Solution- and Solid-Phase Synthesis of Inhibitors of *H. pylori* Attachment and E-Selectin-Mediated Leukocyte Adhesion

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Abstract: Chemical and enzymatic methods have been developed for the synthesis of the oligosaccharides NeuAcα2→3Galβ1→4GlcNAcβ1→3Gal and NeuAcα2→3Galβ1→4(Fucα1→3)GlcNAcβ1→3Gal as inhibitors for *H. pylori* and E-selectin, respectively. Gal, NeuAc, and Fuc were incorporated sequentially into the synthetic primer GlcNAcβ1→3GalβOEt by the corresponding glycosyltransferases to give both the tetrasaccharide and the pentasaccharide. This solution-phase strategy was then extended to the solid-phase synthesis of the tetrasaccharide. A disaccharide primer was first attached to controlled pore glass via a spacer group containing an ester bond, followed by enzymatic incorporation of Gal and NeuAc. Two to three equivalents of sugar nucleotides were used in the enzymatic glycosylation, and the conversion for each step was found to be >98% as indicated in the analysis of products released by treatment with hydrazine.

Introduction

Cell surface carbohydrates are highly diverse and serve many functions in cellular processes, such as cell–cell communication, receptor–ligand interactions, and cell adhesion.[1] A well-known example is the sialyl Lewis x (SLe^x) antigen (**1**, Figure 1), which mediates the early stage of adhesion of leukocytes to activated endothelial cells.[2] The SLe^x receptor on the endothelial cell surface is the protein E-selectin,[3] which is expressed in response to cytokines released by distressed tissue. More recently, it was discovered that Lewis b and related carbohydrate antigens mediate the attachment of ulcer causing *Helicobacter pylori* to human gastric mucosa.[4] Among carbohydrates which act as inhibitors of the bacterial attachment are NeuAcα2–3Galβ1–4GlcNAc conjugates.[5]

Our interest was to develop new methods for the synthesis of inhibitors to block the adhesion process mediated by E-selectin and *H. pylori*,[6,7] and we were particularly interested in the development of solid-phase techniques for the synthesis of such carbohydrate inhibitors.[8–10] The initial target analogs chosen for our study were the pentasaccharide **2a** and tetrasaccharide **2b** (Figure 1). The solution-phase synthesis of **2a** and **2b** (R = Et) utilized a combined chemical and enzymatic approach.[11] A small disaccharide primer corresponding to the reducing end of **2b** was chemically synthesized, and the remaining three sugar residues were then incorporated enzymatically.[12] Chemistry for the synthesis of **2a** and **2b** in solution phase was to be the basis for the solid-phase synthesis of **2b** (R = $(CH_2)_5CONHNH_2$), in which the primer was first attached to a solid support via a cleavable spacer group followed by enzymatic attachment of Gal and NeuAc to the primer.

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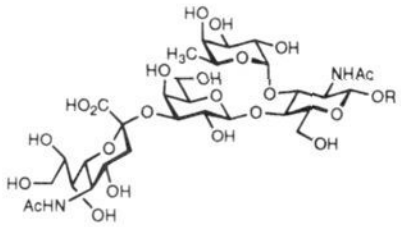
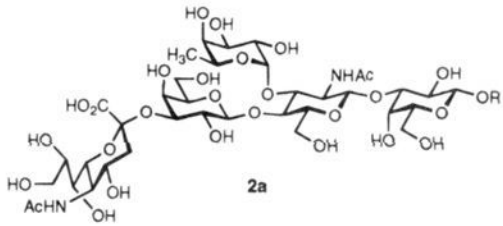
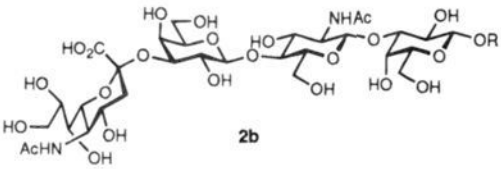


Sialyl Lewis X antigen (1)



2a



2b

Figure 1.

Potential advantages of such a solid-phase enzymatic synthesis over corresponding solution-phase methods include facilitation of product purification, reduction of the time required to assemble a complex oligosaccharide, and possible implementation of automated procedures. Additionally, enzymatic methods have the advantage that internal deletions in an oligosaccharide sequence are minimized. A major disadvantage, however, is that the narrow substrate specificity of glycosyltransferases makes the synthesis of various modified oligosaccharides difficult.

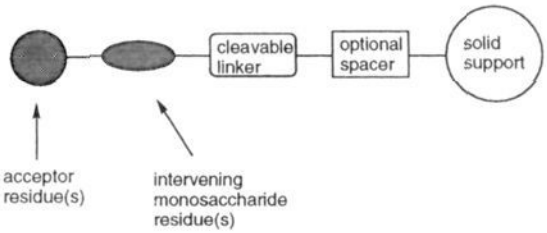
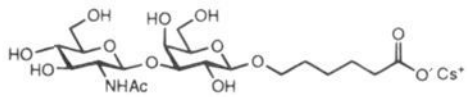


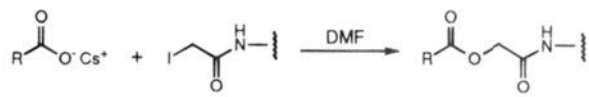
Figure 2. General blueprint.



3

Figure 3.

Scheme 1



The general blueprint for the solid-phase synthesis of an oligaccharide such as **2b** is illustrated in Figure 2. A requirement for the solid support was that it would be suitable for use in both water and organic solvents, such as DMF. A support which would meet this requirement would either swell in both water and DMF or would be rigid so as not to be compressed in water. Additionally, it must not sequester enzymes when used in aqueous enzymatic reactions. Controlled pore glass (CPG) was found to be a suitable support. The spacer simply would provide distance between the support and the acceptor residue to suppress steric problems.

The conditions placed on the cleavable linker were that it could be cleaved under basic and/or neutral conditions. Effort was made to avoid acid-labile linkers,[13] since some of the glycosidic linkages might not withstand the cleavage conditions. It was felt that an ester linkage would be suitable for this purpose. The technique of Gisin was utilized to attach the acceptor moiety to the solid support.[14,15] The method involves a nucleophilic displacement of a halide on the support-bound linker with the cesium salt of a carboxylic acid. In practice, an α-haloacetate was employed (Scheme 1).

It was also felt that an intervening monosaccharide residue between the linker, and the acceptor monosaccharide would serve as a hydrophilic buffer zone and would possibly facilitate the enzymatic glycosylation. Therefore the initial synthetic target became the disaccharide **3** (Figure 3). The galactose was to serve as the intervening hydrophilic buffer residue, and the cesium salt of the carboxylate was to serve as the handle for attachment to the resin support.

First, the solution phase chemical/enzymatic synthesis of the pentasaccharide **2a** and tetrasaccharide **2b** (R = Et) is described, along with the chemical synthesis of primer **3**. Then the enzymatic solid-phase synthesis of **2b** ($R = (CH_2)_5CONHNH_2$) is illustrated.

