimal protecting group manipulation, as illustrated in the synthesis of an octasaccharide in a very short period of time.

Introduction

N-Acetyllactosamine oligomer is a type-2 glycan composed of repeating β(1,3) linked *N*-acetyllactosamine (LacNAc) residues.[1] As a precursor to a number of blood group antigens, these oligomers also serve as an acceptor substrate for a number of glycosyltransferases in the production of different glycoconjugates such as sialyl Lewis- X, tumor-related fucosylated poly-*N*-acetyllactosamine; it also serves as a spacer to present sugar ligands from glycoproteins to their receptors (Figure 1).[2,3] Since many of the glycosyltransferases with *N*-acetyllactosamine oligomers as starting substrates are available, development of effective syntheses of *N*-acetyllactosamine oligomers will therefore provide a new chemoenzymatic entry to a number of important glycoconjugates.[4] Previous syntheses of *N*-acetyllactosamine oligomers often begin with a fully protected lactosamine, which is obtained either from lactal or glycosylation of galactosyl and glucosaminyl precursors. The final product is obtained after a series of protecting group and anomeric leaving group manipulations.[4,5] We report here our effort to simplify this lengthy operation using the principle of programmable reactivity-based one-pot synthesis of oligosaccharide to design building blocks with defined reactivity for the rapid assembly of various *N*-acetyllactosamine oligomers.

The programmable reactivity-based one-pot strategy is based on thioglycoside building blocks with defined relative reactivity values (RRV).[6] Different from the qualitative one-pot synthesis, the reactivity of each thioglycoside building block is determined quantitatively rather than by qualitative estimation.[7] These RRV values form a reactivity database that, together with the "OptiMer" computer program, provides an optimized set of thioglycoside building blocks for use in the reactivity-based one-pot synthesis of a given oligosaccharide (Figure 2). Using this strategy, we have successfully prepared a small oligosaccharide library,[8] the breast cancer antigenic determinant Globo H,[9] and the colon cancer antigen Lewis Y.[10] We have now added the newly designed building blocks for *N*-acetyllactosamine oligomers to our database, which will further expand the scope of the one-pot approach for the synthesis of other biologically important oligosaccharides.

Results and Discussion

The initial design and synthesis of galactosyl and glucosaminyl building blocks is a key step in our synthetic venture. Selection of appropriate hydroxyl and amino protecting groups was crucial to create a reactivity profile for the different lactosaminyl building blocks and subsequent implementation of reavtivity-based one-pot

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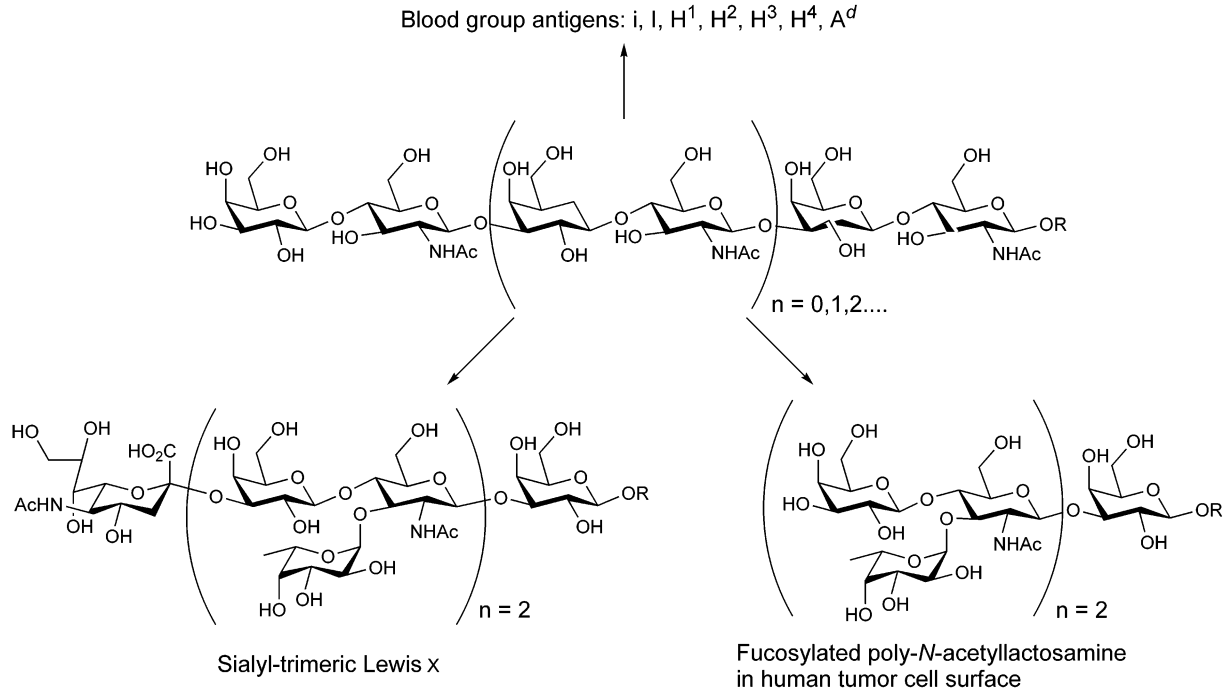


FIGURE 1. Poly-*N*-acetyllactosamine and their derivatives.

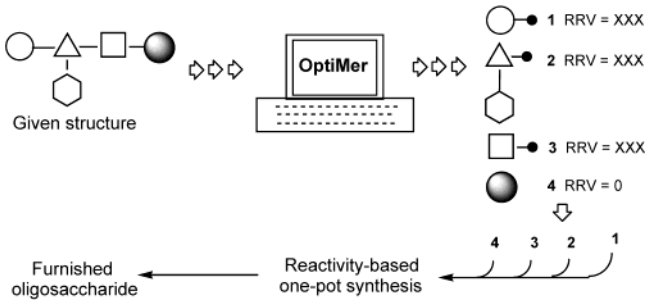


FIGURE 2. Illustration of the programmable one-pot synthesis of oligosaccharide.

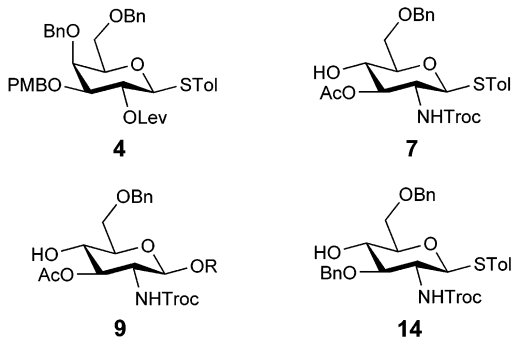
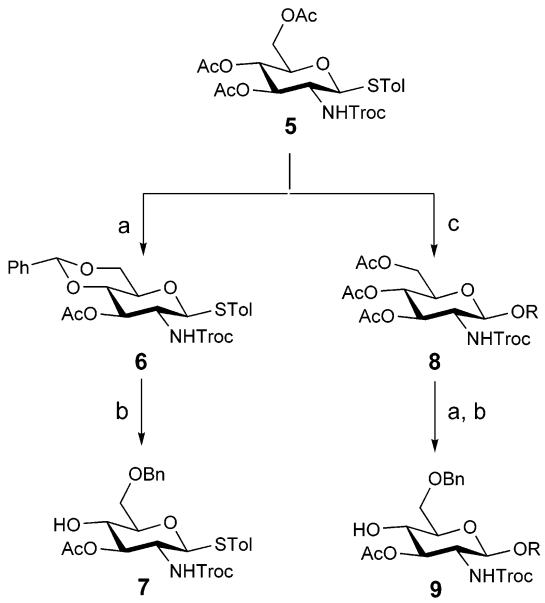


FIGURE 3. Galactosyl and glucosaminyl thioglycoside building blocks.

synthesis of oligomers. Hence, galactosyl building block **4** and glucosaminyl building blocks **7**, **9**, and **14** were prepared whereas **4** and **9** have been reported (Figure 3).[10] All the glucosaminyl building blocks **7**, **9**, and **14** possess a free C-4 hydroxyl and a trichloroethoxylcarbonyl protecting group (Troc) at the C-2 amino functionality. The former provides an acceptor site for the galactosyl donor, while the later directs the β-glycosidic bond formation.

