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Articles

A Highly Convergent Synthesis of a Complex Oligosaccharide Derived from Group B Type III *Streptococcus*

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An efficient synthesis of a heptasaccharide derived from group B type III *Streptococcus* carrying an artificial spacer (**1**) is described. Rapid assembly of a protected heptasaccharide (**16a**) is accomplished from readily available building blocks **2**−**5** without a single protecting group manipulation between glycosylation steps. The synthetic strategy may be applied to the assembly of other branched complex oligosaccharides. The deprotected heptasaccharide **1** was coupled to a poly[*N*-(acryloyloxy)succinimide, and the resulting material will be used for the development of an ELISA assay to detect antibodies against GBS, type III in pregnant women.

Introduction

The Gram-negative bacteria, group B type III *Streptococcus* (GBS, type III), is the most prevalent cause of neonatal sepsis.[1] Mortality and morbidity rates from these infections continue to be substantial, and a method to prevent this illness is urgently needed. Active immunization of newborn babies is not practical, since most cases occur within the first month of life. However, newborns may be protected by vaccination of pregnant mothers who are deficient in antibodies specific for the native, type III GBS polysaccharides.[2,3] Antibodies raised by these women will pass the placenta and supply the newborns with protective levels of antibodies. The feasibility of this approach was supported by a study of Baker and co-workers[4] in which purified GBS capsular polysaccharide was administered to women during the third trimester of pregnancy. Among women with low or undetectable preexisting levels of specific antibodies, 57% developed a rise in antibody titer. The low response rate and the absence of T-lymphocyte stimulation of vaccination with GBS capsular polysaccharides were addressed by conjugation of the capsular polysaccharide to a carrier protein. Successful preclinical trials with these conjugates led to phase-1 and phase-2 trials that assessed safety, immunogenicity, and dosing of GBS conjugated vaccines.[5]

Polysaccharide−protein conjugates have been prepared by several different coupling procedures. In general, these methods suffer from low reproducibility, protein cross-linking, or destruction of vital immunological domains.

(1) Wald, E. R.; Bergman, I.; Taylor, H. G.; Chiponis, D.; Porter, C.; Kubek, K. *Pediatrics* **1986**, *77*, 217−221.
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(3) Baker, C. J.; Rench, M. A.; Edwards, M. S.; Carpenter, R. J.; Hays, B. M.; Kasper, D. L. *New Eng. J. Med.* **1988**, *319*, 1180−1185.
(4) Baker, C. J.; Kasper, D. L. *New Engl. J. Med.* **1976**, *294*, 753−756.
(5) (a) Paoletti, L. C.; Kasper, D. L.; Michon, F.; Difabio, J.; Holme, K.; Jennings, H. J.; Wessels, M. R. *J. Biol. Chem.* **1990**, *265*, 18278−18283. (b) Lagergard, T.; Shiloach, J.; Robbins, J. B.;. Schneerson, R. *Infect. Immun.* **1990**, 58, 687−694.

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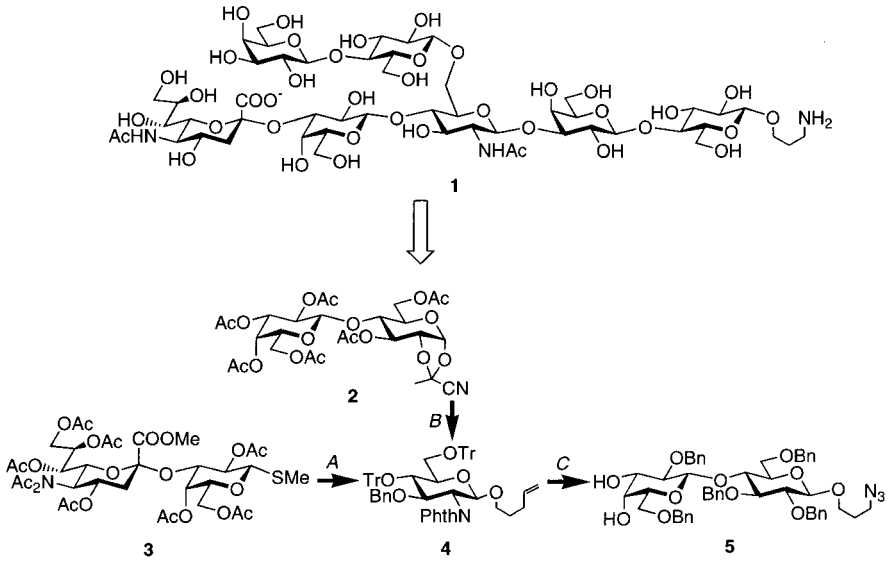
Scheme 1. Retrosynthetic Analysis of 1



On the other hand, synthetic oligosaccharides that are equipped with an artificial spacer that has a unique chemical functionality can be coupled to proteins in a more controlled and reproducible manner.[6]

We report here a highly convergent synthesis of a heptasaccharide (**1**, Scheme 1) derived from type III GBS oligosaccharide. The compound **1**, which represents the smallest saccharide structure that can raise relevant antibodies,[7] is equipped with an artificial aminopropyl spacer. This spacer allows selective coupling to carrier proteins to give highly immunogenic conjugates. In this study, the heptasaccharide was coupled to an activated polymer for the preparation of a material that can be used for the development of an ELISA assay. Such an assay will make it possible to detect antibody levels in pregnant women.

Results and Discussion

Ideally, complex oligosaccharides are synthesized by a highly convergent strategy whereby glycosyl donors and acceptors are assembled into oligomeric structures involving a minimal number of synthetic steps.[8] The strategic plan for a convergent synthesis for **1** that meets this requirement is summarized in retrosynthetic Scheme 1. Thioalkyl and *n*-pentenyl glycosides **3** and **4** were selected as key saccharide building blocks. The anomeric constituents of these compounds are stable under many protecting group manipulations, therefore offering efficient protection during the preparation of targeted glycosyl donors and acceptors. In the presence of an appropriate activating reagent, however, thioglycosides[9] and *n*-pentenyl glycosides[10] can be activated and act as highly reactive glycosyl donors. The second important strategic issue was the use of triphenylmethyl (trityl, Tr) ethers as glycosyl acceptors. Trityl ethers are often used as protecting groups, but they can also act as efficient glycosyl acceptors. More importantly, secondary trityl ethers are much more reactive in glycosylations than primary ones.[11] These features permitted first glycosylation of the secondary trityl ether at C-4 of **4** with sialic acid containing thioglycosyl donor **3** followed by lactosylation of the primary trityl group with cyanoethylidene glycosyl donor **2**. In general, it is attractive to first glycosylate a hydroxyl of low reactivity followed by glycosylation of more reactive (primary) ones. A critical aspect was the exploitation of the finding that thioglycosides can be activated with methyl trifluoromethanesulfonate (methyl triflate, MeOTf) without affecting an *n*-pentenyl functionality. This feature made it possible that the *n*-pentenyl glycoside of **4** could act as a glycosyl acceptor in the glycosylation with thioglycoside **3**. Another key aspect was that the acetamido group at C-5 of the sialic acid moiety of **3** was protected as an *N*-acetylacetamido group. This protection prevented the undesirable N-methylation of the acetamido group at C-5′ of the glycosyl donor **3** during the MeOTf-mediated glycosylation. In addition, as it was found, this functionality facilitates the synthesis of **3**. Finally, the cheaply available disaccharide D-lactose was utilized for the preparation of the building blocks **2** and **5**, therefore reducing the number of required glycosylations. These strategic issues facilitated the assembly of **16a** in a convergent manner form the building blocks **2**−**5** without a single protecting group manipulation between glycosylation steps.

The preparation of building blocks **3**−**5** is shown in Scheme 2. Compound **3** was synthesized by the following sequence of manipulations. Coupling of **6b**[12] with **7**[13] in the presence of *N*-iodosuccinimide (NIS) and a catalytic

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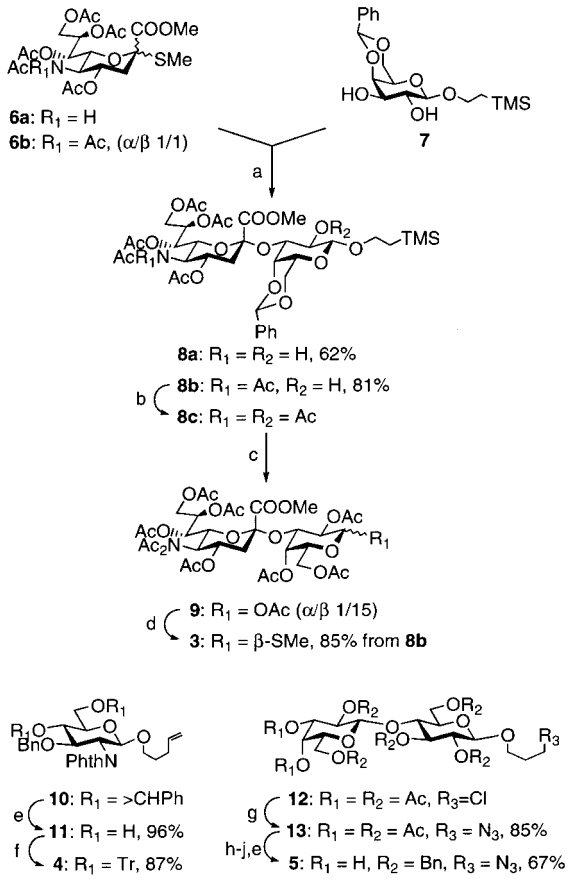
Scheme 2. Synthesis of the Building Blocks 3−5[a]