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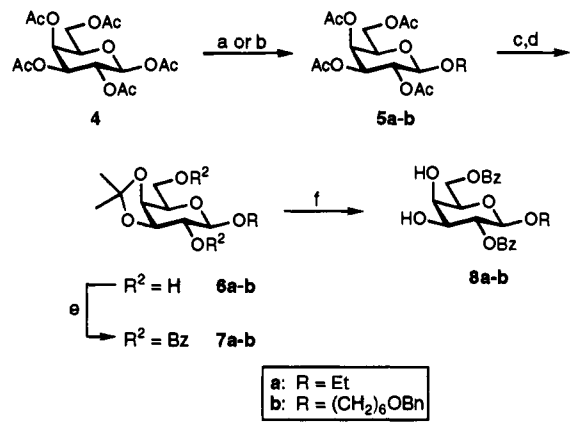
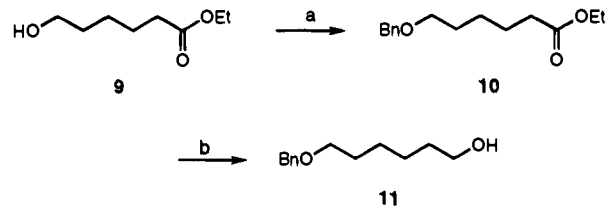
Scheme 2[a]



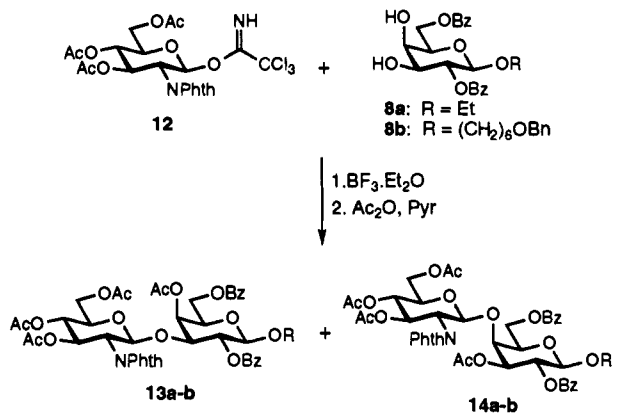
[a] a. 1. HBr, AcOH; 2. EtOH, $AgCO_3$. b. 1. $BnNH_2$; 2. CCl_3CN, DBU; 3. $BF_3{\cdot}Et_2O$, **11**. c. NaOMe, MeOH. d. 2,2-dimethoxypropane, TsOH. e. BzCl, pyr. f. AcOH, H_2O.

Scheme 3[a]



[a] a. $BnOC(NH)CCl_3$, TfOH. b. $LiAlH_4$.

Scheme 4

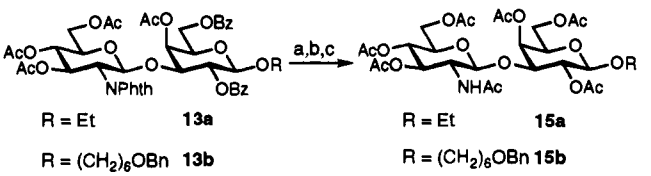


Results and Discussion

A. Solution-Phase Synthesis of Pentasaccharide 2a. The syntheses of two galactose derivatives which were suitably protected for glycosylation are illustrated in Scheme 2.[16] The ethyl glycoside **8a** was chosen for the solution-phase synthesis of the pentasaccharide model. The glycoside **8b** was also chosen since it contains a functionalized aglycon which can be elaborated into a suitable linker. The acceptor **11**, which was to become the six-carbon linker, was synthesized according to Scheme 3.

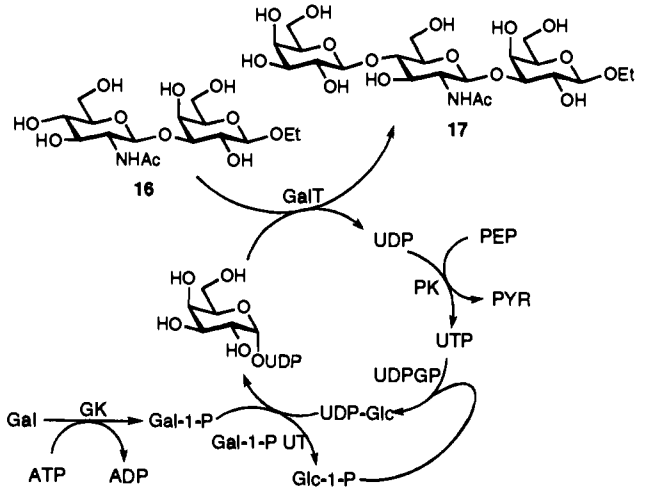
Compounds **8a,b** were regioselectively glycosylated with the imidate **12** to give desired **13a,b** as the major products, respectively (Scheme 4).[16] In each case, a mixture of 1 → 3 (**13**) and 1 → 4 (**14**) linked disaccharides was obtained in a ratio of about 2.5−3:1. The mixture of disaccharides was directly acetylated to aid in purification. Treatment of **13a** and **13b** with hydrazine and then NaOMe effected complete deprotection of the nonanomeric hydroxyl groups (Scheme 5). Subsequent acetylation afforded **15a** and **15b**, respectively.

Scheme 5[a]

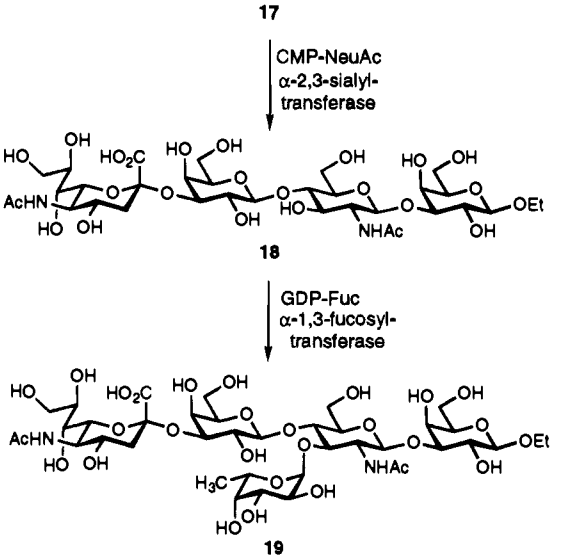


[a] a. H_2NNH_2, MeOH. b. NaOMe. c. Ac_2O, pyr.

Scheme 6



Scheme 7



Deacetylation of **15a** with NaOMe in MeOH gave compound **16**, which was the primer for the enzymatic glycosylations (Scheme 6). Enzymatic glycosyation of **16** with galactosyltransferase, employing the cofactor regeneration scheme previously reported from this group for *in situ* synthesis of the donor UDP-Gal,[17] gave compound **17**. The sialic acid and fucose units were added using α-2−3-sialyltransferase[18] and α-1−3-fucosyltransferase,[19] respectively, to give the pentasaccharide **19** (Scheme 7).