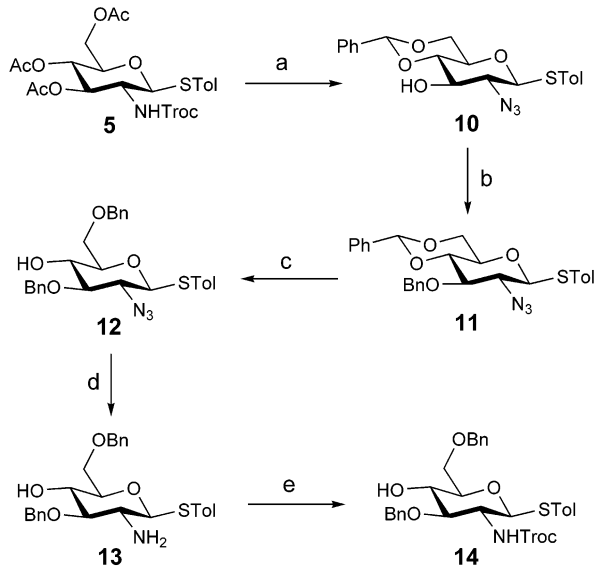
SCHEME 1[a]



[a] Reagents and conditions: (a) (i) NaOMe, MeOH/CH_2Cl_2, −0 °C; (ii) $Bn(OMe)_2$, CSA, CH_3CN, rt; (iii) Ac_2O, pyr, ca.t DMAP, CH_2Cl_2, 60% over three steps. (b) Et_3SiH, TFA, CH_2Cl_2, 0 °C, 90%. (c) DMTST, MS, CH_2Cl_2, −20 to 0 °C, 80%.

Synthesis of glucosaminyl building blocks **7** and **9** followed standard procedure and started with the known compound **5** (Scheme 1).[6] For compound **7**, deacetylation under Zemplén conditions was followed by C-4/C-6 hydroxyls benzylidenation and C3−OH acetylation to furnish compound **6**.[11] The benzylidene ring of **6** was reductively opened in the presence triethylsilane (Et_3SiH) and trifluoroacetic acid (TFA) to yield the glucosaminyl

SCHEME 2[a]



[a] Reagents and conditions: (a) (i) Zn dust, CH_2Cl_2/Ac_2O (1:1), cat. DMAP; (ii) NaOMe, CH_2Cl_2/MeOH (1:1); (iii) TfN_3, K_2CO_3, cat. $ZnCl_2$, CH_2Cl_2/MeOH/H_2O (3:3:1); (iv) $Bn(OMe)_2$, cat. CSA, CH_3CN, 60% over 4 steps. (b) BnBr, NaH, Bu_4NI, DMF, 0 °C to rt, 82%. (c) Et_3SiH, TFA, CH_2Cl_2, 0 °C, 90%. (d) 1,3-Dithiopropane, TEA, MeOH/CH_2Cl_2 (1:1), 40 °C, 80%. (e) TrocCl, $NaHCO_3$, THF, 90%.

building block **7**,[12] while for **9**, thioglycoside **5** was first converted to *O*-glycoside **8** with methyl 6-hydroxyhexanate in the presence of dimethyl (thiomethyl) sulfonium triflate (DMTST) and then followed the same reaction course as for the synthesis of **7**, the glucosaminyl building block **9** was obtained.

Nevertheless, additional protecting group manipulation was required for the synthesis of **14** because the C-2 amino Troc protection could not survive the basic conditions necessary for benzylation of the C-3 hydroxyl (Scheme 2). The solution was to install a temporary azide protection first and subsequently reduce it to amine after benzylation of the C-3 hydroxyl. Starting from known compound **5**, *N*-Troc protection was removed by zinc dust reduction, and followed by Zemplén deacetylation. The free C-2 amino group was converted to an azide via a modified diazo transfer reaction and the C-4/C-6 hydroxyls were protected as a benzylidene acetal to yield compound **10**.[13] Benzylation of **10** with sodium hydride and benzyl bromide gave compound **11**, which was subjected to reductive benzylidene ring opening with Et_3SiH and TFA to furnish **12**. Subsequent Staudinger reduction of the C-2 azide of **12** was sluggish and successful reduction was achieved by the use dithiopropane in the presence of TEA to give **13**, which was reacted with TrocCl in the presence of $NaHCO_3$ to give the desired acceptor **14**.[14]

With the established competitive HPLC assay, the RRVs of thioglycoside building blocks **7** and **14** were determined to be 1.8×10^4 and 302, respectively (Scheme 3).[6] The 60-fold difference is apparently attributed to a change of electron-donating benzyl ether to electron-withdrawing acetyl protecting group at C-3 hydroxyl. On the basis of the obtained RRV values, we proceeded to the syntheses of lactosaminyl building blocks (Scheme 3). However, galactosyl building block **4** could not be a donor for glucosaminyl building block **14** because **14** (RRV = 1.8×10^4) was more reactive than the **4** (RRV = 4150). Instead, peracetylated galactosyl bromide **15** was used and acceptor **14** was glycosylated with **15** in the presence of silver triflate (AgOTf) and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) furnishing the nonreducing end lactosaminyl building block **16** in 70% yield.[15] Precursor **17** of the bridging lactosaminyl building block was prepared by glycosylating glucosaminyl acceptor **7** (RRV = 302) with reactive galactosyl donor **4** (RRV = 4150) in the presence of *N*-iodosuccinimide and triflic acid (NIS/TfOH).[16] Conversion of **17** to the functional bridging lactosaminyl building block **18** was achieved by removal of the *p*-methoxyl benzyl ether (PMB) at the C′-3 hydroxyl with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). For the lactosaminyl building blocks **19** and **20**, their syntheses have been reported.[10]

For the functional tetrasaccharide building block **22**, its precursor **21** was first obtained by glycosylating lactosaminyl building block **20** with **17** in the presence of NIS/TfOH. However, unlike compound **17** and **19**, subsequent DDQ removal of the PMB ether of compound **21** led to product degradation. A milder deprotection procedure with the use of 10% TFA in CH_2Cl_2 was used to obtain the functional tetrasaccharide building block **22** in 80% yield. With the building blocks **16**, **18**, **20**, and **22** in hand, the RRV data for **16** and **18** were determined to be 1.3×10^4 and 246, respectively.

Synthesis of the *N*-acetyllactosamine oligomers is depicted in Scheme 4. Guided by the RRVs, the less reactive bridging lactosaminyl building block **18** (RRV = 246) was first glycosylated with the more reactive lactosaminyl building block **16** (RRV = 1.3×10^4) in the presence of NIS/TfOH at −35 °C and the reaction was monitored by TLC. Complete consumption of donor **16** was followed by addition of the third lactosaminyl building block **20** along with another molar equivalent of NIS. The resulting hexasaccharide **23** was obtained in 55% yield. Synthesis of octasaccharide **24** was identical with that of **23** except that the final acceptor used was tetrasaccharide **22**, and a higher reaction temperature (−20 °C) was required for the second glycosylation. **24** was obtained in 35% yield. The lower yield of **24** as compared to that of **23** is due to extensive chromatographic purification. Global deprotection of **22**, **23**, and **24** was performed in three consecutive steps: (i) *N*-Troc was removed by zinc reduction in the presence of acetic anhydride with simultaneous acetylation of the free amine, (ii) the acyl protecting groups were removed with Zemplén deacylation, and (iii) benzyl ethers were removed with palladium-black catalyzed hydrogenation in acidified methanol. *N*-Acetyllactosamine oligomers **1**, **2**, and **3** were then fully characterized by HRMS and proton NMR.

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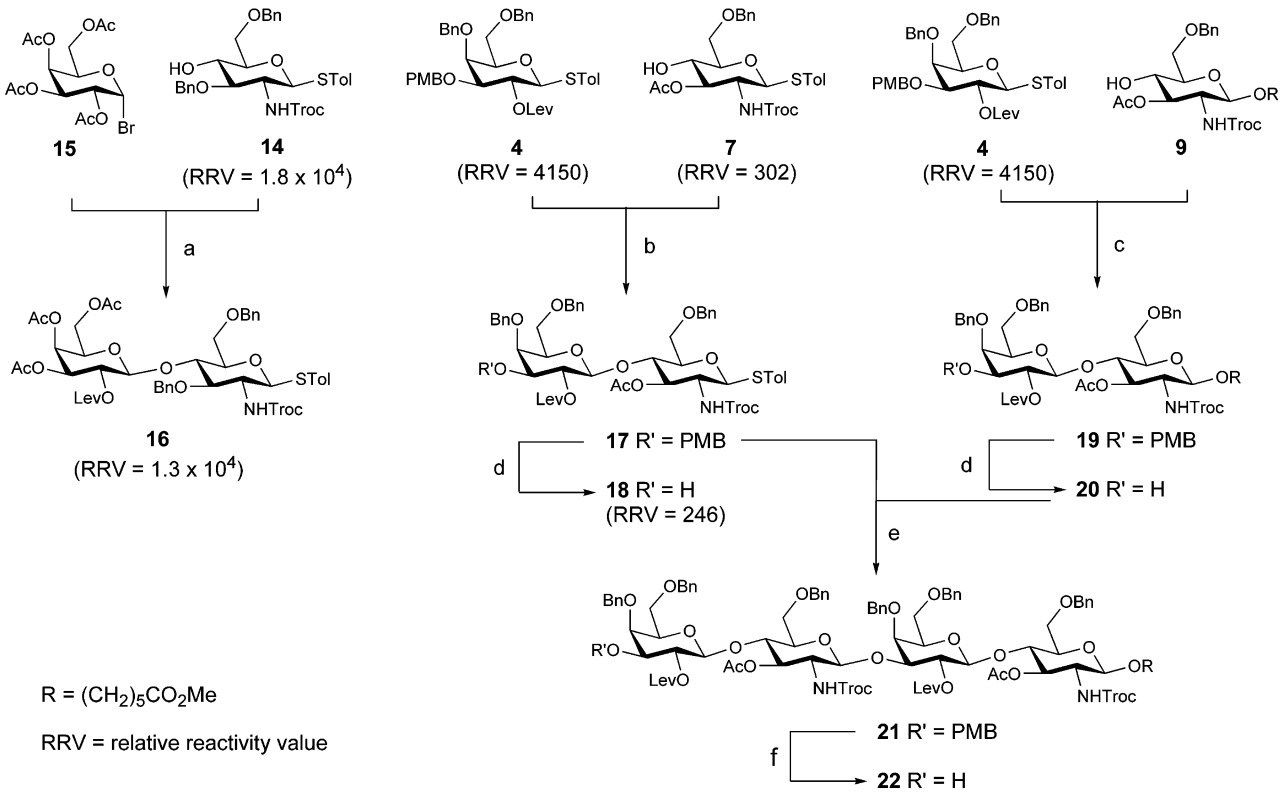
SCHEME 3[a]