[a] Reagents: (a) NIS/TfOH, DCM; (b) Ac_2O/pyridine; (c) Ac_2O, $BF_3{\cdot}Et_2O$, DCM; (d) TMSSMe, TMSOTf, DCM; (e) TFA, DCM/H_2O; (f) $TrClO_4$, γ-collidine, DCM; (g) NaN_3, KI, DMF; (h) MeONa/MeOH; (i) TMSCl, acetone; (j) BnBr, NaH, DMF.

amount of trifluoromethanesulfonic (triflic) acid in acetonitrile at −35 °C gave disaccharide **8b** in an exceptional yield of 81%. On the other hand, glycosylation of **7** with the popular methyl thio sialyl donor **6a**[14] with **7** under similar conditions gave a much lower yield (62%) of the corresponding disaccharide **8a**. In addition, the reaction time for the preparation of **8b** was significantly shorter than that for **8a** (5 min vs 2.5−3 h). These featureshighlight the fact that the *N*-acetylacetamido moiety of **6b** significantly improves its glycosyl donor properties. O-Acetylation of **8a** with acetic anhydride in pyridine (**8c**) followed by acetolysis of the anomeric TMSEt group and benzylidene acetal with acetic anhydride in the presence of BF_3-etherate gave anomeric acetate **9** mainly as a β-anomer (α/β = 1/15). O-Acetylation prior to the acetolysis was found to be the most efficient way to direct the latter reaction toward stereoselective formation of a β-acetate. This is an important requirement since the corresponding α-acetate showed poor reactivity in a subsequent thiomethylation reaction. Thus, conversion of **9** into a methyl thioglycosyl donor **3** was accomplished by treatment with TMSSMe in the presence of a catalytic amount of TMSOTf. Thioglycoside **3** was isolated only as a β-anomer in 85% overall yield from **8b**.

Key compound **4** was prepared from the known *n*-pentenyl glycoside **10**[15] by trifluoroacetic acid mediated cleavage of the benzylidene acetal to give intermediate **11** in a 96% yield, which was di-*O*-tritylated by treatment with trityl perchlorate[16] in the presence of γ-collidine. After silica gel column chromatography, compound **4** was isolated in a yield of 87%.

Spacer-containing lactosyl acceptor **5** was synthesized by starting from the known (3-chloropropyl) glycoside **12**[17] (Scheme 2) by treatment with sodium azide to give (3-azidopropyl) glycoside **13**, which was deacetylated under Zemplén conditions. The 2,3-*cis* diol of the resulting compound was selectively protected as an isopropylidene acetal by treatment with acetone and TMSCl, and the remaining hydroxyls were benzylated with benzyl bromide and NaH in DMF. Finally, the isopropylidene acetal of the fully protected derivative was removal by treatment with TFA in DCM/water to give **5** in 67% overall yield from **12**.

With significant quantities of glycosyl acceptors and donors in hand, the assembly of the protected heptasaccharide **16a** was undertaken. Thus, coupling of thioglycoside **3** with di-*O*-tritylated acceptor **4** in the presence of MeOTf[18] proceeded with absolute regio- and stereoselectivity and trisaccharide **14** was obtained in an excellent yield of 96% (Scheme 3). The coupling reaction was performed in the presence of a relatively large amount of activated molecular sieves (3 Å) to prevent cleavage of the secondary trityl ether. The prevention of hydrolysis is very important since the analogous saccharide having a free 4-hydroxyl group could not be glycosylated under the described reaction conditions. This observation indicates that the C-4 hydroxyl is activated by tritylation and the increase of reactivity probably arises from steric repulsion between the two trityl ethers resulting in lengthening and therefore polarization of the C−O bond of the secondary trityl ether.[11] Next, the less reactive primary trityl ether of **14** was glycosylated with the cyanoethylidene derivative **2**[19] in the presence of a catalytic amount of trityl perchlorate to furnish pentasaccharide **15** in a good yield of 82%. The use of ethyl per-*O*-acetyl thiolactoside instead of **2** was only modestly successful when MeOTf was used as the promoter in the absence of molecular sieves. Probably, this glycosylation route requires cleavage of the trityl group prior to glycosylation, which may be achieved with the strong triflic acid formed in situ. The proposed reaction path is supported by the fact that in the presence of molecular sieves (acid scavenger) no glycosylation occurred and only destruction of the thioglycosyl donor was observed.[20]

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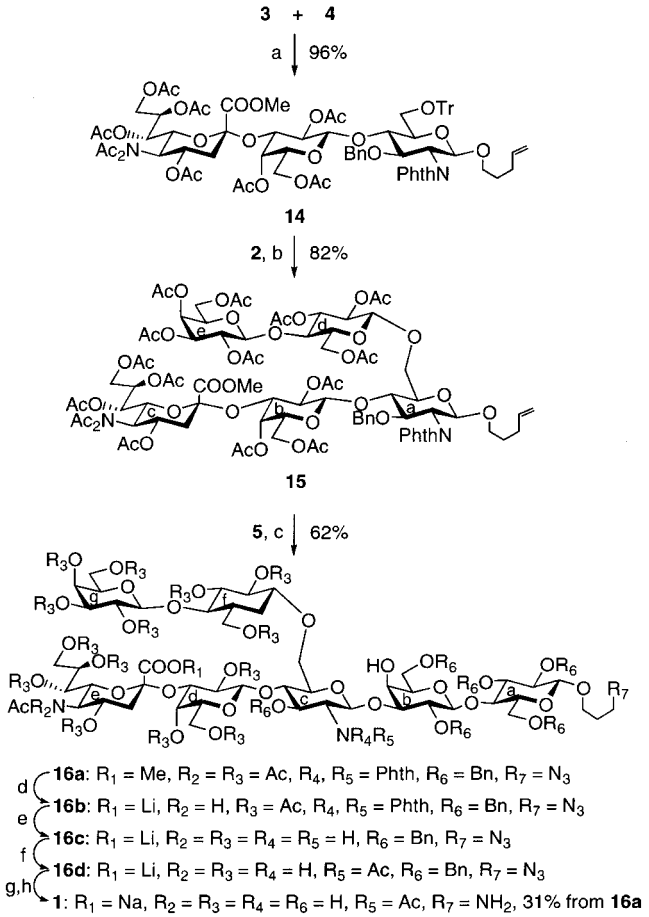
(18) (a) Lönn H., *Carbohydr. Res.* **1985**, *139*, 105−113. (b) Several other promoters were examined including DMTST, IDCP, NIS/TfOH, and NIS/TMSOTf, but these reagents proved uncompatible with the *n*-pentenyl moiety of glycosyl acceptor **14**.

(19) (a) Kochetkov, N. K.; Nifant′ev, N. E.; Backinowsky, L. V. *Tetrahedron* **1987**, *43*, 3109−3122. (b) Betaneli, V. I.; Ovchinnikov, M. V.; Backinowsky, L. V.; Kochetkov, N. K. *Carbohydr. Res.* **1979**, *68*, c11-c13.

(20) Presumably, harsh reaction conditions required for the glycosylation of primary trityl functionalities (NIS/ TMSOTf) are not appropriate in this particular case, since it is expected that the *n*-pentenyl moiety would be activated: Boons, G. J.; Bowers S.; Coe D. M. *Tetrahedron Lett.* **1997**, *38*, 3773−3776.

Scheme 3. Assembly of and Deblocking of a Heptasaccharide from GBS[a]

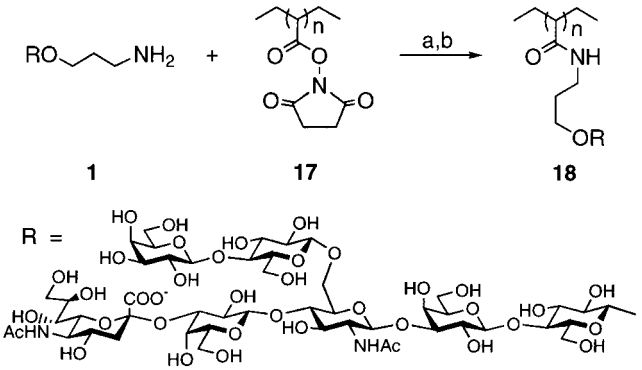


[a] Reagents: (a) MeTOf, MS 3 Å, DCM; (b) $TrCO_4$, DCM; (c) NIS/TMSOTf, MS 3 Å, CM; (d) LiI, pyridine; (e) $(NH_2CH_2)_2$, *n*-BuOH; (f) Ac_2O/MeOH; (g) Pd/C, EtOH/H_2O; (h) 1 N aq NaOH.

The *n*-pentenyl moiety of the pentasaccharide **15** has remained intact throughout the above-discussed synthetic steps leaving it available to serve as an efficient anomeric leaving group.[10] Thus, coupling of **15** with **5** in the presence of NIS/TMSOTf gave the requisite heptasaccharide **16a** in a high yield of 62%.