B. Solid-Phase Enzymatic Glycosylation. The synthesis

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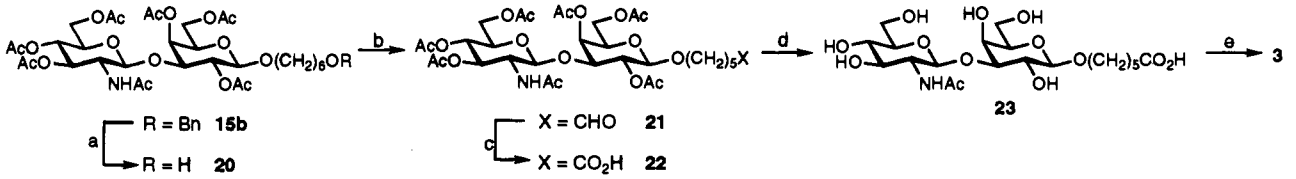
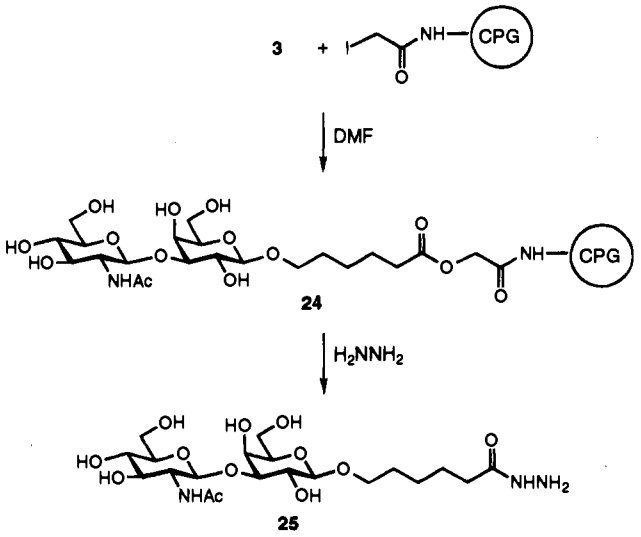
Scheme 8[a]



[a] a. H_2, Pd-C. b. $(COCl)_2$, DMSO; Et_3N. c. $NaClO_2$. d. NaOMe, MeOH; H_2O. e. 1. Cs_2CO_3 (ca. 0.5 equiv); 2. lyophilize.

Scheme 9



of the cesium carboxylate **3** is illustrated in Scheme 8. The benzyl ether of **15b** was hydrogenolyzed to give the primary alcohol **20**. Swern oxidation[20] gave **21**, and subsequent Lingren oxidation[21] gave the carboxylic acid **22**. Saponification of the acetate groups then gave compound **23**, which was converted into its cesium salt by adding an aqueous solution of Cs_2CO_3 to a solution of **23** until pH 7 was reached. Finally, lyophilization of the resulting solution provided **3**.[14]

Commercially available *N*-iodoacetyl aminopropyl controlled pore glass was the support chosen to test the feasibility of the system. This resin could, in fact, be derivatized with **3** by a nucleophilic esterification reaction (Scheme 9). That **3** had indeed been loaded onto the resin was determined by treating the adduct **24** with hydrazine. The released product was the hydrazide **25**.

The solid-supported acceptor **24** was then subjected to the conditions of enzymatic glycosylation (Scheme 10). Treatment of **24** with UDP-Gal and β-1,4-galactosyltransferase produced what was tentatively assumed to be **26**. Upon hydrazinolysis of **26**, trisaccharide **27** was released from the support. To demonstrate that **3** was not simply glycosylated while sequestered within pores in the support, and later released in the presence of hydrazine, compound **28** was synthesized from **3** for purposes of comparison. No **28** was found in the produced mixture. The glycosylation appeared to go virtually to completion in the time period of the reaction, since no **25** could be detected by TLC and NMR.

The solid supported trisaccharide **26** was then sialylated upon treatment with CMP-NeuAc and α-2,3-sialyltransferase to produce **29** (Scheme 11). Cleavage of the tetrasaccharide conjugate **29** with hydrazine yielded **30** as the only observed product. Again, no starting material could be detected.

Summary

In conclusion, a combined chemical-enzymatic synthesis of the pentasaccharide **2a** was accomplished. This chemistry was used to develop new strategies for glycosyltransferase-based solid-phase oligosaccharide synthesis. A synthetic disaccharide primer was first attached to a solid support, and the peripheral sugar residues were then added enzymatically. The feasibility of these techniques was demonstrated in the solid-phase synthesis of **2b**, an inhibitor of the attachment of *H. pylori* to mucous cells. This solid-phase strategy is expected to be of general use when glycosyltransferases become readily available.

Experimental Section

General Methods. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. α-1—3-fucosyltransferase and α-2—3-sialyltransferase were gifts from Cytel Corporation, San Diego. The ^1H spectra were recorded on a Bruker AM-300 or a Bruker AMX-500 in the indicated solvent at the indicated field. Silica gel 60 (230—400 mesh) from Mallinckrodt was used in flash chromatography. Biogel P-2 gel (fine, 65 ± 20 μm) was purchased from Bio-Rad Laboratories.

Ethyl 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranoside (5a). Compound **4** (20.0 g, 51.3 mmol) was dissolved in AcOH (40 mL) and Ac_2O (40 mL), and to this solution was added 150 mL of 48% HBr in AcOH. The mixture was stirred at room temperature for 20 h, after which it was added to 800 mL of CH_2Cl_2 and washed with 3 × 300 mL of H_2O and 2 × 300 mL of saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. Residual AcOH was removed by coevaporating with toluene. The product bromide was taken up in 300 mL of CH_2Cl_2, and anhydrous EtOH (40 mL) and Ag_2CO_3 (13.8 g) was added. After stirring for 24 h, the mixture was filtered through Celite and concentrated under vacuum. The residue was chromatographed (silica gel, hexane/EtOAc 7:3 → 6:4) to give 16.6 g (86%) of **5a**: 1H NMR (300 MHz, $CDCl_3$) δ 5.39 (dd, 1 H, J = 3.5, 1.0 Hz, H-4), 5.51 (dd, 1 H, J = 10.5, 8.0 Hz, H-2), 5.02 (dd, 1 H, J = 10.4, 3.4 Hz, H-3), 4.48 (d, 1 H, J = 7.9 Hz, H-1), 4.20 (app dd, 1 H, J = 11.2, 6.6 Hz, H-6_a), 4.13 (app dd, 1 H, J = 11.2, 6.8 Hz, H-6_b), 3.98—3.88 (m, 2 H, H-5, one of OCH_2CH_3), 3.59 (dq, 1 H, J = 9.7, 7.0 Hz, one of OCH_2CH_3), 2.16 (s, 3 H, Ac), 2.07 (s, 3 H, Ac), 2.06 (s, 3 H, Ac), 1.99 (s, 3 H, Ac), 1.22 (t, 3 H, J = 7.1 Hz, CH_2CH_3); HRMS calcd for $C_{16}H_{24}O_{10}Cs$ ($M + Cs^+$) 509.9424, found 509.0424.