[a] Reagents and conditions: (a) AgOTf, DTBMP, CH_2Cl_2/toluene (2:1), −10 °C, 70%. (b) NIS, cat. TfOH, CH_2Cl_2, −45 °C, 40%. (c) NIS, cat. TfOH, CH_2Cl_2, −45 °C, 75%. (d) DDQ, CH_2Cl_2/PO_4 buffer (10:1), 75%. (e) NIS, cat. TfOH, CH_2Cl_2, −30 °C, 88%. (f) TFA, CH_2Cl_2, anisole, 0 °C to rt, 81%.

Conclusion

We have demonstrated the preparation of a series of biologically relevant *N*-acetyllactosamine oligomers using the reactivity-based one-pot approach combined with segment condensation. This new combination takes advantage of minimizing tedious protecting group manipulations and reaction intermediate isolation. It provides a useful strategy for the programmable synthesis of large oligosaccharides and complements the automated solid-phase synthesis strategy.[17] We are in the process of adding more newly designed building blocks to the OptiMer database for use in the development of programmable one-pot synthesis to target other biologically important oligosaccharides.

Experimental Section

General. All chemicals were purchased as reagent grade and used without further purification. Dichloromethane (CH_2Cl_2), toluene, and acetonitrile (CH_3CN) were distilled over calcium hydride whereas tetrahydrofuran (THF) and ether (Et_2O) were distilled over sodium/benzophenone ketyl. Anhydrous DMF was purchased from a commercial source. Molecular sieves (MS) used for glycosylation were AW-300, which was ground into powdered form before use. Reactions were monitored with analytical thin-layer chromatography (TLC) on silica gel 60 F254 plates and visualized under UV (254 nm) and/or by staining with acidic ceric ammonium molybdate. Flash column chromatography was performed on silica gel (35−75 μm). ^{1}H NMR spectra were recorded on a 500- or 600-Hz NMR spectrometer at 20 °C. Chemical shift (in ppm) was determined relative to either tetramethylsilane in deuterated chloroform (δ 0 ppm) or acetone in deuterated water (δ 2.05 ppm). Coupling constant(s) in hertz (Hz) were measured from one-dimensional spectra. ^{13}C Attatched Proton Test (C-Apt) spectra were obtained with the NMR-500 spectrometer (125 Hz) and were calibrated with $CDCl_3$ (δ 77.00 ppm).

Global Deprotection for *N*-Acetyllactosamine Oligomers. To the solution of protected *N*-acetyllactosamine oligomer **1**, **2**, or **3** in Ac_2O/CH_2Cl_2 was added DMAP and activated Zn dust (prewashed with 0.5 M HCl, followed by H_2O, MeOH, and Et_2O). The reaction mixture was stirred at rt under Ar for 4 h and filtered with Zn. After the solvent was evaporated in a vacuum, the residue was dissolved in CH_2Cl_2, washed with H_2O and brine, dried ($MgSO_4$), and concentrated for flash column chromatography. The N-Troc deprotected product was dissolved in CH_2Cl_2/MeOH (1:1) and added NaOMe (25% in MeOH). The reaction mixture was stirred for 10 h and then neutralized with IRC-50 resin (H^+). After the resin was filtered and the solvent removed, the deacylated product was dissolved in MeOH/AcOH (5:1) and palladium-black (Pd-black) was added. The reaction mixture was stirred at rt under 1 atm of H_2 for 18 h. After the Pd-black was filtered and the solvent removed in a vacuum, the product was purified by C-18 reverse-phase chromatography (H_2O/MeOH, 100:0 gradient to 50:50). For tetrasaccharide **1**: ^{1}H NMR (600 MHz, D_2O) δ 4.51 (d, J = 8.3 Hz, 1H; H-1), 4.32 (d, J = 7.4 Hz, 1H; H-1), 4.29 (d, J = 7.9 Hz, 1H; H-1), 4.27 (d, J = 7.9 Hz, 1H; H-1), 3.97 (d, J = 3.1 Hz, 1H), 3.80−3.47 (m, 23H), 3.41−3.34 (m, 5H), 2.21 (t, J = 7.5 Hz, 2H; aglycon-CH_2), 1.85 (s, 3H; CH_3C=O), 1.84 (s, 3H; CH_3C=O), 1.42 (p, J = 8.2 Hz, 2H; aglycon-CH_2), 1.37 (p, J = 6.5 Hz, 2H; aglycon-CH_2), 1.17−1.12 (m, 2H; aglycon-CH_2); HRMS calcd for $C_{35}H_{60}N_2O_{23}Na$ (M + Na)$^+$ 899.3479, found 899.3473. For hexasaccharide **2**: ^{1}H NMR (600 MHz,

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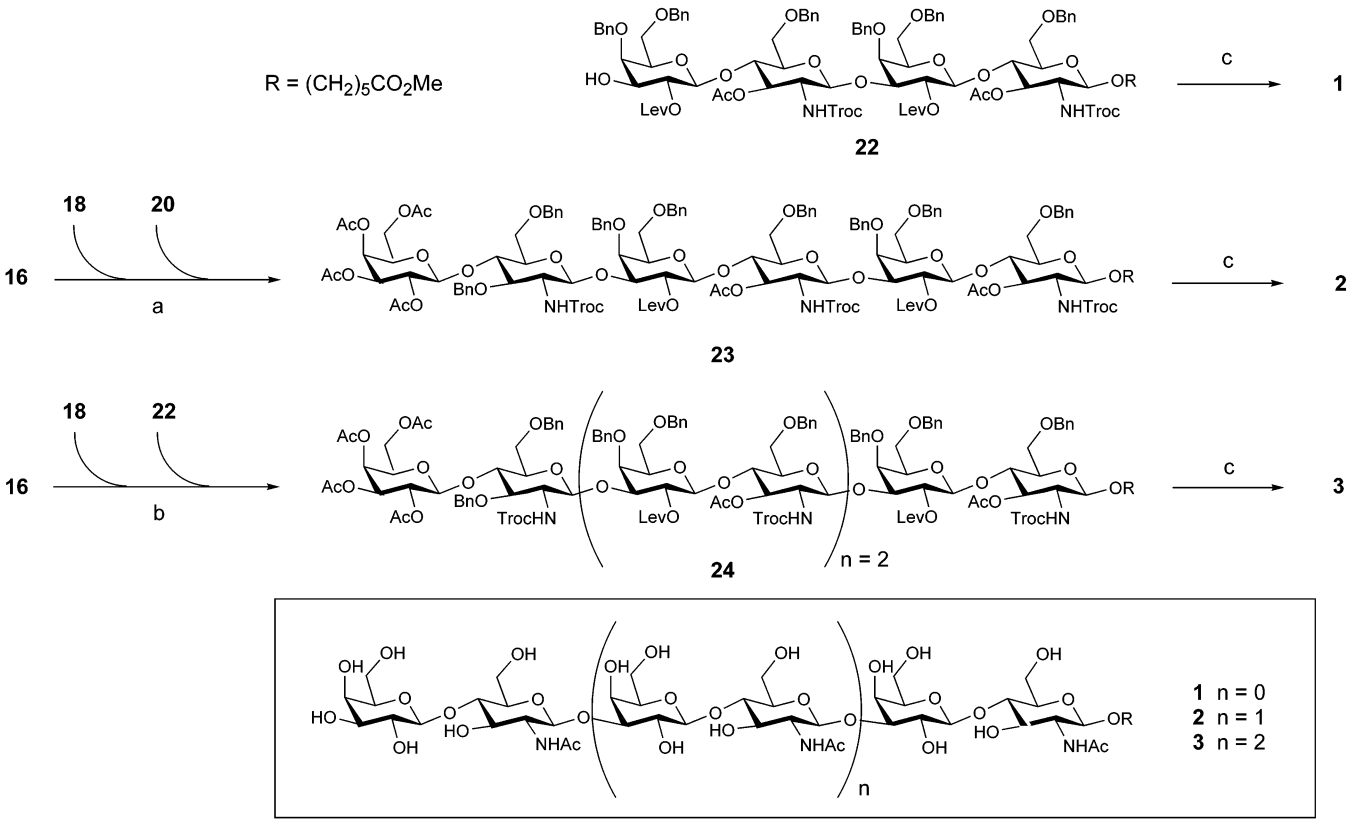
SCHEME 4[a]