Compound **16a** was deprotected by a five-step procedure. The methyl ester of the sialic acid moiety of **16a** was saponified by treatment with LiI in pyridine to give a lithium carboxylate **16b**, which was purified by silica gel column chromatography. Under these conditions, the secondary *N*-acetyl functionality of the sialic acid moiety of **16a** was cleaved. Next, reaction of **16b** with ethylenediamine in *n*-butanol removed the *O*-acetyl esters and phthalimido protecting groups to give a free amine **16c**, which was immediately N-acetylated by the treatment with acetic anhydride in methanol to give **16d**. Next, catalytic hydrogenation over Pd/charcoal removed the benzyl ethers with concomitant reduction of the azido moiety to an amine. Finally, the deprotected compound was treated with 1 N aqueous NaOH and purified by size-exclusion column chromatography on Sephadex G-25 to afford **1** in 31% overall yield from **16a**. A similar sequence of deprotection reactions was performed with a heptasaccharide that had the amino group of the spacer protected as benzyloxycarbonyl group. However, this functionality was cleaved when the phthalimido group was removed under a variety of different reaction conditions.

Scheme 4. Synthesis of Polyacrylamide-Based Conjugate with GBS[a]



[a] Reagents: (a) Et_3N, DMF; (b) aq NH_4OH.

The structure of **1** was confirmed by COSY, TOCSY, HSQC, HSQC−TOCSY, and ROESY NMR experiments. Large coupling constants ($J_{1,2}$ = 7.7−8.6 Hz) were detected for the anomeric protons (H-1^{A-D}, -1^{F}, and -1^{G}) in **1**, which proofed unambiguous the β-configuration of these glycosidic linkages. The anomeric assignment of the α-linked *N*-acetylneuraminic acid (unit E) was based on empirical rules for the H-3^{E}eq signals (δ = 2.73 ppm), which is downshifted in comparison to that of a β-anomer (δ = 2.25−2.40 ppm).[21]

Compound **1** was coupled to a poly(*N*-acryloyloxy)-succinimide (pNAS) polymer,[22,23] which was prepared by a procedure described by Whitesides and co-workers. Thus, **17** was coupled with 0.17 equiv of **1** in DMF/Et_3N for 20 h (Scheme 4). The remaining *N*-hydroxysuccinimide esters were converted into amides by treatment with 20% aqueous ammonia solution. The resulting glycopolymer **18** was dialyzed exhaustively and then lyophilized to give a pure glycopolymer.

Conclusions

In conclusion, we have described a highly convergent synthesis of a heptasaccharide derived from the group B type III *Streptococcus* polysaccharide. This saccharide, which is equipped with an artificial aminopropyl spacer, was coupled to an activated pNAS polymer. Currently, the resulting material is used for the development of an ELISA assay to detect antibodies against the capsular polysaccharide of group B type III *Streptococcus* in pregnant women. Important strategic aspects of the synthesis of **1** include the use of a thioglycosyl donor and *n*-pentenyl acceptor/donor. Furthermore, tritylation of the C-4 and C-6 of a glycosamine derivative allows first glycosylation of the secondary position (C-4) followed by glycosylation of the primary one (C-6). Another important aspect was the use of the neuraminic acid donor **6b** that has an *N*-acetylacetamido functionality at C-5. The additional acetyl moiety increases the reactivity of the glycosyl donor and prevents methylation of the acetamido group during a MeOTf-promoted glycosylation. It is to be expected that the strategic principles used for the

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(22) Bovin, N. V. *Glycoconjugate J.* **1998**, *15*, 431−446 and references therein.
(23) Mammen, M.; Dahmann, G.; Whitesides, G. M. *J. Med. Chem.* **1995**, *38*, 4179−4190.

synthesis of **1** will be used for the assembly of other oligosaccharides.

Experimental Section

Column chromatography was performed on silica gel 60 (EM Science, 70−230 mesh), HPLC chromatography was performed on Prodigy 5 μm silica 100 Å column (250 × 10 mm), and reactions were monitored by TLC on Kieselgel 60 F_{254} (EM Science). The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at <40 °C. DCM, $MeNO_2$, and MeCN were distilled from CaH_2 (twice) and stored over molecular sieves (3 Å). Anhydrous DMF and benzene (EM Science) were used without further purification. Methanol was dried by refluxing with magnesium methoxide, distilled, and stored under argon. Pyridine was dried by refluxing with CaH_2 and then distilled and stored over molecular sieves (3 Å). Molecular sieves (3 Å), used for reactions, were crushed and activated in vacuo at 390 °C during 8 h in the first instance and then for 2−3 h at 390 °C directly prior to application. Melting points were measured with an Electrothermal 9200 melting point apparatus, optical rotations with a JASCO P-1020 polarimeter. The assignments of pairs of signals marked with * or # in ^{13}C NMR spectra may be interchanged.

2-(Trimethylsilyl)ethyl 4,6-*O*-Benzylidene-3-*O*-[methyl 4,7,8,9-tetra-*O*-acetyl-5-(*N*-acetylacetamido)-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate]-*β*-D-galactopyranoside (8b). A mixture of 2-(trimethylsilyl)ethyl 4,6-*O*-benzylidene-*β*-D-galactopyranoside[13] (**7**, 89 mg, 0.24 mmol), methyl [methyl 4,7,8,9-tetra-*O*-acetyl-5-(*N*-acetylacetamido)-3,5-dideoxy-2-thio-D-*glycero*-α,*β*-D-*galacto*-non-2-ulopyranosid]onate[12] (**6b**, 157 mg, 0.28 mmol), and activated molecular sieves (3 Å, 600 mg) in MeCN (3.5 mL) was stirred for 3 h under an atmosphere of argon. The mixture was cooled to −40 °C, and NIS (95 mg, 0.42 mmol) and TfOH (3.5 μL, 0.04 mmol) were added. TLC analysis after stirring for 10 min indicated that the reaction had gone to completion. The reaction mixture was diluted with DCM (20 mL), the solid was filtered off, and the residue was washed with DCM (3 × 10 mL). The combined filtrates (~50 mL) were washed with aqueous $Na_2S_2O_3$ (20%, 20 mL) and water (3 × 20 mL). The organic phase was dried ($MgSO_4$) and filtered and the filtrate concentrated in vacuo. The residue was purified by silica gel column chromatography (5% gradient acetone in toluene) to afford **8b** as a white foam (172 mg, 81%): R_f 0.5 (acetone/toluene, 3/7, v/v); $[\alpha]^{26}_D = +51.8$ ($c = 1.00$, DCM); mp +174.4−175.1 °C (diethyl ether−hexane); MALDI-TOF m/z = 906.5 $[M + Na]^+$; ^1H NMR δ 7.25−7.55 (m, 5H, aromatic), 5.49 (m, 1H, $J_{4',5'} = 10.0$ Hz, H-4′), 5.40 (s, 1H, >C*H*Ph), 5.37 (m, 1H, $J_{8',9'a} = 2.6$ Hz, $J_{8',9'b} = 5.5$ Hz, H-8′), 5.17 (dd, 1H, $J_{7',8'} = 8.5$ Hz, H-7′), 4.96 (dd, 1H, $J_{6',7'} = 1.5$ Hz, H-6′), 4.46 (d, 1H, $J_{1,2} = 7.5$ Hz, H-1), 4.33 (dd, 1H, $J_{9'a,9'b} = 12.5$ Hz, H-9′a), 4.28 (dd, 1H, $J_{6a,6b} = 12.5$ Hz, H-6a), 4.26 (dd, 1H, $J_{3,4} = 3.6$ Hz, H-3), 4.17 (dd, 1H, $J_{5',6'} = 10.0$ Hz, H-5′), 4.09 (dd, 1H, H-9′b), 4.08 (dd, 1H, H-6b), 4.02−4.09 (m, 1H, $-OCH_2{}^a-$), 3.97 (dd, 1H, $J_{4,5} = 1.0$ Hz, H-4), 3.83 (dd, 1H, $J_{2,3} = 9.8$ Hz, H-2), 3.72 (s, 3H, $-COOCH_3$), 3.62−3.68 (m, 1H, $-OCH_2{}^b-$), 3.45 (m, 1H, H-5), 2.88 (dd, 1H, $J_{3'e,4'} = 5.1$ Hz, $J_{3'e,3'a} = 13.0$ Hz, H-3′e), 2.73 (br s, 1H, 2-OH), 2.29, 2.37 [2s, 6H, $-N(COCH_3)_2$], 1.96, 2.03, 2.13, 2.17 (4s, 12H, 4 × $-OCOCH_3$), 1.95 (dd, 1H, $J_{3'e,4'} = 10.6$ Hz, H-3′a), 0.96−1.15 (m, 2H, $-CH_2$TMS), 0.00 (s, 9H, TMS); ^{13}C NMR δ 168.18−174.41 (7 × >C=O), 126.03−128.87 (aromatic), 102.30 (C-1), 100.96 (>*C*HPh), 97.25 (C-2′), 75.39 (C-3), 74.13 (C-4), 70.03 (C-6′), 69.21 (C-6), 68.66 (C-2), 68.42 (C-8′), 66.88 (C-7′), 66.78 (C-4′), 66.60 ($-OCH_2-$), 66.17 (C-5), 62.03 (C-9′), 56.86 (C-5′), 52.96 ($-COOCH_3$), 39.10 (C-3′), 25.97, 27.92 [$-N(COCH_3)_2$], 20.69−21.22 (4 × $-OCOCH_3$), 18.11 ($-CH_2$TMS), −1.386 (TMS); HR−FAB MS $[M + Na]^+$ calcd for $C_{40}H_{57}NO_{19}NaSi$ 906.319178, found 906.321120.