6-(Phenylmethoxy)-1-hexyl-2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (5b). $BF_3{\cdot}Et_2O$ (100 μL) was added to a solution of 2,3,4,6-tetra-*O*-acetylgalactopyranosyl trichloroacetimidate (9.68 g, 19.65 mmol) and **11** (4.8 g) in CH_2Cl_2 at 0 °C. The mixture was stirred for 1.5 h at 0 °C after which it was quenched with saturated $NaHCO_3$. The mixture was added to 200 mL of CH_2Cl_2 and washed with 100 mL of saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed (silica gel, hexane/EtOAc 7:3 → 1:1) to give 70% of **5b**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.40—7.25 (m, 5 H, ArH), 5.38 (d, 1 H, J = 3.4 Hz, H-4), 5.20 (dd, 1 H, J = 10.5, 8.1 Hz, H-2), 5.02 (dd, 1 H,

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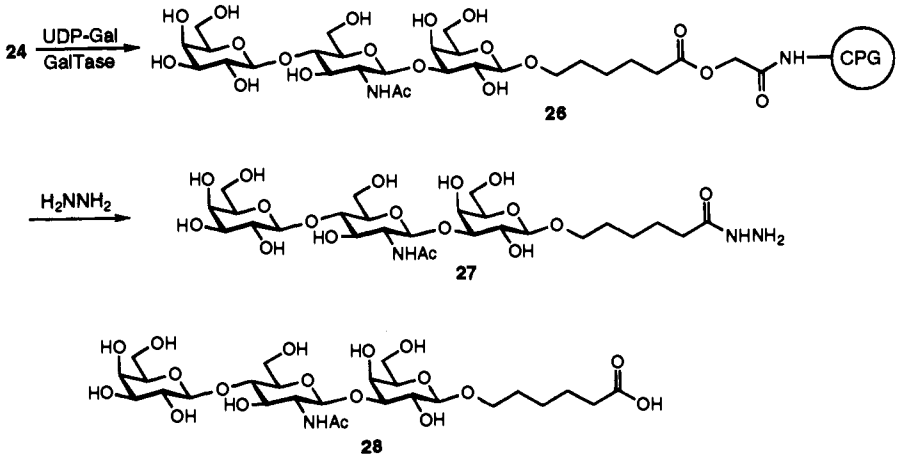
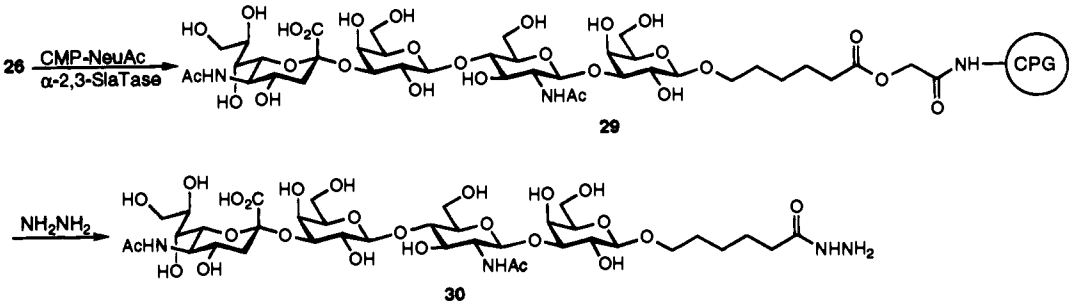
Scheme 10



Scheme 11



J = 10.5, 3.4 Hz, H-3), 4.51 (s, 2 H, CH_2Ph), 4.45 (d, 1 H, J = 8.1 Hz, H-1), 4.22–4.05 (m, 2 H, H-6_a, H-6_b), 3.90–3.85 (m, 2 H, H-5, one of $GalOCH_2$), 3.52–3.40 (m, 3 H, one of $GalOCH_2$, CH_2OBn), 2.18 (s, 3 H, Ac), 2.03 (s, 3 H, Ac), 2.02 (s, 3 H, Ac), 1.98 (s, 3 H, Ac), 1.70–1.40 (m, 8 H, 4 × CH_2 of hexyl).

Ethyl 3,4-*O*-Isopropylidene-β-D-galactopyranoside (6a). A solution of compound **5a** (10.6 g, 28.2 mmol) and a catalytic amount of NaOMe in 50 mL MeOH was stirred at room temperature for 6 h. Dowex-50 (H^+) was added, and the mixture was stirred for another 1 h. The mixture was filtered through Celite, and the filtrate was concentrated under vacuum to give 5.67 g (97%) of the tetraol. This tetraol (5.17 g, 24.83 mmol) was dissolved in 2,2-dimethoxypropane (40 mL), and 100 mg of *p*-toluenesulfonic acid was added. The mixture was stirred at room temperature for 18 h after which it was neutralized by the addition of 2 mL of Et_3N. The mixture was concentrated under vacuum, and the residue was chromatographed (silica gel, $CHCl_3$/MeOH 97:3 → 94:6) to give 4.304 g (70%) of **6a**: ^1H NMR (500 MHz, $CDCl_3$) δ 4.21 (d, 1 H, J = 8.0 Hz, H-1), 4.17 (dd, 1 H, J = 5.5, 2.0 Hz, H-4), 4.11 (dd, 1 H, J = 7.0, 5.5 Hz, H-3), 4.04–3.96 (m, 2 H, one of OCH_2CH_3, H-6_a), 3.90–3.83 (m, 2 H, H-5, H-6_b), 3.61 (dq, 1 H, J = 9.5, 7.0 Hz, one of OCH_2CH_3), 3.56 (t, 1 H, J = 8.0 Hz, H-2), 2.48 (m, 1 H, OH), 2.14 (m, 1 H, OH), 1.53 (s, 3 H, acetonide CH_3), 1.35 (s, 3 H, acetonide CH_3), 1.27 (t, 3 H, J = 7.0 Hz, CH_2CH_3).

6-(Phenylmethoxy)-1-hexyl 3,4-*O*-Isopropylidene-β-D-galactopyranoside (6b). Synthesized in a similar manner to **6a**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5 H, ArH), 4.51 (s, 2 H, CH_2Ph), 4.18 (d, 1 H, J = 7.9 Hz, H-1), 4.17–4.07 (m, 2 H, H-3, H-4), 4.02–3.80 (m, 4 H, H-6_a, H-6_b, H-5, one of $GalOCH_2$), 3.59–3.49 (m, 2 H, H-2, one of $GalOCH_2$), 3.47 (t, 2 H, J = 6.5 Hz, CH_2OBn), 2.50 (m, 1 H, OH), 2.17 (m, 1 H, OH), 1.70–1.59 (m, 4 H, 2 × CH_2), 1.53 (s, 3 H, acetonide CH_3), 1.47–1.38 (m, 4 H, 2 × CH_2), 1.37 (s, 3 H, acetonide CH_3).

Ethyl 2,6-Di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranoside (7a). A solution of **6a** (2.276 g, 9.17 mmol), benzoyl chloride (3.4 mL), and DMAP (300 mg) in pyridine (40 mL) was stirred at room temperature for 24 h. The reaction was quenched by adding saturated $NaHCO_3$. The mixture was added to 300 mL of CH_2Cl_2 and washed with 100 mL of saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. Residual pyridine was removed by coevaporating with toluene. The residue was chromatographed (silica gel, hexane/EtOAc 7:3 → 6:4) to give 3.971 g (95%) of **7a**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.10–8.04 (m, 4 H, ArH), 7.62–7.53 (m, 2 H, ArH), 7.49–7.40 (m, 4 H, ArH), 5.25 (dd, 1 H, J = 7.8, 7.2 Hz, H-2), 4.70 (app dd, 1 H, J = 11.6, 5.1 Hz, H-6_a), 4.64 (app dd, 1 H, J = 11.6, 7.3 Hz, H-6_b), 4.54 (d, 1 H, J = 8.1 Hz, H-1), 4.38 (dd, 1 H, J = 7.1, 5.5 Hz, H-3), 4.31 (dd, 1 H, J = 5.4, 2.1 Hz, H-4), 4.21 (ddd, 1 H, J = 7.2, 5.1, 2.1 Hz, H-5), 3.89 (dq, 1 H, J = 9.8, 7.0 Hz, one of $GalOCH_2$), 3.56 (dq, 1 H, J = 9.8, 7.1 Hz, one of $GalOCH_2$), 1.64 (s, 3 H, acetonide CH_3), 1.37 (s, 3 H, acetonide CH_3), 1.14 (t, 3 H, J = 7.1 Hz, CH_2CH_3).