[a] Reagents and conditions: (a) (i) NIS, cat. TfOH, CH_2Cl_2, −35 °C; (ii) **20**, NIS, −35 °C, 55%. (b) (i) NIS, cat. TfOH, CH_2Cl_2, −35 °C; (ii) **22**, NIS, −20 °C, 35%. (c) (i) Zn dust, Ac_2O/CH_2Cl_2 (1:1), cat. DMAP; (ii) cat. NaOMe, MeOH; (iii) Pd-black, H_2, MeOH/AcOH (4:1), 30% over 3 steps.

D_2O) δ 4.52 (d, J = 8.4 Hz, 1H; H-1), 4.51 (d, J = 8.4 Hz, 1H; H-1), 4.33 (d, J = 7.9 Hz, 1H; H-1), 4.29 (d, J = 7.9 Hz, 1H; H-1), 4.28 (d, J = 7.9 Hz, 1H; H-1), 4.27 (d, J = 7.9 Hz, 1H; H-1), 3.97 (br, 2H), 3.80−3.47 (m, 32H), 3.41−3.34 (m, 7H), 2.21 (t, J = 7.9 Hz, 2H; aglycon-CH_2), 1.85 (s, 6H; CH_3C═O), 1.84 (s, 3H; CH_3C═O), 1.42 (p, J = 8.2 Hz, 2H; aglycon-CH_2), 1.37 (p, J = 6.5 Hz, 2H; aglycon-CH_2), 1.17−1.13 (m, 2H; aglycon-CH_2); HRMS calcd for $C_{49}H_{83}N_3O_{33}Na$ $(M + Na)^+$ 1264.4801, found 1264.4810. For octasaccharide **3**: ^{1}H NMR (600 MHz, D_2O) δ 4.51 (d, J = 8.3 Hz, 3H; H-1), 4.33 (d, J = 7.9 Hz, 1H; H-1), 4.30−4.26 (m, 4H; H-1), 4.28 (d, J = 7.9 Hz, 1H; H-1), 4.27 (d, J = 7.9 Hz, 1H; H-1), 3.97 (br, 3H), 3.80−3.47 (m, 41H), 3.41−3.34 (m, 9H), 2.21 (t, J = 7.5 Hz, 2H; aglycon-CH_2), 1.85 (s, 9H; CH_3C═O), 1.84 (s, 3H; CH_3C═O), 1.42 (p, J = 7.5 Hz, 2H; aglycon-CH_2), 1.37 (p, J = 6.5 Hz, 2H; aglycon-CH_2), 1.17−1.13 (m, 2H; aglycon-CH_2); HRMS calcd for $C_{63}H_{106}N_4O_{43}Na$ $(M + Na)^+$ 1629.6123, found 1629.6115.

Compound 6. 5 (2 g, 3.3 mmol) in MeOH/CH_2Cl_2 (1/1, 10 mL) was stirred at 0 °C and NaOMe (25% in MeOH, 0.1 mL) was added. The reaction mixture was stirred at 0 °C under Ar for 2 h and then neutralized with IRC-50 resin(H^+). The resin was filtered off and the reaction solvent was evaporated in a vacuum, followed by coevaporation with toluene (×2). The residue suspended in CH_3CN and (±)-10-camphorsulfonic acid (CSA) (9 mg, 17 μmol) was added to the mixture. Benzaldehyde dimethyl acetal (1.6 mL, 10 mmol) was added and reaction mixture was stirred at room temperature for 2 h then neutralized with triethylamine (TEA). The solvent was removed by rotaevaporator. The resulting residue and DMAP (40 mg, 0.33 mmol) were dissolved in CH_2Cl_2. Acetic anhydride (Ac_2O) (0.94 mL, 10 mmol) and pyridine (pyr) (1.6 mL, 20 mmol) were added. The reaction mixture was stirred at room temperature for 2 h and then washed t with 0.5 M HCl × 2, H_2O, and brine and dried ($MgSO_4$). The organic phase was concentrated for flash column chromatography (hexane/CH_2Cl_2/EtOAc, 2:1:0.5). Compound **6** (1.17 g, 60% over 3 steps) was obtained as a white glassy solid. For compound **6**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.32 (m, 8H; aromatic), 7.13 (d, J = 8.1 Hz, 2H; aromatic), 5.48 (s, 1H), 5.43 (d, J = 9.5 Hz, 1H), 5.30 (t, J = 9.5 Hz, 1H), 4.78 (dd, J = 36.7, 12.1 Hz, 2H), 4.73 (d, J = 10.3 Hz, 1H; H-1), 4.33−4.29 (m, 1H), 3.81−3.75 (m, 2H), 3.65 (t, J = 9.6 Hz, 1H), 3.54−3.49 (m, 1H), 2.37 (s, 3H; PhMe), 2.05 (s, 3H; MeC═O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.79, 154.20, 138.61, 136.78, 133.41, 129.78, 129.13, 128.40, 128.22, 128.20, 126.09, 101.33, 88.22, 78.38, 74.53, 72.44, 70.59, 68.40, 55.51, 21.17, 20.82; HRMS calcd for $C_{25}H_{26}Cl_3NO_7SNa$ $(M + Na)^+$ 612.0338, found 612.0381.

Compound 7. Compound **6** (0.7 g, 1.2 mmol) in CH_2Cl_2 (8 mL) was stirred at 0 °C under Ar. Et_3SiH (2 mL, 12 mmol) was added and followed by TFA (0.9 mL, 12 mmol). The reaction mixture was stirred for 1 h. Then the mixture was diluted with CH_2Cl_2 (20 mL) and cautiously washed with sat. $NaHCO_3$ (×3), H_2O, and brine and dried ($MgSO_4$). The organic phase was concentrated for flash column chromatography (hexane/CH_2Cl_2/EtOAc, 3:1:1). **7** (0.63 g, 90%) was obtained as a glassy white solid. For compound **7**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.05 (m, 9H; aromatic), 5.31 (d, J = 9.5 Hz, 1H), 5.04 (t, J = 9.5 Hz, 1H), 4.76 (dd, J = 52.8, 12.1 Hz, 2H), 4.66 (d, J = 10.3 Hz, 1H), 4.56 (dd, J = 18.4, 11.8 Hz, 2H), 3.82−3.77 (m, 2H), 3.73−3.66 (m, 2H), 3.57−3.52 (m, 1H), 3.02 (d, J = 4.0 Hz, 1H), 2.31 (s, 3H; PhMe), 2.07 (s, 3H; MeC═O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.69, 154.13, 138.31, 137.58, 133.15, 129.71, 128.58, 128.47, 127.88, 127.74, 87.26, 78.11, 76.16, 74.48, 73.76, 70.55, 70.25, 54.77, 21.13, 20.90; HRMS calcd for $C_{25}H_{28}Cl_3NO_7SNa$ $(M + Na)^+$ 614.0544, found 614.0543.

Compound 8. 5 (3 g, 5.1 mmol) in CH_2Cl_2 (15 mL) was suspended with MS (AW-300, 3.75 g) for 1 h at rt under Ar.