Methyl 2,4,6-Tri-*O*-acetyl-3-*O*-[methyl 4,7,8,9-tetra-*O*-acetyl-5-(*N*-acetylacetamido)-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate]-1-thio-*β*-D-galactopyranoside (3). A solution of **8b** (698 mg, 0.79 mmol) in a mixture of Ac_2O (4 mL) and pyridine (6 mL) was kept for 16 h at room temperature. The reaction was quenched with MeOH (15 mL) and the resulting solution concentrated in vacuo. The residue was coevaporated from toluene (3 × 15 mL) and then dried under high vacuum to give pure 2-(trimethylsilyl)ethyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-[methyl 4,7,8,9-tetra-*O*-acetyl-5-(*N*-acetylacetamido)-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate]-*β*-D-galactopyranoside **(8c)** as a white foam: R_f 0.40 (acetone/toluene, 1/4, v/v). Compound **8c** was dissolved in a mixture of DCM (16 mL), and Ac_2O (521 μL, 5.53 mmol) was added. The solution was placed under an atmosphere of argon and cooled (0 °C), and $BF_3{\cdot}Et_2O$ (250 mL, 1.98 mmol) was added dropwise. After being stirred for 3.5 h at room temperature, the reaction mixture was diluted with DCM (55 mL) and washed with water (20 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL), and water (3 × 20 mL). The organic phase was dried ($MgSO_4$) and filtered and the filtrate concentrated in vacuo. The residue was purified by silica gel column chromatography (5% gradient acetone in toluene) to afford 3-*O*-[methyl 4,7,8,9-tetra-*O*-acetyl-5-(*N*-acetylacetamido)-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate]-1,2,4,6-tetra-*O*-acetyl-α/*β*-D-galactopyranose [**9**, α/*β* = 1/15, R_f 0.25 (ethyl acetate/ toluene, 1/1, v/v)]. Ratio of the anomers was established by comparison of integral intensities of the corresponding signals 6.29 (d, 1H, $J_{1,2} = 3.6$ Hz, H-1α) and 5.84 (d, 1H, $J_{1,2} = 8.4$ Hz, H-1*β*) in the ^1H NMR spectrum. A solution of **9** in DCM (12 mL) was placed under an atmosphere of argon. TMSSMe (410 μL, 2.90 mmol) and TMSOTf (157 μL, 0.87 mmol) were added, and the reaction mixture was stirred for 60 h at room temperature. It was then diluted with DCM (50 mL) and washed with water (25 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL), and water (3 × 25 mL). The organic phase was dried ($MgSO_4$) and filtered and the filtrate concentrated in vacuo. The residue was purified by silica gel column chromatography (5% gradient ethyl acetate in toluene) to afford **3** as a white foam (17.0 g, 85% over three steps) as a mixture of anomers (α/*β* = 17/1) that were used without further purification. Analytical data for *β*-**3**: R_f 0.40 (toluene/acetone, 3/1, v/v); $[\alpha]^{26}_D = +6.2$ ($c = 1.10$, DCM); MALDI-TOF m/z = 874.4 $[M + Na]^+$; ^1H NMR δ 5.50−5.60 (m, 1H, $J_{4',5'} = 11.2$ Hz, H-4′), 5.45−5.50 (m, 1H, $J_{8',9'} = 2.6$ Hz, $J_{8'9'b} = 5.1$ Hz, H-8′), 5.17 (dd, 1H, $J_{7',8'} = 8.8$ Hz, H-7′), 5.08 (dd, 1H, $J_{2,3} = 9.7$ Hz, H-2), 5.03 (dd, 1H, $J_{4,5} = 0.8$ Hz, H-4), 4.68 (dd, 1H, $J_{3,4} = 3.3$ Hz, H-3), 4.61 (dd, 1H, $J_{6',7'} = 2.3$ Hz, H-6′), 4.55 (d, 1H, $J_{1,2} = 10.0$ Hz, H-1), 4.31 (dd, 1H, $J_{5',6'} = 10.3$ Hz, H-5′), 4.30 (dd, 1H, $J_{9'a,9'b} = 12.5$ Hz, H-9′a), 3.98−4.10 (m, 3H, H-6a, 6b, 9′b), 3.90−3.93 (m, 1H, H-5), 3.89 (s, 3H, $-COOCH_3$), 2.65 (dd, 1H, $J_{3'e,4'} = 5.0$ Hz, $J_{3'e,3'a} = 12.0$ Hz, H-3′e), 2.28, 2.35 [2s, 6H, $-N(COCH_3)_2$], 1.94, 2.02, 2.03, 2.03, 2.08, 2.17, 2.18, 2.22 (8 s, 24H, 7 × $-OCOCH_3$, $-SCH_3$), 1.59 (dd, 1H, $J_{3'a,4'} = 10.0$ Hz, H-3′a); ^{13}C NMR δ 166.00−175.12 (>C=O), 96.94 (C-2′), 83.14 (C-1), 74.57 (C-5), 72.59 (C-3), 69.78 (C-6′), 68.32 (C-4), 68.06 (C-2), 67.95 (C-8′), 67.36 (C-7′), 67.28 (C-4′), 62.55 (C-6), 62.47 (C-9′), 56.27 (H-5′), 53.38 ($-COOCH_3$), 26.83, 27.90 [$-N(COCH_3)_2$], 20.05−21.18 (7 × $-OCOCH_3$), 12.22 ($-SCH_3$). Anal. Calcd for $C_{35}H_{49}NO_{21}Si$ (851.25): C, 49.35; H, 5.80; N, 1.64. Found: C, 49.56; H, 5.92; N, 1.70.

Pent-4-enyl 3-*O*-Benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (11). A solution of pent-4-enyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-*β*-D-glucopyranoside[15] (**10**, 640 mg, 1.15 mmol) in a mixture of TFA (5 mL), DCM (25 mL) and water (400 μL) was kept for 10 min at room temperature and then diluted with DCM (100 mL) and washed with water (50 mL), saturated aqueous $NaHCO_3$ (2 × 30 mL), and water (3 × 40 mL). The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (15% gradient ethyl acetate in toluene) to afford **11** as a white foam (115 mg, 96%): R_f 0.25 (ethyl acetate/toluene, 1/1, v/v); $[\alpha]_D{}^{26} = +27.2$ ($c = 1.00$, DCM); MALDI-TOF m/z = 489.8 $[M + Na]^+$; ^1H NMR δ 6.96−7.90 (m, 9H, aromatic), 5.48−5.64 (m, 1H, $-CH=$), 5.17 (d, 1H, $J_{1,2} = 8.7$ Hz, H-1), 4.66−4.81 (m, 2H, $CH_2=$), 4.62 (dd, 2H, $J^2 = 12.5$ Hz, $-CH_2$Ph), 4.28 (dd, 1H, $J_{3,4} = 8.7$ Hz, H-3), 4.15 (dd, 1H, $J_{2,3} = 10.0$,

H-2), 3.96 (dd, 1H, $J_{6a,6b}$ = 12.5 Hz, H-6a), 3.84 (dd, 1H, H-6b), 3.73−3.85 (m, 2H, H-4, $-OCH_2{}^a-$), 3.49−3.58 (m, 1H, H-5), 3.35−3.45 (m, 1H, $-OCH_2{}^b-$), 2.46 (br s, 1H, 4-OH), 2.07 (br s, 1H, 6-OH, 1.74−1.92 (m, 2H, $-CH_2CH=$), 1.38−1.60 (m, 2H, $-OCH_2CH_2-$); ^{13}C NMR δ 134.10 ($-CH=$), 127.96−128.51 (aromatic), 114.89 ($CH_2=$), 98.69 (C-1), 79.65 (C-3), 75.34 (C-5), 74.73 ($-CH_2Ph$), 72.57 (C-4), 69.31 ($-OCH_2-$), 62.89 (C-6), 55.91 (C-2), 30.14 ($-CH_2-CH=$), 28.87 ($-CH_2-CH_2O-$). Anal. Calcd for $C_{26}H_{29}NO_7$ (467.19): C, 66.80; H, 6.25; N, 3.00. Found: C, 66.54; H, 6.31; N, 3.08.