6-(Phenylmethoxy)-1-hexyl 2,6-Di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranoside (7b). Synthesized similarly to **7a** in 86%: ^1H NMR (300 MHz, $CDCl_3$) δ 8.10–8.00 (m, 4 H, ArH), 7.60–7.25 (m, 11 H, ArH), 5.24 (t, 1 H, J = 6.3 Hz, H-2), 4.73–4.60 (m, 2 H, H-6_a, H-6_b), 4.49 (d, 1 H, J = 6.9 Hz, H-1), 4.43 (s, 2 H, CH_2Ph), 4.37 (dd, 1 H, J = 5.9, 4.4 Hz, H-3), 4.31 (dd, 1 H, J = 4.5, 1.9 Hz, H-5), 4.23–4.17 (m, 1 H, H-5), 3.85 (dt, 1 H, J = 8.1, 5.0 Hz, one of $GalOCH_2$), 3.44 (dt, 1 H, J = 8.1, 5.0 Hz, one of $GalOCH_2$), 3.32 (t, 2 H, J = 6.5 Hz, CH_2OBn), 1.66 (s, 3 H, CH_3), 1.58–1.45 (m, 4 H, 2 × CH_2 of hexyl), 1.37 (s, 3 H, CH_3), 1.25–1.15 (m, 4 H, 2 × CH_2 of hexyl).

Ethyl 2,6-Di-*O*-benzoyl-β-D-galactopyranoside (8a). A solution of **7a** (3.97 g, 8.70 mmol) in AcOH (960 mL) and H_2O (20 mL) was stirred at 60 °C for 8 h. The solvent was removed under vacuum by coevaporating with toluene. The residue was chromatographed (silica gel, hexane/EtOAc 4:6) to give 3.493 g (96%) of **8a**: ^1H NMR (500 MHz, $CDCl_3$) δ 8.10–8.03 (m, 4 H, ArH), 7.67–7.57 (m, 2 H, ArH), 7.50–7.43 (m, 4 H, ArH), 5.17 (dd, 1 H, J = 9.5, 7.9 Hz, H-2), 4.74 (dd, 1 H, J = 11.4, 6.8 Hz, H-6_a), 4.63 (d, 1 H, J = 7.9 Hz, H-1), 4.58 (dd, 1 H, J = 11.3, 6.5 Hz, H-6_b), 4.03 (m, 1 H, H-4), 3.95 (dq, 1 H, J = 9.8, 7.2 Hz, one of OCH_2CH_3), 3.91 (m, 1 H, H-3), 3.85 (m, 1 H, H-5), 3.64 (dq, 1 H, J = 9.7, 7.0 Hz, one of OCH_2CH_3), 3.45 (d, 1 H, J = 6.5 Hz, OH), 2.89 (d, 1 H, J = 4.3 Hz, OH), 1.19 (t, 1 H, J = 7.0 Hz, CH_3).

6-(Phenylmethoxy)-1-hexyl 2,6-Di-*O*-benzoyl-β-D-galactopyranoside (8b): Prepared similarly to **8a** in 94%.

Ethyl 6-(Phenylmethoxy)hexanoate (10). Trifluoromethanesulfonic acid (20 μL) was added to a solution of ethyl 6-hydroxyhexanoate **9** (26 g, 162 mmol) and benzyl trichloroacetimidate (45.6 g, 180.6 mmol) in CH_2Cl_2 (100 mL) at 0 °C. After being kept at 0 °C for 18 h, the mixture was diluted with 200 mL of hexane, and the resulting mixture was filtered through Celite. The filtrate was washed with 100 mL of saturated $NaHCO_3$ and 100 mL of saturated NaCl. The residue was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed (silica gel, hexane/EtOAc 8:2) to give 42.06 g of **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (m, 5 H), 4.52 (s, 2 H), 4.14 (q, 2 H, J = 7 Hz), 3.48 (t, 2 H, J = 7 Hz), 2.33 (t, 2 H, J = 7 Hz), 1.70−1.35 (m, 6 H), 1.26 (t, 3 H, J = 7 Hz).

6-(Phenylmethoxy)hexan-1-ol (11). $LiAlH_4$ (3 g) was slowly added to a solution of **10** (42.06 g) in THF (200 mL) at 0 °C. After addition of $LiAlH_4$ was complete, the mixture was stirred at room temperature for 6 h. The reaction was quenched by the slow addition of HCl until the pH was constantly acidic. The mixture was filtered through Celite and concentrated. The residue was chromatographed (silica gel, hexane/EtOAc 7:3) to give 25 g of crude **11** which was purified further by silica gel chromatography: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (m, 5 H), 4.50 (s, 2 H), 3.64 (t, 2 H, J = 7 Hz), 3.47 (t, 2 H, J = 7 Hz), 1.70−1.30 (m, 8 H).

Ethyl *O*-(3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)(1 → 3)-4-*O*-acetyl-2,6-di-*O*-benzoyl-β-D-galactopyranoside (13a) and Ethyl *O*-(3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)(1 → 4)-3-*O*-acetyl-2,6-di-*O*-benzoyl-β-D-galactopyranoside (14a). A solution of the diol **8a** (750 mg, 1.803 mmol) and imidate **12** (891 mg, 1.537 mmol) in CH_2Cl_2 (20 mL) was stirred with 3A MS for 1 h. The mixture was cooled to −43 °C, and $BF_3{\cdot}Et_2O$ (25 μL) was added. After stirring for 1 h, the solution was allowed to warm to −15 °C, and the reaction was quenched by adding Et_3N (100 μL). The mixture was added to 100 mL of CH_2Cl_2 and washed with 50 mL of saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Column chromatography (silica gel, hexane/EtOAc 1:1 → 3:1) gave an inseparable mixture of 1 → 3 and 1 → 4 linked disaccharides. This mixture was taken up in pyridine (15 mL) and Ac_2O (15 mL) along with DMAP (10 mg) and stirred for 12 h. The volatiles were removed by coevaporating with toluene, and the residue was chromatographed (silica gel, hexane/EtOAc 6:4 → 4:6) to give 308 mg (23%) of the higher R_f **14a** and 788 mg (59%) of **13a**. **13a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08−8.04 (m, 2 H, ArH), 7.67−7.64 (m, 2 H, ArH), 7.60−7.43 (m, 8 H, ArH), 7.33−7.28 (m, 2 H, ArH), 5.66 (dd, 1 H, J = 10.7, 9.1 Hz, H-3′), 5.61 (d, 1 H, J = 3.5 Hz, H-4), 5.47 (d, 1 H, J = 8.3 Hz, H-1′), 5.27 (dd, 1 H, J = 10.0, 8.0 Hz, H-2), 5.15 (t, 1 H, J = 9.3 Hz, H-4′), 4.48 (d, 1 H, J = 8.0 Hz, H-1), 4.43 (app dd, 1 H, J = 11.5, 7.2 Hz, H-6$_a$), 4.39 (app dd, 1 H, J = 11.6, 5.6 Hz, H-6$_b$), 4.32 (dd, 1 H, J = 12.2, 2.5 Hz, H-6$_a$′), 4.22 (dd, 1 H, J = 10.8, 8.3 Hz, H-2′), 4.16 (dd, 1 H, J = 12.2, 4.1 Hz, H-6$_b$′), 4.00 (dd, 1 H, J = 9.8, 3.4 Hz, H-3), 3.99 (m, 1 H, H-5), 3.81 (m, 1 H, H-5′), 3.78 (dq, 1 H, J = 10.0, 7.1 Hz, one of OCH_2CH_3), 3.45 (dq, 1 H, J = 9.9, 7.0 Hz, one of OCH_2CH_3), 2.20 (s, 3 H, Ac), 2.07 (s, 3 H, Ac), 2.00 (s, 3 H, Ac), 1.78 (s, 3 H, Ac), 0.98 (t, 3 H, J = 7.1 Hz, CH_2CH_3). **14a**: 8.10−8.00 (m, 3 H, ArH), 7.85−7.65 (m, 5 H, Ar), 7.60−7.55 (m, 1 H, ArH), 7.53−7.45 (m, 3 H, ArH), 7.38−7.32 (m, 2 H, ArH), 5.92 (dd, 1 H, J = 10.7, 9.1 Hz, H-3′), 5.41 (d, 1 H, J = 8.3 Hz, H-1′), 5.16 (t, 1 H, J = 9.3 Hz, H-4′), 5.09 (dd, 1 H, J = 10.5, 2.7 Hz, H-3), 5.01 (dd, 1 H, J = 10.5, 7.8 Hz, H-2), 4.69 (dd, 1 H, J = 11.5, 5.7 Hz, H-6$_a$), 4.52 (d, 1 H, J = 7.8 Hz, H-1), 4.47 (dd, 1 H, J = 10.8, 8.4 Hz, H-2′), 4.44 (dd, 1 H, J = 11.5, 6.4 Hz, H-6$_b$), 4.22 (d, 1 H, J = 2.5 Hz, H-4), 4.14 (dd, 1 H, J = 12.3, 4.3 Hz, H-6$_a$′), 3.95 (dd, 1 H, J = 12.3, 2.3 Hz, H-6$_b$′), 3.92 (m, 1 H, H-5), 3.82−3.78 (m, 1 H, H-5′), 3.78 (dq, 1 H, J = 9.8, 7.1 Hz, one of OCH_2CH_3), 3.52 (dq, 1 H, J = 9.9, 7.1 Hz, one of OCH_2CH_3), 2.06 (s, 3 H, Ac), 2.01 (s, 3 H, Ac), 1.89 (s, 6 H, 2 × Ac), 1.07 (t, 3 H, J = 7.1 Hz, CH_2CH_3).