The reaction mixture was cooled to −20 °C and dimethyl thiomethyl sulfonium triflate (DMTST) (6.45 g, 25 mmol) in CH_2Cl_2 (10 mL) [freshly prepared from mixing methyl triflate (MeOTf) (2.8 mL, 25 mmol) and dimethyl disulfide (Me_2S_2) (2.2 mL, 25 mmol)] was added to the reaction mixture. The reaction mixture was stirred until the temperature went from −20 to 0 °C and kept at 0 °C for 4 h. The reaction was quenched with TEA. MS was filtered off and the filtrate was washed with sat. $NaHCO_3$, H_2O, and brine and dried ($MgSO_4$). The organic phase was concentrated for flash chromatography (hexane/EtOAc, 1.5:1). **8** (4 g, 80%) was obtained as a colorless oil. For compound **8**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (d, J = 8.6 Hz, 1H), 5.32 (t, J = 9.9 Hz, 1H), 5.07 (t, J = 9.2 Hz, 1H), 4.72 (dd, J = 48.5, 12.1 Hz, 2H), 4.65 (d, J = 8.2 Hz, 1H), 4.28 (dd, J = 12.1, 4.8 Hz, 1H), 4.13 (d, J = 10.3 Hz, 1H), 3.92−3.88 (m, 1H; aglycon-CH_2), 3.71−3.69 (m, 1H), 3.68 (s, 3H; CO_2Me), 3.62 (dd, J = 19.4, 8.8 Hz, 1H), 3.52−3.47 (m, 1H; aglycon-CH_2), 2.33−2.29 (m, 2H; aglycon-CH_2), 2.09 (s, 3H; MeC═O), 2.03 (s, 3H; MeC═O), 1.67−1.55 (m, 2H; aglycon-CH_2), 1.40−1.34 (m, 2H; aglycon-CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.24, 170.69, 170.57, 169.45, 154.01, 100.76, 74.36, 71.89, 71.70, 69.71, 68.69, 56.29, 51.55, 33.72, 28.89, 25.19, 24.28, 20.73, 20.63, 20.60; HRMS calcd for $C_{22}H_{32}Cl_3NO_{12}Na$ $(M + Na)^+$ 630.0882, found 630.0890.

Compound 10. Zn dust (2 g, activated with 0.1 M HCl before use) was added to **5** (1 g, 1.7 mmol) in MeOH/AcOH/CH_2Cl_2 (8 mL, 2:1:1) and the mixture was stirred at room temperature under Ar for 1 h. Then the Zn dust was filtered off and the organic filtrate was diluted with CH_2Cl_2, which was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated for flash column chromatography (EtOAc) to yield the *N*-Troc deprotected product. The crude product from the previous step was dissolved in MeOH/CH_2Cl_2 (5 mL, 1:1) to which a solution of NaOMe (25% in MeOH, 0.1 mL) was added. The reaction mixture was stirred at room temperature for 2 h and neutralized with concentrated HCl. Solvent was removed in a vacuum, and the crude deacetylated product was taken directly into the diazo transfer reaction. To the crude residue in MeOH/H_2O (5 mL, 4:1) was added K_2CO_3 (0.5 g, 3.4 mmol), $ZnCl_2$ (11 mg, 0.085 mmol), and freshly prepared triflyl azide (TfN_3) in CH_2Cl_2 (6 mL) (freshly prepared from triflic anhydride and sodium azide) and the mixture was stirred at room temperature for 18 h. After solvent removal, the residue was taken up with a EtOAc and water mixtureand product was extracted with EtOAc (×2). The pooled organic phase was concentrated for flash column chromatography (hexane/EtOAc, 1:4). The resulting C2-azido compound was then dissolved in CH_3CN (4 mL) and CSA (18 mg, 0.08 mmol) and benzaldehyde dimethyl acetal (0.25 mL, 1.54 mmol) were added. After the mixture was stirred at room temperature under Ar for 12 h, the reaction was quenched with addition of TEA. Subsequent solvent removal and flash column chromatographic purification (hexane/CH_2Cl_2/EtOAc, 2:1:0.25) furnished **10** (0.41 g, 60% from **5**) as a white glassy solid. For compound **10**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.36 (m, 7H; aromatic), 7.17 (d, J = 8.1 Hz, 2H; aromatic), 5.52 (s, 1H), 4.48 (t, J = 10.3 Hz, 1H), 4.37 (dd, J = 10.6, 4.4 Hz, 1H), 3.78−3.73 (m, 2H), 3.47−3.41 (m, 2H), 3.32 (t, J = 9.5 Hz, 1H), 2.72 (d, J = 2.9 Hz, 1H), 2.37 (s, 3H; PhMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.12, 136.68, 134.28, 129.91, 129.43, 128.40, 126.70, 126.21, 101.92, 86.81, 80.17, 74.10, 70.22, 68.42, 65.97, 21.20; HRMS calcd for $C_{20}H_{21}N_3O_4SNa$ $(M + Na)^+$ 422.1145, found 422.1147.

Compound 11. A solution of compound **10** (0.18 g, 0.45 mmol) in DMF (2 mL) was added to a suspension of NaH (13 mg, 0.54 mmol), Bu_4NI (17 mg, 0.045 mmol), and BnBr (0.11 mL, 0.9 mmol) in DMF (3 mL) at 0 °C. The reaction mixture was stirred under Ar and brought to room temperature. After 3 h the reaction was quenched with the addition of MeOH. After concentration in a vacuum, the residue was dissolved in CH_2Cl_2 and washed with 0.1 M HCl, H_2O, and brine, dried ($MgSO_4$), and concentrated for flash column chromatography purification (hexane/CH_2Cl_2/Et_2O, 2.5:1:0 to 2.5:1:0.1). Compound **11** (0.18 g, 82%) was obtained as a white glassy solid. For compound **11**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.27 (m, 12H; aromatic), 7.14 (d, J = 8.1 Hz, 2H; aromatic), 5.56 (s, 1H), 4.90 (d, J = 10.6 Hz, 1H), 4.77 (d, J = 10.6 Hz, 1H), 4.42 (d, J = 10.3 Hz, 1H), 4.38 (dd, J = 10.6, 5.1 Hz, 1H), 3.77 (t, J = 10.3 Hz, 1H), 3.65 (t, J = 9.2 Hz, 1H), 3.60 (t, J = 9.2 Hz, 1H), 3.46−3.41 (m, 1H), 3.32 (dd, J = 10.3, 8.8 Hz, 1H), 2.35 (s, 3H; PhMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.14, 137.50, 137.03, 134.52, 129.89, 129.06, 128.43, 128.33, 128.29, 128.01, 126.40, 125.92, 101.19, 86.50, 81.26, 80.96, 75.21, 70.41, 68.47, 64.42, 21.19; HRMS calcd for $C_{27}H_{27}N_3O_4SNa$ $(M + Na)^+$ 512.1614, found 512.1604.

Compound 12. To compound **11** (0.18 g, 0.37 mmol) and Et_3SiH (0.6 mL, 3.7 mmol) in CH_2Cl_2 (2 mL) was added TFA (0.3 mL, 3.7 mmol). The reaction mixture was stirred under Ar at 0 °C for 1 h and quenched with $NaHCO_3$. The product was extracted with CH_2Cl_2 (×2) and the organic phase was washed with brine, dried ($MgSO_4$), and concentrated for flash column chromatography (hexane/CH_2Cl_2/EtOAc, 3:1:0.3). Compound **12** (0.16 g, 90%) was obtained as a colorless viscous oil. For compound **12**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 6.6 Hz, 2H; aromatic), 7.36−7.29 (m, 10H; aromatic), 7.06 (d, J = 7.7 Hz, 2H; aromatic), 4.84 (dd, J = 35.6, 10.6 Hz, 2H), 4.56 (dd, J = 24.6, 12.1 Hz, 2H), 4.35 (d, J = 9.9 Hz, 1H), 3.78−3.71 (ddd, J = 23.1, 10.2, 4.8 Hz, 2H), 3.59 (dt, J = 9.6, 2.2 Hz, 1H), 3.43−3.40 (m, 1H), 3.34 (t, J = 9.1 Hz, 1H), 3.26 (t, J = 9.3 Hz 1H), 2.73 (d, J = 2.6 Hz, 1H), 2.31 (s, 3H; PhMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.69, 137.77, 137.64, 134.14, 19.72, 128.57, 128.42, 128.18, 128.06, 127.79, 127.64, 126.96, 86.06, 84.52, 77.91, 75.41, 73.67, 71.84, 70.20, 64.25, 21.12; HRMS calcd for $C_{27}H_{29}N_3O_4SNa$ $(M + Na)^+$ 514.1771, found 514.1780.