Pent-4-enyl 3-*O*-Benzyl-2-deoxy-2-phthalimido-4,6-di-*O*-trityl-β-D-glucopyranoside (4). A solution of γ-collidine (580 μL, 4.40 mmol) in DCM (12 mL) was added to a flask containing **11** (515 mg, 1.10 mmol) and triphenylmethyl perchlorate[13] (1.13 g, 3.30 mmol), and the resulting mixture was stirred until all solid dissolved. After the reaction mixture was stirred in the dark for 20 h at room temperature, pyridine (1 mL) was added and the mixture was diluted with DCM (20 mL) and washed with water (4 × 15 mL). The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (5% gradient of ethyl acetate in hexane) and crystallized from Et_2O/hexane to afford **4** as colorless needless (910 mg, 87%): R_f 0.50 (ethyl acetate/hexane, 3/7, v/v); $[\alpha]^{26}_D$ = +54.1 (c = 1.18, DCM); mp 196.1−197.0 °C (diethyl ether−hexane); MALDI-TOF m/z = 975.0 $[M + Na]^+$; ^{1}H NMR, δ, 6.50−7.68 (m, 39H, aromatic), 5.52−5.61 (m, 1H, $-CH_2=$), 5.18 (s, 1H, $J_{1,2}$ = 8.6 Hz, H-1), 4.66−4.75 (m, 2H, $CH_2=$), 4.58 (dd, 1H, $J_{3,4}$ = 7.9 Hz, H-3), 4.20 (m, 1H, H-5), 3.90−3.95 (m, 1H, $-OCH_2{}^a-$), 3.90 (dd, 1H, $J_{2,3}$ = 10.3 Hz, H-2), 3.86 (dd, 2H, J^2 = 11.7 Hz, $-CH_2Ph$), 3.49−3.56 (m, 1H, $-OCH_2{}^b-$), 3.29 (dd, 1H, $J_{5,6a}$ = 1.4 Hz, $J_{6a,6b}$ = 9.6 Hz, H-6a), 2.81 (dd, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 2.56 (dd, 1H, $J_{5,6b}$ = 9.3 Hz, H-6b), 1.79−1.89 (m, 2H, $-CH_2CH=$), 1.46−1.61 (m, 2H, $-CH_2CH_2O-$); ^{13}C NMR, δ, 144.71 ($-CH=$), 123.40−138.68 (aromatic), 114.89 ($CH_2=$), 97.91 (C-1), 86.56, 88.91 (2 × $-CPh_3$), 81.05 (C-3), 76.31 (C-5), 74.58 ($-CH_2Ph$), 73.88 (C-4), 68.84 ($-OCH_2-$), 66.33 (C-6), 57.27 (C-2), 29.01, 30.33 ($-CH_2CH_2CH=$). Anal. Calcd for $C_{64}H_{57}NO_7$ (951.41): C, 80.73; H, 6.03; N, 1.47. Found: C, 81.00; H, 5.99; N, 1.43.

3-Azidopropyl 4-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (13). A mixture of 3-chloropropyl 4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside[17] (**12**, 1.08 g, 1.52 mmol) and KI (505 mg, 3.04 mmol) in DMF was stirred for 30 min at 50 °C. After addition of NaN_3 (988 mg, 15.2 mg), the reaction mixture was refluxed for another 30 min and then poured into ice−water (30 mL). The aqueous layer was extracted with ethyl acetate/Et_2O (1/1, v/v, 3 × 15 mL). The combined organic layers were washed with water (3 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo to dryness. The residue was purified by silica gel column chromatography (10% gradient ethyl acetate in toluene) to afford **13** as a white foam (929 mg, 85%): R_f 0.55 (ethyl acetate/toluene, 3/2, v/v), $[\alpha]^{26}_D$ = −4.7 (c = 1.59, DCM); MALDI-TOF m/z = 741.8 $[M + Na]^+$; ^{1}H NMR δ 5.34 (dd, 1H, $J_{4',5'}$ = 0.5 Hz, H-4′), 5.19 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 5.10 (dd, 1H, $J_{2',3'}$ = 10.4 Hz, H-2′), 4.95 (dd, 1H, $J_{3',4'}$ = 3.5 Hz, H-3′), 4.88 (dd, 1H, $J_{2,3}$ = 9.3 Hz, H-2), 4.49 (dd, 1H, $J_{5',6'a}$ = 1.9 Hz, H-6′a), 4.48 (d, 1H, $J_{1',2'}$ = 8.0 Hz, H-1′), 4.46 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.03−4.17 (m, 3H, H-5′, 6a, 6′b), 3.81−3.92 (m, 2H, H-6b, $-OCH_2{}^a-$), 3.79 (dd, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 3.53−3.64 (m, 2H, H-5, $-OCH_2{}^b-$), 3.30−3.40 (m, 2H, $-CH_2N_3$), 1.96, 2.04, 2.04, 2.04, 2.06, 2.12, 2.14 (7s, 21H, 7 × $-OCOCH_3$), 1.74−1.90 (m, 2H, $-CH_2-$); ^{13}C NMR δ 168.04−170.42 (7 × >C=O), 101.29 (C-1′), 100.80 (C-1), 76.50 (C-4), 73.05 (C-3), 72.97 (C-5), 71.94 (C-2), 71.26 (C-5′), 70.99 (C-3′), 69.42 (C-2′), 66.91 (C-4′), 66.74 ($-OCH_2-$), 62.23 (C-6′), 61.10 (C-6), 48.28 ($-CH_2N_3$), 29.33 ($-CH_2-$), 20.85−21.19 (7 × $-OCOCH_3$). Anl. Calcd for $C_{29}H_{41}N_3O_{18}$ (719.24): C, 48.40; H, 5.74; N, 5.84. Found: C, 48.56; H, 5.77; N, 5.80.

3-Azidopropyl 4-*O*-(2,6-Di-*O*-benzyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (5). A mixture of **13** (899 mg, 1.25 mmol) and NaOMe (3 mg, 0.05 mmol) in MeOH was kept for 16 h at room temperature and then neutralized (Dowex, H^+) and filtered, and the filtrate was concentrated in vacuo to afford 3-azidopropyl 4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranoside as white solid (R_f 0.15, MeOH/DCM, 1/4, v/v), which was dissolved in a mixture of TMSCl (4 mL) and acetone (10 mL). The reaction mixture was kept for 3 h at room temperature, and then hexane (10 mL) was added and the mixture was concentrated in vacuo. The residue was coevaporated from acetone/toluene (1/2, v/v, 3 × 15 mL), dried ($MgSO_4$), and then dissolved in DMF (5 mL). Benzyl bromide (884 mL, 7.43 mmol) and NaH (360 mg, 8.93 mmol) were added to the solution, and the reaction mixture was vigorously stirred for 1 h at room temperature and then poured into ice−water (50 mL). The aqueous layer was extracted with ethyl acetate/Et_2O (1/1, v/v, 3 × 25 mL). The combined organic layers were washed with water (3 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in a mixture of TFA (5 mL), DCM (20 mL), and water (400 μL). After being stirred for 5 min at room temperature, the reaction mixture was diluted with DCM (50 mL) and washed with water (30 mL), saturated aqueous $NaHCO_3$ (2 × 25 mL), and water (3 × 30 mL). The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (10% gradient ethyl acetate in hexane) to afford **5** as a white solid (733 mg, 67% over four steps): R_f 0.50 (ethyl acetate/hexane, 1/1, v/v); $[\alpha]^{26}_D$ = +17.3 (c = 1.39, DCM); MALDI-TOF m/z = 898.8 $[M + Na]^+$; ^{1}H NMR δ 7.16−7.36 (m, 25H, aromatic), 4.85 (dd, 2H, J^2 = 11.0 Hz, $-CH_2Ph$), 4.76 (dd, 2H, J^2 = 11.2 Hz, $-CH_2Ph$), 4.72 (dd, 2H, J^2 = 11.5 Hz, $-CH_2Ph$), 4.49 (dd, 2H, J^2 = 12.2 Hz, $-CH_2Ph$), 4.41 (d, 1H, $J_{1',2'}$ = 6.8 Hz, H-1′), 4.39 (dd, 2H, J^2 = 12.0 Hz, $-CH_2Ph$), 4.30 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 3.97 (dd, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 3.91−3.96 (m, 1H, $-OCH_2{}^a-$), 3.91 (ps, 1H, H-4′), 3.78 (dd, 1H, $J_{5,6a}$ = 4.2 Hz, $J_{6a,6b}$ = 11.0 Hz, H-6a), 3.71 (dd, 1H, $J_{5,6b}$ = 1.7 Hz, H-6b), 3.59 (dd, 1H, $J_{5',6'a}$ = 6.4 Hz, H-6′a), 3.57−3.62 (m, 1H, $-OCH_2{}^b-$), 3.56 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 3.48 (dd, 1H, $J_{5',6'b}$ = 5.1 Hz, $J_{6'a,6'b}$ = 9.8 Hz, H-6′b), 3.32−3.42 (m, 7H, H-2, 2′, 3′, 5, 5′, $-CH_2N_3$), 2.38, 2.45 (2d, 2H, 3′-OH, 4′-OH), 1.80−1.91 (m, 2H, $-CH_2-$); ^{13}C NMR, δ 127.45−128.69 (aromatic), 103.80 (C-1), 102.80 (C-1′), 83.11 (C-3), 82.04 (C-3′), 80.32 (C-2), 76.88 (C-4), 75.18, 75.28, 75.40, 75.51 (3 × $-CH_2Ph$, C-5*), 73.22, 73.52, 73.79, 73.79 (2 × $-CH_2Ph$, C-2′, 5′*), 68.54, 69.00, 69.10 (C-4′, 6, 6′), 66.79 ($-OCH_2-$), 48.67 ($-CH_2N_3$), 29.65 ($-CH_2-$). Anal. Calcd for $C_{50}H_{57}N_3O_{11}$ (875.40): C, 68.55; H, 6.56; N, 4.80. Found: C, 68.39; H, 6.48; N, 4.89.