6-(Phenylmethoxy)-1-hexyl *O*-(3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)(1 → 3)-4-*O*-acetyl-2,6-di-*O*-benzoyl-β-D-galactopyranoside (13b) and 6-(phenylmethoxy)-1-hexyl *O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1 → 4)-3-*O*-acetyl-2,6-di-*O*-benzoyl-β-D-galactopyranoside (14b). Synthesized in a similar manner to **13a** and **14a** in 55 and 21%, respectively. **13b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08−8.04 (m, 2 H, ArH), 7.67−7.43 (m, 9 H, ArH), 7.35−7.25 (m, 7 H, ArH), 7.20−7.10 (m, 1 H, ArH), 5.68 (dd, 1 H, J = 10.7, 9.1 Hz, H-3′), 5.60 (d, 1 H, J = 3.4 Hz, H-4), 5.47 (d, 1 H, J = 8.3 Hz, H-1′), 5.26 (dd, 1 H, J = 10.0, 8.0 Hz, H-2), 5.15 (t, 1 H, J = 9.6 Hz, H-4′), 4.44 (d, 1 H, J = 8.0 Hz, H-1), 4.43 (dd, 1 H, J = 11.6, 7.2 Hz, H-6$_a$), 4.40 (s, 2 H, OCH_2Ph), 4.38 (dd, 1 H, J = 11.6, 5.6 Hz, H-6$_b$), 4.32 (dd, 1 H, J = 12.2, 2.5 Hz, H-6$_a$′), 4.22 (dd, 1 H, J = 10.8, 8.3 Hz, H-2′), 4.16 (dd, 1 H, J = 12.2, 4.1 Hz, H-6$_b$′), 4.01−3.97 (m, 2 H, H-3, H-5), 3.80 (ddd, 1 H, J = 10.1, 3.8, 2.6 Hz, H-5′), 3.75 (dt, 1 H, J = 9.8, 6.0 Hz, one of $GalOCH_2$), 3.34−3.28 (m, 1 H, one of $GalOCH_2$), 3.23 (t, 2 H, J = 6.6 Hz, CH_2OBn), 2.19 (s, 3 H, Ac), 2.07 (s, 3 H, Ac), 2.00 (s, 3 H, Ac), 1.78 (s, 3 H, Ac), 1.43−1.20 (m, 4 H, 2 × CH_2 of hexyl), 1.13−0.90 (m, 4 H, 2 × CH_2 of hexyl). **14b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05−8.00 (m, 3 H, ArH), 7.85−7.65 (m, 5 H, ArH), 7.59−7.54 (m, 1 H, ArH), 7.50−7.42 (m, 3 H, ArH), 7.35−7.25 (m, 7 H, ArH), 5.92 (dd, 1 H, J = 10.7, 9.3 Hz, H-3′), 5.41 (d, 1 H, J = 8.3 Hz, H-1′), 5.16 (t, 1 H, J = 9.6 Hz, H-4′), 5.09 (dd, 1 H, J = 10.5, 2.7 Hz, H-3), 5.01 (dd, 1 H, J = 10.5, 7.8 Hz, H-2), 4.68 (dd, 1 H, J = 11.5, 5.8 Hz, H-6$_a$), 4.49 (d, 1 H, J = 7.8 Hz, H-1), 4.47 (dd, 1 H, J = 10.6, 8.3 Hz, H-2′), 4.44 (dd, 1 H, J = 11.4, 6.5 Hz, H-6$_b$), 4.43 (s, 2 H, OCH_2Ph), 4.22 (d, 1 H, J = 2.6 Hz, H-4), 4.14 (dd, 1 H, J = 12.3, 2.6 Hz, H-6$_a$′), 3.95 (dd, 1 H, J = 12.3, 2.3 Hz, H-6$_b$′), 3.91 (t, 1 H, J = 6.1 Hz, H-5), 3.80 (ddd, 1 H, J = 10.1, 4.0, 2.4 Hz, H-5′), 3.73 (dt, 1 H, J = 9.7, 6.3 Hz, one of $GalOCH_2$), 3.41 (dt, 1 H, J = 9.7, 6.9 Hz, one of $GalOCH_2$), 3.31 (t, 2 H, J = 6.7 Hz, CH_2OBn), 2.06 (s, 3 H, Ac), 2.01 (s, 3 H, Ac), 1.89 (s, 3 H, Ac), 1.88 (s, 3 H, Ac), 1.44−1.33 (m, 4 H, 2 × CH_2 of hexyl), 1.20−1.10 (m, 4 H, 2 × CH_2 of hexyl).