Compound 13. To compound **12** (0.15 g, 0.31 mmol) in MeOH/CH_2Cl_2 (2 mL, 1:1) was added 1,3-dithiopropane (0.15 mL, 1.5 mmol) and TEA (0.20 mL, 1.5 mmol). The reaction mixture was stirred at 40 °C under Ar overnight and then coevaporated with toluene (×2). The residue was dissolved in CH_2Cl_2 and washed with H_2O and brine, dried ($MgSO_4$), and concentrated for flash column chromatography purification (hexane/CH_2Cl_2/EtOAc, 2:1:0.5). Compound **13** (0.12 g, 80%) was obtained as a white glassy solid. For compound **13**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 8.1 Hz, 2H; aromatic), 7.38−7.26 (m, 10H; aromatic), 7.05 (d, J = 7.7 Hz, 2H; aromatic), 4.94 (d, J = 11.3 Hz, 1H), 4.75 (d, J = 11.7 Hz, 1H), 4.57 (dd, J = 22.0, 12.1 Hz, 2H), 4.40 (d, J = 9.5 Hz, 1H), 3.78 (ddd, J = 34.1, 9.9, 4.8 Hz, 2H), 3.68 (t, J = 9.2 Hz, 1H), 3.50−3.46 (m, 1H), 3.33 (t, J = 9.1 Hz, 1H), 2.28 (t, J = 9.6 Hz 1H), 2.30 (s, 3H; PhMe), 1.69 (br, 2H;); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.43, 138.17, 137.64, 133.34, 129.61, 128.56, 128.43, 128.02, 127.97, 127.88, 127.80, 127.71, 89.06, 86.30, 77.71, 75.14, 73.73, 72.95, 70.92, 54.69, 21.09; HRMS calcd for $C_{27}H_{31}NO_4SNa$ $(M + Na)^+$ 488.1866, found 488.1868.

Compound 14. To compound **13** (0.12 g, 0.29 mmol) in THF (3 mL) was added $NaHCO_3$ (49 mg, 0.58 mmol) and 2,2,2-trichloroethyl chloroformate (TrocCl) (48 μL, 0.35 mmol). The reaction mixture was stirred at room temperature under Ar for 4 h and then filtered, and THF was removed in a vacuum. The residue was dissolved in CH_2Cl_2 and washed with H_2O and brine, dried ($MgSO_4$), and concentrated for flash column chromatography (hexane/CH_2Cl_2/EtOAc, 3:1:0.5 to 3:1:1). Compound **14** (0.17 g, 90%) was obtained as a white glassy solid. For compound **14**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.26 (m, 12H; aromatic), 7.05 (d, J = 8.1 Hz, 2H; aromatic), 5.11 (d, J = 7.7 Hz, 1H), 4.90 (d, J = 10.2 Hz, 1H), 4.76 (s, 4H), 4.57 (dd, J = 11.8, 20 Hz, 2H), 3.80−3.73 (m, 3H), 3.67 (t, J = 8.8 Hz, 1H), 3.52−3.50 (m, 1H), 3.35 (dd, J = 19.1, 9.9 Hz, 1H), 2.77 (br, 1H), 2.30 (s, 3H; PhMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.78, 138.21, 137.98, 137.69, 133.19, 129.70, 128.58, 128.46, 128.15, 128.01, 127.82, 127.73, 86.04, 81.77, 77.82, 74.73, 74.44, 73.73, 72.98, 70.57, 56.05, 21.11; HRMS calcd for $C_{30}H_{32}Cl_3NO_6SNa$ $(M + Na)^+$ 662.0908, found 662.0902.

Compound 16. Glucosaminyl acceptor **14** (0.53 g, 0.83 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (0.51 g, 2.5 mmol), and MS (4 Å, 2 g) were suspended in dry CH_2Cl_2/toluene (15 mL, 2:1) and stirred at room temperature for 2 h under Ar. The mixture was cooled to −23 °C and α-bromoacetogalactoside **15** (0.5 g, 1.2 mmol) and silver triflate (AgOTf) (0.3 g, 1.2 mmol) were added. The reaction mixture was stirred at −10 °C for 1.5 h, additional α-bromoacetogalactoside **15** (0.3 g, 0.83 mmol) and AgOTf (0.2 g, 0.83 mmol) were added, and the reaction mixture was stirred again for 1 h. The MS were filtered off and the filtrate was washed with 0.1 M HCl, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated for flash column chromatography (hexane/CH_2Cl_2/EtOAc, 3:1:1). Compound **16** (0.56 g, 70%) was obtained as white glassy solid. For compound **16**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.27 (m, 12H; aromatic), 7.05 (d, J = 8.5 Hz, 1H; aromatic), 5.28 (d, J = 3.3 Hz, 1H), 5.18 (d, J = 7.7 Hz, 1H), 5.13 (dd, J = 10.6, 8.0 Hz, 1H), 4.92 (d, J = 9.2 Hz, 1H), 4.90 (d, J = 10.5 Hz, 1H), 4.87 (dd, J = 10.2, 3.7 Hz, 1H), 4.74 (dd, J = 38.5, 12.1 Hz, 2H), 4.71 (d, J = 11.7 Hz, 1H), 4.60 (d, J = 12.8 Hz, 1H), 4.59 (d, J = 8.0 Hz, 1H), 4.51 (d, J = 12.1 Hz 1H), 4.03−3.96 (m, 2H), 3.90 (dd, J = 11.4, 6.3 Hz, 1H), 3.85 (t, J = 8.8 Hz, 1H), 3.76 (br, 2H), 3.61 (t, J = 7.0 Hz, 1H), 3.45 (d, J = 8.8 Hz, 1H), 3.33 (q, J = 8.8 Hz, 1H), 2.30 (s, 3H; PhMe), 2.09 (s, 3H; MeC═O), 1.99 (s, 3H; MeC═O), 1.97 (s, 6H; MeC═O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.17, 170.53, 169.25, 153.69, 138.29, 138.15, 137.87, 133.44, 129.69, 128.52, 128.26, 128.01, 127.94, 127.84, 127.71, 99.98, 85.54, 79.30, 79.05, 76.28, 74.57, 74.37, 73.57, 70.84, 69.43, 67.94, 66.76, 60.57, 55.99, 21.12, 20.73, 20.61, 20.60, 20.55; HRMS calcd for $C_{44}H_{50}Cl_3NO_{15}SNa$ $(M + Na)^+$ 992.1859, found 992.1862.

Compound 17. Galactosyl donor **4** (1.5 g, 2.16 mmol) and glucosaminyl acceptor **7** (0.85 g, 1.44 mmol) and MS (AW-300, 3 g) were suspended in dry CH_2Cl_2 (15 mL) under Ar at room temperature for 1 h. The reaction mixture was then brought to −45 °C and *N*-iodosuccinimide (NIS) (0.49 g, 2.16 mmol) and 0.5 M trifluoromethane-sulfonic acid in Et_2O (TfOH) (0.43 mL, 0.0216 mmol) were added. The reaction mixture was stirred at −45 °C for 2 h and quenched with addition of sat. $NaHCO_3$ and solid $Na_2S_2O_3$. MS were filtered off and the filtrate was washed with sat. $Na_2S_2O_3$, sat. $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), and concentrated for flash column chromatography (toluene/CH_2Cl_2/EtOAc, 4:1:1). Compound **17** (0.8 g, 40%) was obtained as a white glassy solid. For compound **17**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 8.1 Hz, 2H; aromatic), 7.35−7.21 (m, 17H; aromatic), 7.01 (d, J = 8.1 Hz, 2H; aromatic), 6.87 (d, J = 8.5 Hz, 2H; aromatic), 5.40 (d, J = 9.9 Hz, 1H), 5.13 (dd, J = 10.3, 7.9 Hz, 1H), 5.01 (t, J = 9.6 Hz, 1H), 4.90 (d, J = 11.7 Hz, 1H), 4.74 (dd, J = 31.9, 12.1 Hz, 2H), 4.62 (d, J = 12.1 Hz, 1H), 4.56 (d, J = 10.3 Hz, 1H), 4.55 (d, J = 12.1 Hz, 1H), 4.48 (d, J = 12.1 Hz, 1H), 4.45 (d, J = 12.1 Hz, 1H), 4.41 (d, J = 12.1 Hz, 1H), 4.39 (s, 2H), 4.35 (d, J = 7.7 Hz, 1H), 3.88−3.84 (m, 2H), 3.78 (s, 3H; OMe), 3.76−3.72 (m, 3H), 3.57−3.55 (d, J = 8.4 Hz, 1H), 3.54−3.52 (m, 1H), 3.50 (dd, J = 8.8, 4.8 Hz, 1H), 3.38 (dd, J = 7.7, 5.6 Hz, 1H), 3.34 (dd, J = 9.9, 2.5 Hz, 1H), 2.62−2.59 (m, 2H; Lev-CH_2), 2.41 (t, J = 6.6 Hz, 2H; Lev-CH_2), 2.26 (s, 3H; PhMe), 2.09 (s, 3H; MeC═O), 1.85 (s, 3H; MeC═O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.24, 171.00, 170.58, 159.13, 154.10, 138.42, 137.87, 137.54, 132.94, 129.88, 129.49, 129.02, 128.54, 128.37, 128.23, 128.02, 127.78, 127.73, 127.69, 127.67, 127.52, 127.29, 113.65, 100.34, 95.46, 86.92, 79.63, 78.92, 74.30, 74.21, 73.86, 73.28, 73.02, 72.29, 71.91, 71.34, 67.94, 67.86, 55.12, 55.11, 54.86, 37.56, 29.72, 27.71, 20.98, 20.58; HRMS calcd for $C_{58}H_{64}Cl_3NO_{15}SNa$ $(M + Na)^+$ 1174.2954, found 1174.2963.