Pent-4-enyl *O*-[Methyl 4,7,8,9-tetra-*O*-acetyl-5-(*N*-acetylacetamido)-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate]-(2→3)-*O*-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-3-*O*-benzyl-2-deoxy-2-phthalimido-6-*O*-trityl-β-D-glucopyranoside (14). A suspension of **3** (192.4 mg, 0.226 mmol), **4** (165.4 mg, 0.174 mmol), and activated molecular sieves (3 Å, 800 mg) in DCM (3 mL) was stirred for 3 h under an atmosphere of argon. MeOTf (98 μL, 0.87 mmol) was added, and the reaction mixture was stirred for 2.5 h at room temperature. Then, Et_3N (1 mL) was added, and the mixture was diluted with DCM (30 mL), the solid filtered off, and the residue was washed with DCM (3 × 20 mL). The combined filtrates (∼ 90 mL) were washed with water (3 × 40 mL), the organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (5% gradient acetone in toluene) to afford **14** as a white foam (mg, 96%): R_f 0.45 (acetone/toluene, 3/7, v/v); $[\alpha]^{26}_D$ = + 16.6 (c = 1.30, DCM); mp 176.0−177.2 °C (diethyl ether); MALDI-TOF m/z = 1537.4 $[M + Na]^+$;^{1}H NMR δ 6.78−7.80 (m, 24 H, aromatic), 5.49−5.62 (m, 2H, $J_{4'',5''}$ = 10.7 Hz, H-4″, −CH=), 5.38−5.44 (m, 1H, H-8″), 5.13 (dd, 1H, $J_{7'',8''}$ = 8.8 Hz, H-7″), 5.03 (d, 1H, $J_{1,2}$ = 8.5 Hz, H-1), 5.00 (dd, 1H, $J_{4',5'}$ = 0.3 Hz, H-4′), 4.86 (dd, 1H, $J_{2',3'}$ = 9.7 Hz, H-2′), 4.87 (d, 1H, $J_{1',2'}$ = 7.6 Hz, H-1′), 4.68−4.75 (m, 2H, $CH_2=$), 4.61 (dd, 1H, J^2 = 12.5 Hz, $-CH_2Ph$), 4.60 (dd, 1H, $J_{6'',7''}$ = 2.5 Hz, H-6″), 4.36 (dd, 1H, $J_{3',4'}$ = 3.7 Hz, H-3′), 4.30 (dd, 1H, $J_{5'',6''}$ = 10.4 Hz, H-5″), 4.28 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 4.23 (dd, 1H, $J_{8'',9''a}$ = 2.5 Hz, $J_{9''a,9''b}$ = 12.6 Hz, H-9″a), 4.16 (dd, 1H, $J_{2,3}$ = 9.0 Hz, H-2), 4.13 (dd, 1H, $J_{4,5}$ = 9.0 Hz, H-4), 4.00 (dd, 1H, $J_{8'',9''b}$ = 4.9 Hz, H-9″b), 3.95 (pd, 2H, $J_{6'a,6'b}$ = 6.4 Hz, H-6′a, 6′b), 3.78−3.99 (m, 1H,

−$OCH_2{}^a$−), 3.80 (s, 3H, −$COOCH_3$), 3.78 (m, 1H, $J_{5',6'a} = J_{5',6'b}$ = 6.4 Hz, H-5′), 3.55−3.60 (m, 2H, H-5, 6a), 3.40−3.47 (m, 1H, −$OCH_2{}^b$−), 3.18 (dd, 1H, $J_{5,6b}$ = 5.8 Hz, $J_{6a,6b}$ = 10.1 Hz, H-6b), 2.57 (dd, 1H, $J_{3''e,4''}$ = 5.5 Hz, $J_{3''e,3''a}$ =12.8 Hz, H-3″e), 2.30, 2.35 [2s, 6H, −$N(COCH_3)_2$], 1.82−1.90 (m, 2H, −CH_2−CH_2=), 1.78, 1.93, 1.95, 1.96, 1.96, 2.03, 2.10 (7s, 21H, 7 × −$OCOCH_3$), 1.61 (dd, 1H, $J_{3''a,4''}$ =12.8 Hz, H-3″a), 1.49−1.59 (m, 2H, −OCH_2CH_2−); ^{13}C NMR, δ, 167.78−174.09 (>C=O), 144.24 (−CH=), 123.38−138.82 (aromatic), 114.88 (CH_2=), 99.42 (C-1′), 98.32 (C-1), 97.63 (C-2″), 86.88 (−*C*Ph3), 77.97 (C-3), 77.73 (C-4), 74.52 (C-5, −CH_2Ph), 72.04 (C-3′), 71.60 (C-2′), 70.81 (C-5′), 70.16 (C-6″), 68.78 (−OCH_2−), 68.15 (C-4′, 8″), 67.22 (C-4″, 7″), 62.98 (C-6), 62.26 (C-6′, 9″), 56.53 (C-5″), 56.34 (C-2), 53.41 (−$COOCH_3$), 38.50 (C-3″), 30.32 (−CH_2−CH=), 30.05 (−CH_2CH_2O−), 27.06, 28.42 [−$N(COCH_3)_2$], 21.10−21.63 (7 × −$OCOCH_3$). Anal. Calcd for $C_{79}H_{88}N_2O_{28}$ (1512.55): C, 62.69; H, 5.86; N, 1.85. Found: C, 62.54; H, 6.00; N, 1.91.

Pent-4-enyl *O*-[Methyl 4,7,8,9-tetra-*O*-acetyl-5-(*N*-acetylacetamido)-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate]-(2→3)-*O*-(2,4,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→4)-[(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→6)]-3-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (15). A solution of **14** (151 mg, 0.10 mmol) and **2** (64.5 mg, 0.10 mmol) in benzene (2 mL) was added in one of the limbs of a tuning-fork-shaped tube and a solution $TrClO_4$ (5.1 mg, 15 μmol) in $MeNO_2$ (0.5 mL) in the other limb.[19b] The tube was attached to a high-vacuum system, and the solutions were lyophilized. DCM (∼2 mL) was distilled into the reaction tube, and the solutions of the reactants were mixed. After 40 h at room temperature in the dark, the reaction was quenched by the addition of a drop of pyridine and the resulting mixture was diluted with DCM (50 mL) and washed with water (4 × 15 mL). The organic phase was dried ($MgSO_4$) and filtered and the filtrate concentrated in vacuo. The residue was purified by silica gel column chromatography (10% gradient acetone in toluene) to afford **15** as a white foam (160 mg, 85%): R_f 0.45 (acetone/toluene, 3/7, v/v); $[\alpha]^{26}_D$ = +18.2 (*c* = 2.04, DCM); MALDI-TOF *m*/*z* = 1914.3 [M + Na]$^+$; ^{1}H NMR δ 6.77−7.82 (m, 9H, aromatic), 5.50−5.61 (m, 3H, H-4^C, 8^C, −CH=), 5.33 (dd, 1H, $J_4{}^E{}_{,5}{}^E$ = 0.4 Hz, H-4^E), 5.21 (dd, 1H, $J_7{}^C{}_{,8}{}^C$ = 9.3 Hz, H-7^C), 5.11 (dd, 1H, $J_3{}^D{}_{,4}{}^D$ = 9.3 Hz, H-3^D), 5.10 (dd, 1H, $J_2{}^E{}_{,3}{}^E$ = 8.8 Hz, H-2^E), 5.07 (d, 1H, $J_1{}^A{}_{,2}{}^A$ = 8.2 Hz, H-1^A), 5.04 (dd, 1H, $J_2{}^B{}_{,3}{}^B$ = 8.8 Hz, H-2^B), 4.94−4.98 (m, 2H, H-3^E, 4^B), 4.91 (dd, 1H, $J_2{}^D{}_{,3}{}^D$ = 9.0 Hz, H-2^D), 4.86 (d, 1H, $J_1{}^D{}_{,2}{}^D$ = 7.1 Hz, H-1^D), 4.82 (d, 1H, $J_1{}^B{}_{,2}{}^B$ = 8.0 Hz, H-1^B), 4.69−4.78 (m, 2H, CH_2=), 4.64 (dd, 1H, $J_5{}^C{}_{,6}{}^C{}_a$ = 1.5 Hz, $J_6{}^C{}_{a,6}{}^C{}_b$ = 11.0 Hz, H-6^C), 4.62 (dd, 2H, J^2 = 12.2 Hz, −CH_2Ph), 4.62 (dd, 1H, $J_3{}^B{}_{,4}{}^B$ = 3.8 Hz, H-3^B), 4.49 (d, 1H, $J_1{}^E{}_{,2}{}^E$ = 7.7 Hz, H-1^E), 4.38 (dd, 1H, $J_5{}^D{}_{,6}{}^D{}_a$ = 1.5 Hz, $J_6{}^D{}_{a,6}{}^D{}_b$ = 11.5 Hz, H-6^{D}a), 4.34 (m, 1H, H-5^C), 4.26−4.31 (m, 3H, H-3^A, 6^{A}a, 9^{C}a), 4.16 (dd, 1H, $J_5{}^D{}_{,6}{}^D{}_b$ = 6.0 Hz, H-6^{D}b), 4.12 (dd, 1H, $J_5{}^E{}_{,6}E_a$ = 6.0 Hz, $J_6{}^E{}_{a,6}{}^E{}_b$ = 12.5 Hz, H-6^{E}a), 4.11 (dd, 1H, $J_5{}^E{}_{,6}{}^E{}_b$ = 6.5 Hz, H-6^{E}b), 4.06 (dd, 1H, $J_2{}^A{}_{,3}{}^A$ = 9.9 Hz, H-2^A), 4.03 (dd, 1H, $J_8{}^C{}_{,9}{}^C{}_b$ = 4.6 Hz, $J_9{}^C{}_{a,9}{}^C{}_b$ = 12.5 Hz, H-9^{C}b), 3.97 (dd, 1H, $J_5{}^B{}_{,6}{}^B{}_a$ = 6.0 Hz, $J_6{}^B{}_{a,6}{}^B{}_b$ = 10.5 Hz, H-6^{B}a), 3.88−3.95 (m, 7H, H-4^D, 5^B, 5^E, 6^{B}b, −$COOCH_3$), 3.80−3.88 (m, 2H, H-6^{A}b, −$OCH_2{}^a$−), 3.60−3.71 (m, 3H, H-4^A, 5^A, 5^D), 3.38−3.45 (m, 1H, −$OCH_2{}^b$−), 2.67 (dd, 1H, $J_3{}^C{}_{e,4}{}^C$ = 5.0 Hz, $J_3{}^C{}_{e,3}{}^C{}_a$ = 12.6 Hz, H-3^{C}e), 2.30, 2.36 [2s, 6H, −$N(COCH_3)_2$], 1.92, 1.95, 1.96, 2.03, 2.03, 2.03, 2.03, 2.04, 2.04, 2.10, 2.11, 2.12, 2.20, 2.24 (14 s, 42H, 14 × −$OCOCH_3$), 1.80−1.89 (m, 2H, −CH_2−CH=), 1.63 (dd, 1H, $J_3{}^C{}_{a,4}{}^C$ = 12.1 Hz, H-3^{C}a), 1.48−1.57 (m, 2H, −OCH_2CH_2−); ^{13}C NMR δ 167.87−174.18 (>C=O), 138.59 (−CH=), 123.45−133.88 (aromatic), 115.03 (CH_2=), 101.74 (C-1^B), 101.49 (C-1^E), 100.18 (C-1^D), 98.20 (C-1^A), 96.97 (C-2^C), 80.71 (C-4^A), 77.70 (C-3^A), 77.28 (C-5^A), 76.85 (C-5^E), 75.03 (−CH_2Ph), 73.30 (C-5^D), 72.82 (C-3^D), 72.15 (C-2^D), 71.67 (C-3^B), 71.36 (C-5^B), 71.19 (C-3^E)*, 70.92 (C-4^D), 70.79 (C-2^B), 69.72 (C-6^C), 69.36 (C-2^E, −OCH_2−), 67.98 (C-4^B)*, 67.82 (C-4^C, 8^C), 67.23 (C-6^A, 7^C), 67.03 (C-4^E), 62.67 (C-6^D, 9^C), 61.86 (C-6^B), 61.13 (C-6^E), 56.26 (C-5^C), 55.93 (C-2^A), 53.36 (−$COOCH_3$), 38.64 (C-3^C), 30.09 (−CH_2−CH=), 28.76 (−CH_2CH_2O−), 27.03, 28.44 [-$N(COCH_3)_2$], 20.98−21.89 (−$OCOCH_3$). Anal. Calcd for $C_{86}H_{108}N_2O_{45}$ (1888.62): C, 54.66; H, 5.76; N, 1.48. Found: C, 54.48; H, 7.81; N, 1.53.