Ethyl *O*-(3,4,6-Tri-*O*-acetyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)(1 → 3)-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside (15a). A solution of **13a** (786 mg, 0.897 mmol) and hydrazine hydrate (1.0 mL) in MeOH (10 mL) was heated to 70 °C for 3 h. The mixture was cooled to room temperature, NaOMe (20 mg) was added, and the reaction mixture was stirred for another 24 h. Volatiles were removed under vacuum, and to the residue was added pyridine (5 mL), Ac_2O (5 mL), and DMAP (50 mg). After stirring for 24 h, the solvent was removed by coevaporating with toluene, and the residue was chromatographed (silica gel, hexane/EtOAc 2:8 → EtOAc) to give 579 mg (97%) of **15a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (d, 1 H, J = 6.5 Hz, NH), 5.52 (dd, 1 H, J = 10.5, 9.9 Hz, H-3′), 5.37 (d, 1 H, J = 3.0 Hz, H-4), 5.11 (dd, 1 H, J = 10.0, 8.0 Hz, H-2), 5.07 (d, 1 H, J = 8.0 Hz, H-1′), 5.04 (t, 1 H, J = 9.5 Hz, H-4′), 4.38 (d, 1 H, J = 8.0 Hz, H-1), 4.32 (dd, 1 H, J = 13.0, 2.5 Hz, H-6$_a$′), 4.15−4.06 (m, 3 H, H-6$_b$′, H-6$_a$, H-6$_b$), 3.90 (dq, 1 H, J = 10.0, 7.0 Hz, one of OCH_2CH_3), 3.84 (dd, 1 H, J = 10.0, 3.5 Hz, H-3), 3.81 (m, 1 H, H-5), 3.68 (m, 1 H, H-5′), 3.56 (dq, 1 H, J = 10.0, 7.0 Hz, one of OCH_2CH_3), 3.30 (dt, 1 H, J = 10.5, 8.0 Hz, H-2′), 2.12 (s, 3 H, Ac), 2.11 (s, 3 H, Ac), 2.10 (s, 3 H, Ac), 2.07 (s, 3 H, Ac), 2.02 (s, 3 H, Ac), 2.01 (s, 3 H, Ac), 1.91 (s, 3 H, Ac), 1.20 (t, 3 H, J = 7.0 Hz, CH_2CH_3).

6-(Phenylmethoxy)-1-hexyl *O*-(3,4,6-Tri-*O*-acetyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)(1 → 3)-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside (15b). Synthesized in a manner similar to **15a** in 73%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5 H, ArH), 5.52 (dd, 1 H, J = 10.5, 9.2 Hz, H-3′), 5.52 (d, 1 H, J = 7.7 Hz, NH), 5.36 (d, 1 H, J = 3.4 Hz, H-4), 5.11 (dd, 1 H, J = 10.0, 8.0 Hz, H-2), 5.07 (d, 1 H, J = 8.5 Hz, H-1′), 5.04 (t, 1 H, J = 9.7 Hz, H-4′), 4.50 (s, 2 H, OCH_2Ph), 4.35 (d, 1 H, J = 8.0 Hz, H-1), 4.32 (dd, 1 H, J = 12.2, 2.5 Hz, H-6$_a$′), 4.13 (dd, 1 H, J = 11.5, 6.5 Hz, H-6$_a$), 4.10 (dd, 1 H, J = 12.2, 3.2 Hz, H-6$_b$′), 4.09 (dd, 1 H, J = 11.7, 6.6 Hz, H-6$_b$), 3.86 (dt, 1 H, J = 9.6, 6.1 Hz, one of $GalOCH_2$), 3.83 (dd, 1 H, J = 10.1, 3.6 Hz, H-3), 3.80 (dd, 1 H, J = 6.5 Hz, H-5), 3.70−3.66 (m, 1 H, H-5′), 3.46 (t, 2 H, J = 6.6 Hz, CH_2OBn), 3.44 (dt, 1 H, J = 9.6, 7.0 Hz, one of $GalOCH_2$), 3.30 (dt, 1 H, J = 10.5, 7.9 Hz, H-2′), 2.12 (s, 3 H, Ac), 2.11 (s, 3 H, Ac), 2.08 (s, 3 H, Ac), 2.07 (s, 3 H, Ac), 2.02 (s, 3 H, Ac), 2.01 (s, 3 H, Ac), 1.91 (s, 3 H, Ac), 1.63−1.53 (m, 4 H, 2 × CH_2 of hexyl), 1.39−1.25 (m, 4 H, 2 × CH_2 of hexyl).

Ethyl *O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)(1 → 3)-β-D-galactopyranoside (16). Compound **15a** was deacetylated by stirring with a catalytic amount of NaOMe in methanol at ambient temperature to give **16** in quantitative yield. ^{1}H NMR (500 MHz, D_2O) δ 4.52 (d, 1 H, J = 8.4 Hz, H-1′), 4.22 (d, 1 H, J = 8.1 Hz, H-1), 3.96 (d, 1 H, J = 3.3 Hz, H-4), 3.80 (dq, 1 H, J = 9.8, 7.1 Hz, one of OCH_2CH_3), 3.72 (dd, 1 H, J = 12.6, 2.0 Hz), 3.63−3.48 (m, 7 H), 3.43−3.38 (m,

1 H), 3.37 (dd, 1 H, J = 9.9, 8.0 Hz, H-2′), 3.33−3.27 (m, 2 H), 1.86 (s, 3 H, Ac), 1.05 (t, 3 H, J = 7.1 Hz, CH_2CH_3).

Ethyl *O*-(β-D-Galactopyranosyl)(1 → 4)-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)(1 → 3)-β-D-galactopyranoside (17). A solution of **16** (400 mg, 0.972 mmol), galactose-1-phosphate dipotassium salt (340 mg), glucose-1-phosphate monosodium salt (30 mg), UDP monosodium salt (50 mg), phosphoenol pyruvate trisodium salt (240 mg), dithiothreitol (30 mg), pyruvate kinase (20 U), UDP-glucose pyrophosphorylase (5 U), inorganic pyrophosphatase (100 u), galactose-1-phosphate uridyltransferase (5 U), and β-1,4-galactosyltransferase (5 U) in 10 mL of 50 mM HEPES buffer with 20 mM Mn^{2+} and 10 mM K^+ was stirred for 24 h at room temperature. The mixture was then passed through a column of Dowex-1 (Cl^-), and the fractions containing the product were concentrated under vacuum. The residue was chromatographed on Biogel P-2 (H_2O as eluant) to give 510 mg (91%) of **17**: ^{1}H NMR (500 MHz, D_2O) δ 4.54 (d, 1 H, J = 8.3 Hz), 4.31 (d, 1 H, J = 7.8 Hz), 4.22 (d, 1 H, J = 8.0 Hz), 3.97 (d, 1 H, J = 3.3 Hz), 3.80 (dq, 1 H, J = 9.8, 7.1 Hz), 3.75 (d, 1 H, J = 3.4 Hz), 3.67 (dd, 1 H, J = 12.4, 4.7 Hz), 3.65−3.48 (m, 13 H), 3.41 (m, 1 H), 3.37 (dd, 1 H, J = 9.9, 7.9 Hz), 1.86 (s, 3 H, Ac), 1.05 (t, 3 H, J = 7.1 Hz); HRMS calcd for $C_{22}H_{39}NO_{16}Cs$ (M + Cs^+) 706.1323, found 706.1233.