Compound 18. To compound **17** (0.3 g, 0.26 mmol) in CH_2Cl_2/phosphate buffer mixture (3 mL, 10:1) was added DDQ (0.8 g, 3 mmol) and the reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with CH_2Cl_2, and washed with sat. $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), and concentrated for flash column chromatography (hexane/EtOAc, 1.5:1 gradient to 1:1). Compound **18** (0.2 g, 75%) was obtained as a white glassy solid. For compound **18**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 8.1 Hz, 2H; aromatic), 7.34−7.24 (m, 15H; aromatic), 7.04 (d, J = 7.7 Hz, 2H; aromatic), 5.38 (d, J = 9.9 Hz, 1H), 5.02 (t, J = 9.5 Hz, 1H), 4.83 (t, J = 9.0 Hz, 1H), 4.79 (d, J = 12.1 Hz, 1H), 4.76 (dd, J = 39.7, 12.1 Hz, 2H), 4.71 (d, J = 11.7 Hz, 1H), 4.66 (d, J = 12.1 Hz, 1H), 4.61 (d, J = 12.1 Hz, 1H), 4.58 (d, J = 10.6 Hz, 1H), 4.49 (d, J = 11.7 Hz, 1H), 4.43 (dd, J = 15.0, 11.7 Hz, 2H), 4.37 (d, J = 7.7 Hz, 1H), 3.82 (t, J = 9.5 Hz, 1H), 3.81 (dd, J = 10.6, 3.3 Hz, 2H), 3.76−3.71 (m, 2H), 3.58−3.53 (m, 2H), 3.51 (br, 1H; H-5), 3.49−3.44 (m, 2H), 2.73−2.64 (m, 2H; Lev-CH_2), 2.51−2.43 (m, 2H; Lev-CH_2), 2.28 (s,3H; PhMe), 2.12 (s, 3H; MeC═O), 1.89 (s, 3H; MeC═O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.77, 172.33, 170.59, 154.10, 138.13, 138.03, 137.45, 133.16, 129.54, 128.46, 128.41, 128.34, 128.30, 127.85, 127.72, 127.65, 127.61, 127.56, 100.02, 95.47, 86.98, 78.95, 75.92, 75.03, 74.37, 74.28, 73.91, 73.86, 73.43, 73.32, 72.97, 67.87, 67.68, 54.92, 37.90, 29.69, 27.85, 21.03, 20.67; HRMS calcd for $C_{50}H_{56}Cl_3NO_{14}SNa$ $(M + Na)^+$ 1054.2379, found 1054.2363.

Tetrasaccharide 21. Lactosaminyl donor **17** (0.52 g, 0.45 mmol), acceptor **20** (0.4 g, 0.38 mmol), and MS (AW-300, 1 g) were suspended in dry CH_2Cl_2 (4 mL) under Ar at room temperature for 1 h. The reaction mixture was then brought to −30 °C, followed by addition of NIS (0.1 g, 0.45 mmol) and 0.5 M TfOH in Et_2O (0.1 mL, 0.05 mmol). The reaction mixture was stirred at −30 °C for 3 h and quenched with sat. $NaHCO_3$ and solid $Na_2S_2O_3$. MS was filtered off and the filtrate was washed with sat. $Na_2S_2O_3$, sat. $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), and concentrated for flash column chromatography (toluene/EtOAc, 5.5:4.5). Compound **21** (0.6 g, 88%) was obtained as a white glassy solid. For compound **21**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.17 (m, 32H; aromatic), 6.88 (d, J = 8.4 Hz, 2H; aromatic), 6.25 (d, J = 9.9 Hz, 1H), 5.26 (d, J = 9.2 Hz, 1H), 5.21 (t, J = 9.5 Hz, 1H), 5.15 (d, J = 9.9 Hz, 1H), 5.05 (d, J = 9.5 Hz, 1H), 5.02 (d, J = 11.4 Hz, 1H), 4.98 (d, J = 9.9 Hz, 1H), 4.91 (d, J = 11.7 Hz, 1H), 4.90 (d, J = 12.5 Hz, 1H), 4.74−4.66 (m, 4 H), 4.56 (d, J = 11.7 Hz, 1H), 4.50−4.56 (m, 3H), 4.41−4.32 (m, 9H), 3.93−3.82 (m, 6 H), 3.79 (s, 3H; OMe), 3.78−3.75 (m, 2H), 3.68 (br, 2H), 3.65 (s, 3H; CO_2Me), 3.60−3.56 (m, 2H), 3.52−3.34 (m, 8H), 2.85−2.80 (m, 1H; Lev-CH_2), 2.73−2.56 (m, 2H; Lev-CH_2), 2.53−2.39 (m, 4H; Lev-CH_2), 2.30−2.27 (m, 3H; Lev-CH_2, aglycon-CH_2), 2.21 (s, 3H; MeC═O), 2.12 (s, 3H; MeC═O), 1.87 (s, 3H; MeC═O), 1.85 (s, 3H; MeC═O), 1.63−1.51 (m, 4 H; aglycon-CH_2), 1.37−1.31 (m, 2H; aglycon-CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.24, 206.28, 174.06, 171.04, 170.73, 170.62, 169.97, 159.15, 154.61, 154.21,138.89, 138.51, 137.95, 137.89, 137.69, 137.54, 129.92, 129.00, 128.38, 128.33, 128.13, 128.04, 127.88,127.78, 127.72, 127.67, 127.62, 127.57, 127.27, 127.10, 113.67, 101.38, 101.12, 100.56, 100.12, 95.86, 95.51, 79.79, 77.69, 75.53, 75.00, 74.90, 74.79, 74.59, 74.28, 74.21, 74.17, 73.98, 73.63, 73.41, 73.34, 73.27, 72.96, 72.73, 72.42, 72.38, 72.19, 72.09, 71.28, 69.23, 68.11, 67.93, 67.76, 67.71, 56.44, 55.80, 55.16, 51.42, 37.61, 33.72, 29.86, 29.78, 28.92, 27.74, 25.18, 24.30, 20.63; HRMS calcd for $C_{101}H_{118}Cl_6N_2O_{32}Na$ $(M + Na)^+$ 2103.569, found 2103.564.

Tetrasaccharide 22. To compound **21** (0.2 g, 0.17 mmol) in CH_2Cl_2 (4 mL) were added TFA (0.3 mL) and anisole (0.3 mL) at 0 °C and the reaction mixture was warmed to room temperature over 1 h. Saturated $NaHCO_3$ was added to quench the reaction and product was extracted with CH_2Cl_2 (×3). The pooled organic phase was washed with H_2O and brine, dried ($MgSO_4$), and concentrated for flash column chromatography (hexane/CH_2Cl_2/EtOAc, 1:1:2). Compound **22** (0.16 g, 81%) was obtained as a white glassy solid. For compound **22**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.20 (m, 30H), 6.27 (d, J = 9.5 Hz, 1H), 5.29 (br, 1H), 5.06 (d, J = 8.4 Hz, 1H), 5.03 (d, J = 11.7 Hz, 1H), 4.98 (d, J = 9.9 Hz, 1H), 4.90 (d, J = 12.1 Hz, 1H), 4.85 (t, J = 9.5, 1H), 4.74−4.62 (m, 7H), 4.51−4.34 (m, 11H), 3.95−3.75 (m, 9H), 3.68 (br, 2H), 3.65 (s, 3H; CO_2Me), 3.61−3.41 (m, 11H), 2.86−2.65 (m, 3H; Lev-CH_2), 2.52−2.41 (m, 5H; OH, Lev-CH_2), 2.29−2.26 (m, 3H; Lev-CH_2, aglycon-CH_2), 2.20

(s, 3H; MeC═O), 2.14 (s, 3H; MeC═O), 1.89 (s, 3H; MeC═O), 1.87 (s, 3H; MeC═O), 1.63−1.52 (m, 4 H; aglycon-CH_2), 1.37−1.31 (m, 2H; aglycon-CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.40, 206.65, 174.06, 172.32, 170.76, 170.60, 169.99, 154.62, 154.21, 138.88, 138.13, 137.90, 137.86, 137.67, 137.39, 128.40, 128.37, 128.33, 128.13, 127.90, 127.87, 127.85, 127.73, 127.69, 127.62, 127.57, 127.53, 127.47, 127.12, 101.37, 101.08, 100.15, 100.11, 95.65, 95.51, 77.69, 75.92, 75.51, 75.13, 75.02, 74.97, 74.72, 74.62, 74.27, 74.18, 74.01, 73.63, 73.37, 73.34, 73.28, 73.01, 72.90, 72.84, 72.43, 72.31, 69.22, 68.09, 67.75, 67.53, 56.41, 55.08, 51.42, 37.87, 37.61, 33.72, 29.88, 29.73, 28.92, 27.83, 27.77, 25.18, 24.30, 20.68, 20.62; HRMS calcd for $C_{93}H_{110}Cl_6N_2O_{31}Na$ $(M + Na)^+$ 1983.512, found 1983.519.