3-Azidopropyl *O*-[Methyl 4,7,8,9-tetra-*O*-acetyl-5-(*N*-acetylacetamido)-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate]-(2→3)-*O*-(2,4,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→4)-*O*-[(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→6)]-*O*-(3-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→3)-*O*-(2,6-Di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (16a). A mixture of **5** (48 mg, 0.054 mmol), 15 (51.1 mg, 0.027 mmol), and activated molecular sieves (3 Å, 300 mg) in DCM (1.5 mL) was stirred for 3 h under argon. NIS (18.3 mg, 0.081 mmol) and TMSOTf (1.5 μL, 0.008 mmol) were added. After the reaction mixture was stirred for 24 h at room temperature, it was diluted with DCM (20 mL), the solid filtered off, and the residue washed with DCM (3 × 10 mL). The combined filtrates (∼50 mL) were washed with aqueous $Na_2S_2O_3$ (20%, 20 mL) and water (3 × 20 mL). The organic phase was dried ($MgSO_4$) and filtered and the filtrate concentrated in vacuo. The residue was purified by silica gel column chromatography (3% gradient acetone in toluene) to afford **16a** as a transparent film (45 mg, 62%): R_f 0.45 (acetone/toluene, 1/3, v/v); $[\alpha]^{24}_D$ = +12.9 (*c* = 0.8, DCM); MALDI-TOF *m*/*z* = 2706.8 [M + Na]$^+$; ^{1}H NMR, δ, 6.75−7.45 (m, 34H, aromatic), 5.59 (m, 1H, $J_8{}^E{}_{,9a}{}^E$ = 2.6 Hz, $J_8{}^E{}_{,9b}{}^E$ = 5.8 Hz, H-8^E), 5.53 (m, 1H, $J_4{}^E{}_{,5}{}^E$ = 11.0 Hz, H-4^E), 5.30 (d, 1H, $J_1{}^C{}_{,2}{}^C$ = 8.4 Hz, H-1^C), 5.28 (bs, 1H, H-4^G), 5.19 (dd, 1H, $J_3{}^F{}_{,4}{}^F$ = 9.3 Hz, H-3^F), 5.15 (dd, 1H, $J_7{}^E{}_{,8}{}^E$ = 9.2 Hz, H-7^E), 5.06 (dd, 1H, $J_2{}^G{}_{,3}{}^G$ = 10.4 Hz, H-2^G), 5.00 (dd, 1H, $J_2{}^D{}_{,3}{}^D$ = 10.0 Hz, H-2^D), 4.94 (bd, 1H, $J_4{}^D{}_{,5}{}^D$ = 2.9 Hz, H-4^D), 4.87 (dd, 1H, $J_3{}^G{}_{,4}{}^G$ = 4.8 Hz, H-3^G), 4.86 (d, 1H, $J_1{}^D{}_{,2}{}^D$ = 7.9 Hz, H-1^D), 4.85 (dd, 1H, $J_2{}^F{}_{,3}{}^F$ = 9.3 Hz, H-2^F), 4.72 (dd, 2H, J^2 = 10.4, CH_2Ph), 4.68 (dd, 2H, J^2 = 11.1 Hz, CH_2Ph), 4.68 (d, 1H, $J_1{}^F{}_{,2}{}^F$ = 8.0 Hz, H-1^F), 4.63 (dd, 2H, J^2 = 12.2 Hz, CH_2Ph), 4.61 (dd, 1H, $J_3{}^D{}_{,4}{}^D$ = 2.9 Hz, H-3^D), 4.61 (dd, 1H, $J_6{}^E{}_{,7}{}^E$ = 2.9 Hz, H-6^E), 4.43 (dd, 2H, J^2 = 12.5 Hz, CH_2Ph), 4.30−4.36 (m, 5H, $J_3{}^C{}_{,4}{}^C$ = 9.5 Hz, H-1^G, 3^C, 5^E, 6^{F}a, 9^{E}a), 4.26 (d, 1H, $J_1{}^B{}_{,2}{}^B$ = 7.6 Hz, H-1^B), 4.18 (dd, 2H, J^2 = 11.7 Hz, CH_2Ph), 4.17 (d, 1H, $J_1{}^A{}_{,2}{}^A$ = 6.6 Hz, H-1^A), 4.17 (dd, 1H, $J_2{}^C{}_{,3}{}^C$ = 9.5 Hz, H-2^C), 4.11 (dd, 1H, $J_5{}^F{}_{,6}{}^F{}_b$ = 3.8 Hz, $J_6{}^F{}_{a,6}{}^F{}_b$ = 11.8 Hz, H-6^{F}b), 4.01−4.16 (m, 4H, $J_4{}^B{}_{,5}{}^B$ = 3.2 Hz, H-4^B, 5^C, CH_2Ph), 3.91 (dd, 1H, $J_9{}^E{}_{a,9}{}^E{}_b$ = 12.4 Hz, H-9^{E}b), 3.80−3.94 (m, 8H, H-5^D, 6^{C}a, 6^{D}a, 6^{D}b, $OCH_2{}^a$, $COOCH_3$), 3.73−3.80 (m, 7H, H-4^A, 4^C, 5^G, 6^{G}a, 6^{G}b, 6^{C}b, 6^{B}a), 3.71 (dd, 1H, $J_4{}^F{}_{,5}{}^F$ = 9.1 Hz, H-4^F), 3.62 (m, 1H, H-5^F), 3.49 (m, 3H, H-5^B, 6^{B}b, $OCH_2{}^b$), 3.46 (dd, 1H, $J_3{}^B{}_{,4}{}^B$ = 3.4 Hz, H-3^B), 3.40 (dd, 1H, $J_5{}^A{}_{,6}{}^A{}_a$ = 4.7 Hz, $J_6{}^A{}_{a,6}{}^A{}_b$ = 11.0 Hz, H-6^{A}a), 3.36 (dd, 1H, $J_3{}^A{}_{,4}{}^A$ = 9.0 Hz, H-3^A), 3.35 (dd, 1H, $J_2{}^B{}_{,3}{}^B$ = 9.0 Hz, H-2^B), 3.29−3.35 (m, 3H, H-6^{A}b, CH_2N_3), 3.24 (dd, 1H, $J_2{}^A{}_{,3}{}^A$ = 9.0 Hz, H-2^A), 3.00 (m,1H, H-5^A), 2.72 (bs, 1H, 4^B-OH), 2.63 (dd, 1H, $J_3{}^E{}_{e,4}{}^E$ = 5.3 Hz, $J_3{}^E{}_{e,3}{}^E{}_a$ = 12.3 Hz, H-3^{E}e), 2.29, 2.35 [2s, 6H, $N(COCH_3)_2$], 1.85, 1.94, 1.94, 1.94, 1.96, 1.96, 1.97, 2.00, 2.01, 2.02, 2.10, 2.12, 2.18, 2.28 (14s, 42H, 14 × $OCOCH_3$), 1.79 (m, 2H, −$CH_2CH_2CH_2$−), 1.60 (dd, 1H, $J_3{}^E{}_{a,4}{}^E$ = 12.3 Hz, H-3^{E}a); ^{13}C NMR δ 170.00−171.45 (>C=O), 122.00−136.85 (aromatic), 103.62 (C-1^A), 102.25 (C-1^B), 101.57 (C-1^G), 101.19 (C-1^F), 101.12 (C-1^D), 98.95 (C-1^C), 97.00 (C-2^E), 83.23 (C-3^B), 82.98 (C-3^A), 82.02 (C-2^A), 79.69 (C-4^C)#, 78.46 (C-2^B), 78.19 (C-3^C), 77.07 (C-4^F), 76.51 (C-4^A)#, 75.48 (*C*H_2Ph), 75.45 (C-6^G), 75.25 (*C*H_2Ph), 75.15 (C-5^A), 74.71 (*C*H_2Ph), 74.55 (*C*H_2Ph), 73.38 (*C*H_2Ph), 73.36 (*C*H_2Ph), 73.32 (C-3^F), 73.26 (C-5^B), 72.90 (C-5^F), 72.40 (C-2^F), 71.65 (C-6^E)*, 71.36 (C-3^G), 71.27 (C-5^D), 71.17 (C-2^D), 70.85 (C-6^C), 70.05 (C-5^G), 69.63 (C-3^D)*, 69.30 (C-2^G), 69.08 (C-6^B), 68.21 (C-6^A), 68.01 (C-4^B), 67.88 (C-4^D), 67.61 (C-8^E), 67.39 (C-7^E), 67.27 (C-4^E), 66.85 (C-4^G), 66.60 (OCH_2), 62.83 (C-9^F), 62.53 (C-6^F), 62.10 (C-6^D), 60.96 (C-5^C), 56.18 (C-5^E), 55.98 (C-2^C), 53.37 ($COOCH_3$), 48.70 (CH_2N_3), 38.49 (C-3^E), 29.44, 29.92 [$N(COCH_3)_2$], 28.60 (−$CH_2CH_2CH_2$−), 20.00−21.85 ($OCOCH_3$). Anal. Calcd for $C_{131}H_{155}N_5O_{55}$ (2677.95): C, 58.72; H, 5.83; N, 2.61. Found: C, 58.58; H, 6.01; N, 2.61.

3-Aminopropyl *O*-(5-*N*-Acetamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosyl)-(2→3)-*O*-(β-D-glucopyranosyl)-(1→4)-*O*-[(β-D-galactopyranosyl)-(1→4)-(β-D-glucopyranosyl)-(1→6)]-*O*-(2-acetamido-2-deoxy-β-D-

glucopyranosyl)-(1→3)-*O*-(*β*-D-galactopyranosyl)-(1→4)-*β*-D-glucopyranoside (1). A mixture of **16a** (34 mg, 12.4 μmol) and LiI (25 mg, 0.19 mmol) in pyridine (2 mL) was heated for 24 h at 85 °C. The reaction mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography (gradient 2% MeOH in DCM) to afford **16b**. Compound **16b** was dissolved in *n*-butanol (2 mL), and ethylenediamine (400 μL) was added. After being stirred for 16 h at 90 °C, the reaction mixture was then concentrated in vacuo, and the residue was coevaporated from toluene (2 × 10 mL) and EtOH (2 × 5 mL). The crude **16c** was dissolved in MeOH (1.5 mL), and acetic anhydride (400 μL) was added. After being stirred for 6 h at room temperature, the reaction mixture was concentrated under reduced pressure. The residue **16d** was dissolved in 50% aqueous EtOH (2 mL), and Pd/C (20 mg) was added. The reaction mixture was stirred under an atmosphere of H_2 for 40 h. Then, the catalyst was filtered off and the filtrate concentrated under reduced pressure. The residue was dissolved in water (1 mL), and 1 M aqueous NaOH (200 μL) was added. After being stirred for 15 min, the reaction mixture was purified by Sephadex G-25 size-exclusion column chromatography (35 cm^3, water elution) to afford **1** as an amorphous powder (5.9 mg, 31%): $[\alpha]^{24}_D = +2.09$ ($c = 0.4$, 70% aqueous ethanol); selected ^{1}H NMR data δ 4.68 (d, 1H, $J_{1^C,2^C} = 8.6$ Hz, H-1^C), 4.58 (d, 1H, $J_{1^D,2^D} = 8.0$ Hz, H-1^D), 4.51 (d, 1H, $J_{1^F,2^F} = 7.7$ Hz, H-1^F), 4.45 (d, 1H, $J_{1^A,2^A} = 8.2$ Hz, H-1^A), 4.42 (d, 1H, $J_{1^G,2^G} = 7.9$ Hz, H-1^G), 4.40 (d, 1H, $J_{1^B,2^B} = 7.9$ Hz, H-1^B), 4.26 (br d, 1H, H-5^C), 4.14 (br s, 1H, H-4^B), 4.07 (br d, 1H, H-3^D), 3.94 (br s, 1H, H-4^D), 3.90 (br s, 1H, H-4^G), 3.85 (dd, 1H, H-4^C), 3.78 (dd, 1H, H-2^C), 3.70 (dd, 1H, H-3^C), 3.70 (dd, 1H, H-3^B), 3.66 (m, 1H, H-4^E), 3.65 (dd, 1H, H-3^G), 3.64 (m, 2H, H-3^F, 4^F), 3.62 (dd, 1H, H-3^A), 3.58 (dd, 1H, H-4^A), 3.56 (dd, 1H, H-2^B), 3.54 (dd, 1H, H-2^D), 3.52 (dd, 1H, H-2^G), 3.33 (dd, 1H, H-2^F), 3.28 (dd, 1H, H-2^A), 2.73 (dd, 1H, H-3^{E}e), 2.02 (s, 6H, NCOCH_3 × 2), 1.79 (dd, 1H, H-3^{E}a); selected ^{13}C NMR signals δ 104.26 (C-1^B), 104.26 (C-1^G), 104.02 (C-1^C), 103.92 (C-1^F), 103.53 (C-1^D), 103.38 (C-1^A), 83.35, 79.76, 78.81, 76.92, 76.59, 76.28, 76.01, 75.68, 74.70, 74.18, 74.04, 73.95, 73.78, 73.34, 73.02, 72.23, 71.29, 70.66, 69.87, 69.75, 69.56, 69.49, 69.31, 68.97, 68.83, 63.92, 62.23, 61.39, 59.80, 56.40, 52.95, 40.91 (C-3^E), 24.17, 24.17.

Preparation of a Polymer Containing GBS Heptasaccharide (18). The conjugation was performed in accordance with a previously described procedure.[23] A solution of **1** (1.16 mg, 0.828 μmol) in triethylamine (1.5 mL) was added to a stirred solution of poly[*N*-(acryloxy)succinimide] (**17**, 0.828 mg, 4.87 mmol of *N*-hydroxysuccinimide ether, 17% theoretical loading) in DMF (0.2 mL). The solution was stirred at room temperature for 20 h, heated at 65 °C for 6 h, and then cooled to room temperature. An aqueous solution of NH_4OH (20%, 0.1 mL) was added, and the mixture was stirred at room temperature for 24 h. The resulting mixture was dialyzed against distilled water and then freeze-dried to afford **18** as a white powder: selected ^{1}H NMR data δ 4.68 (d, 1H, $J = 8.6$ Hz), 4.58 (d, 1H, $J = 8.0$ Hz), 4.51 (d, 1H, $J = 7.7$ Hz), 4.45 (d, 1H, $J = 8.2$ Hz), 4.42 (d, 1H, $J = 7.9$ Hz), 4.40 (d, 1H, $J = 7.9$ Hz).

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Supporting Information Available: Copies of NMR spectra for compounds **1**, **3**−**5**, **8b**, **11**, **13**−**15**, and **16a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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