Hexasaccharide 23. Lactosaminyl building blocks **16** (0.155 g, 0.16 mmol), **18** (0.1 g, 0.097 mmol), and MS (AW-300, 0.5 g) were suspended in dry CH_2Cl_2 (2 mL) under Ar at room temperature for 1 h, then cooled to −45 °C. NIS (36 mg, 0.16 mmol) and 0.5 M TfOH in Et_2O (30 μL, 15 μmol) were added to the mixture. The solution was then stirred at −35 °C for 1.5 h and the progress of the reaction was monitored by TLC (developed by hexane/EtOAc, 4:3). When all **16** was reacted, the third lactosaminyl building block **20** (0.25 g, 0.24 mmol) was added, together with additional NIS (44 mg, 0.194 mmol) and 0.5 M TfOH in Et_2O (20 μL, 10 μmol). The mixture was stirred at −35 °C for an additional 2.5 h and quenched with sat. $NaHCO_3$ and solid $Na_2S_2O_3$. MS were filtered off and the filtrate was washed with sat. $Na_2S_2O_3$, sat. $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), and concentrated for flash column chromatography (hexane/EtOAc, 3:4). Hexasaccharide **23** (0.15 g, 55% with respect to **18**) was obtained as a white glassy solid. For compound **23**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.20 (m, 40H; aromatic), 6.33 (d, J = 9.2 Hz, 1H), 6.36 (d, J = 9.9 Hz, 1H), 5.25 (d, J = 3.3 Hz, 1H), 5.21 (br, 2H), 5.13 (dd, J = 10.3, 8.1 Hz, 1H), 5.10−4.97 (m, 5H), 4.90 (dd, J = 11.0, 8.8 Hz, 2H), 4.84 (dd, J = 10.3, 3.3 Hz, 1H), 4.76−4.66 (m, 8H), 4.61 (d, J = 8.1 Hz, 1H; H-1), 4.51−4.45 (m, 6H), 4.40−4.34 (m, 8H), 3.99 (t, J = 8.8 Hz, 1H), 3.95−3.91 (m, 2H), 3.88−3.81 (m, 7H), 3.73 (br, 6H), 3.68 (br, 2H), 3.66 (s, 3H; CO_2Me), 3.56−3.51 (m, 5H), 3.49−3.42 (m, 5H), 2.84 (br, 2H; Lev-CH_2), 2.58−2.42 (m, 4H; Lev-CH_2), 2.29 (t, J = 7.3 Hz, 4H; Lev-CH_2, aglycon-CH_2), 2.22 (s, 3H; MeC═O), 2.21 (s, 3H; MeC═O), 2.11 (s, 3H; MeC═O), 1.98 (s, 3H; MeC═O), 1.97 (s, 3H; MeC═O), 1.96 (s, 3H; MeC═O), 1.86 (s, 3H; MeC═O), 1.85 (s, 3H; MeC═O), 1.61−1.52 (m, 4H; aglycon-CH_2), 1.37−1.31 (m, 2H; aglycon-CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.67, 209.38, 174.12, 170.80, 170.73, 170.65, 170.12, 170.10, 170.00, 169.95, 169.31, 154.68, 154.49, 154.26, 138.96, 138.87, 138.70, 137.97, 137.92, 137.71, 137.66, 128.54, 128.46, 128.40, 128.14, 128.06, 128.02, 127.95, 127.82, 127.78, 127.75, 127.66, 127.22, 127.19, 127.15, 101.46, 101.31, 101.18, 100.33, 100.28, 100.18, 95.88, 95.84, 95.54, 79.71, 78.14, 77.83, 75.65, 75.36, 75.11, 75.06, 74.77, 74.71, 74.62, 74.35, 74.26, 74.10, 74.04, 73.75, 73.71, 73.56, 73.41, 73.38, 73.35, 73.11, 72.80, 72.44, 70.96, 70.39, 69.64, 69.32, 68.09, 67.93, 67.79, 66.75, 60.61, 57.43, 56.49, 55.86, 51.49, 37.68, 37.45, 33.77, 30.21, 29.91, 28.98, 27.83, 27.65, 25.24, 24.35, 20.75, 20.67, 20.58, 20.52; ESI-MS calcd for $C_{130}H_{152}Cl_9N_3O_{46}Na$ $(M + Na)^+$ 2829, found 2829.

Octasaccharide 24. Lactosaminyl building blocks **16** (0.1 g, 0.1 mmol), **18** (0.1 g, 0.097 mmol), and MS (AW-300, 0.5 g) were suspended in dry CH_2Cl_2 (2.5 mL) at room temperature under Ar for 1 h and then brought to −45 °C. NIS (23 mg, 0.1 mmol) and 0.5 M TfOH in Et_2O (30 μL, 15 μmol) were then added to the mixture. The reaction mixture was stirred at −35 °C for 1.5 h and the reaction was monitored by TLC (developed by toluene/EtOAc, 2:1). When all **16** was reacted, tetrasaccharide building block **22** (0.26 g, 0.13 mmol) was added, followed by an additional NIS (29 mg, 0.13 mmol) and 0.5 M TfOH in Et_2O (20 μL, 10 μmol). The reaction temperature was raised to −20 °C and stirred for another 2.5 h. The reaction was quenched with sat. $NaHCO_3$ and solid $Na_2S_2O_3$. MS were filtered off and the filtrate was washed with sat. $Na_2S_2O_3$, sat. $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), and concentrated for flash column chromatography (toluene/CH_2Cl_2/EtOAc, 4:2:3). Octasaccharide **24** (0.14 g, 35% with respect to **18**) was obtained as a white glassy solid. For compound **24**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49−7.27 (m, 55H; aromatic), 6.45−6.34 (m, 3H), 5.42−4.91 (m, 15H), 4.90−4.69 (m, 10H), 4.65−4.41 (m, 20H), 4.11−3.73 (m, 30H), 3.70−3.50 (m, 15H), 3.03−2.87 (m, 3H; Lev-CH_2), 2.69−2.51 (m, 6H; Lev-CH_2), 2.47−2.32 (m, 8H; Lev-CH_2, aglycon-CH_2, MeC═O), 2.30 (s, 3H; MeC═O), 2.19 (s, 3H; MeC═O), 2.08 (s, 3H; MeC═O), 2.07 (s, 3H; MeC═O), 2.06 (s, 3H; MeC═O), 2.04 (s, 3H; MeC═O), 1.95 (s, 3H; MeC═O), 1.94 (s, 3H; MeC═O), 1.93 (s, 3H; MeC═O), 1.76−1.63 (m, 4H; aglycon-CH_2), 1.50−1.42 (m, 2H; aglycon-CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.64, 209.34, 174.08, 170.79, 170.70, 170.63, 170.07, 170.05, 169.96, 169.25, 154.62, 154.44, 154.23, 138.83, 138.62, 137.90, 137.84, 137.80, 137.64, 137.61, 128.48, 128.40, 128.33, 128.30, 128.10, 128.05, 127.96, 127.92, 127.72, 127.69, 127.60, 127.18, 127.14, 101.39, 101.23, 101.18, 100.27, 100.11, 95.82, 95.50, 79.64, 78.05, 77.73, 76.94, 75.57, 75.30, 75.00, 74.73, 74.65, 74.57, 74.21, 74.07, 73.99, 73.71, 73.65, 73.50, 73.34, 73.30, 73.25, 73.05, 72.90, 72.75, 72.39, 70.90, 70.34, 69.57, 69.25, 68.05, 67.87, 67.76, 66.70, 60.56, 57.37, 56.42, 55.79, 51.43, 37.62, 37.39, 33.71, 30.14, 29.86, 29.84, 28.92, 27.78, 27.60, 25.18, 24.28, 20.69, 20.61, 20.51, 20.46; MALDI-TOF MS calcd for $C_{173}H_{200}Cl_{12}N_4O_{60}Na$ $(M + Na)^+$ 3736, found 3736.

Supporting Information Available: Spectral data for all the compounds **1**−**3**, **6**−**8**, **10**−**14**, **16**−**18**, and **21**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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