Ethyl *O*-(5-Acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonic acid)(2 → 3)-*O*-(β-D-galactopyranosyl)(1 → 4)-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)(1 → 3)-β-D-galactopyranoside (18). A solution of **17** (17 mg, 0.0296 mmol), CMP-NeuAc (16.2 mg, 0.0255 mmol), DTT (1 mg), Triton-X (10 μL), alkaline phosphatase (10 U), α-2,3-sialyltransferase (0.025 U), and BSA (1 mg) in 1.3 mL of sodium cacodylate buffer (50 mM, pH 7.5) was gently stirred at room temperature for 24 h. The mixture was chromatographed on Biogel P-2 (H_2O mobile phase) to give 20.5 mg (80%) of **18**: ^{1}H NMR (500 MHz, D_2O) δ 4.53 (d, 1 H, J = 8.3 Hz), 4.38 (d, 1 H, J = 7.9 Hz), 4.21 (d, 1 H, J = 8.0 Hz), 3.97 (d, 1 H, J = 3.4 Hz), 3.94 (dd, 1 H, J = 9.8, 3.0 Hz), 3.83−3.76 (m, 3 H), 3.75−3.33 (m, 22 H), 2.58 (dd, 1 H, J = 12.5, 4.7 Hz), 1.85 (s, 6 H), 1.62 (t, 1 H, J = 12.2 Hz), 1.05 (t, 3 H, J = 7.1 Hz).

Ethyl *O*-(5-Acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonic acid)(2 → 3)-*O*-(β-D-galactopyranosyl)(1 → 4)[*O*-(6-deoxy-α-D-galactopyranosyl(1 → 3))]-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)(1 → 3)-β-D-galactopyranoside (19). A solution of **18** (3.2 mg, 0.0037 mmol), GDP-Fuc (2.3 mg), and α-1,3-fucosyltransferase (ca. 10 mU) in HEPES buffer (50 mM, 700 μL) containing 20 mM $MnCl_2$ was gently stirred at room temperature for 5 days. The mixture was purified by gel filtration (BioGel P-6, H_2O), preparative TLC (eluting with EtOAc/2-PrOH/H_2O 2:2:1), and again by gel filtration (BioGel P-6, H_2O) to give 1.8 mg of **19**: ^{1}H NMR (500 MHz, D_2O) δ 5.04 (d, 1 H, J = 4.0 Hz), 4.63 (d, 1 H, J = 8.0 Hz), 4.45 (d, 1 H, J = 8.0 Hz), 4.30 (d, 1 H, J = 3.3 Hz), 4.01 (dd, 1 H, J = 9.7, 3.0 Hz), 3.92−3.41 (m, 30 H), 2.68 (dd, 1 H, J = 12.5, 3.7 Hz), 1.95 (s, 6 H), 1.71 (t, 1 H, J = 12.2 Hz), 1.14 (t, 3 H, J = 7.1 Hz), 1.08 (d, 3 H, J = 6.6 Hz).

6-Hydroxy-1-hexyl *O*-(3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)(1 → 3)-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside (20). A mixture of **15c** (1.385 g, 1.672 mmol) and catalytic 10% Pd/C in 20 mL of EtOAc was stirred under 1 atm H_2 for 24 h. The mixture was filtered through Celite and concentrated under vacuum to give 1.223 g (99%) of **20**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59 (d, 1 H, J = 7.8 Hz, NH), 5.53 (dd, 1 H, J = 10.5, 9.3 Hz, H-3′), 5.37 (d, 1 H, J = 3.4 Hz, H-4), 5.12 (dd, 1 H, J = 10.0, 8.0 Hz, H-2), 5.08 (d, 1 H, J = 8.1 Hz, H-1′), 5.04 (t, 1 H, J = 9.7 Hz, H-4′), 4.36 (d, 1 H, J = 8.0 Hz, H-1), 4.32 (dd, 1 H, J = 12.3, 2.6 Hz, H-6_a′), 4.15−4.07 (m, 3 H, H-6_a, H-6_b, H-6_b′), 3.87 (dt, 1 H, J = 9.6, 6.2 Hz, one of $GalOCH_2$), 3.84 (dd, 1 H, J = 10.0, 3.6 Hz, H-3), 3.81 (t, 1 H, J = 6.6 Hz, H-5), 3.70−3.67 (m, 1 H, H-5′), 3.64 (t, 2 H, J = 6.5 Hz, CH_2CH_2OH), 3.46 (dt, 1 H, J = 9.5, 6.5 Hz, one of $GalOCH_2$), 3.30 (dt, 1 H, J = 10.6, 7.9 Hz, H-2′), 2.12 (s, 3 H, Ac), 2.11 (s, 3 H, Ac), 2.10 (s, 3 H, Ac), 2.08 (s, 3 H, Ac), 2.021 (s, 3 H, Ac), 2.018 (s, 3 H, Ac), 1.91 (s, 3 H, Ac), 1.62−1.53 (m, 4 H, 2 × CH_2 of hexyl), 1.45−1.33 (m, 4 H, 2 × CH_2 of hexyl).

6-[*O*-(3,4,6-Tri-*O*-acetyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)(1 → 3)-2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl]oxyhexanal (21). Oxalyl chloride (90 μL) was added to a solution of DMSO (140 μL) in CH_2Cl_2 (5 mL) at −78 °C. After stirring for 10 min, a solution of **20** (565 mg, 0.768 mmol) in CH_2Cl_2 (5 mL) was added. The mixture was stirred for 10 min after which Et_3N (500 mL) was added. The reaction mixture was allowed to slowly warm to room temperature. The mixture was added to 100 mL of CH_2Cl_2 and washed with 50 mL of saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed (silica gel, EtOAc) to give 338 mg (60%) of **21**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (t, 1 H, J = 1.5 Hz, aldehyde CH), 5.60 (d, 1 H, J = 8.0 Hz, NH), 5.52 (dd, 1 H, J = 10.5, 9.0 Hz, H-3′), 5.37 (br d, 1 H, J = 3.5 Hz, H-4), 5.11 (dd, 1 H, J = 10.0, 8.0 Hz, H-2), 5.08 (d, 1 H, J = 8.0 Hz, H-1′), 5.04 (t, 1 H, J = 9.5 Hz, H-4′), 4.36 (d, 1 H, J = 8.0 Hz, H-1), 4.32 (dd, 1 H, J = 12.0, 2.5 Hz, H-6_a′), 4.15−4.06 (m, 3 H, H-6_a, H-6_b, H-6_b′), 3.88 (dt, 1 H, J = 9.5, 6.0 Hz, one of $GalOCH_2$), 3.84 (dd, 1 H, J = 10.0, 3.5 Hz, H-3), 3.82−3.79 (m, 1 H, H-5), 3.69 (ddd, 1 H, J = 10.0, 4.0, 3.0 Hz, H-5′), 3.48−3.42 (m, 1 H, H-2′), 3.31 (dt, 1 H, J = 10.5, 8.0 Hz, one of $GalOCH_2$), 2.46−2.42 (m, 2 H, CH_2CHO), 2.12 (s, 3 H, Ac), 2.11 (s, 3 H, Ac), 2.10 (s, 3 H, Ac), 2.08 (s, 3 H, Ac), 2.022 (s, 3 H, Ac), 2.019 (s, 3 H, Ac), 1.91 (s, 3 H, Ac), 1.70−1.53 (m, 4 H, 2 × CH_2 of aglycon), 1.45−1.30 (m, 2 H, CH_2 of aglycon).

6-[*O*-(3,4,6-Tri-*O*-acetyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)(1 → 3)-2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl]oxyhexanoic acid (22). A mixture of **21** (320 mg, 0.436 mmol), NaH_2PO_4 (350 mg), $NaClO_2$ (350 mg), *tert*-butyl alcohol (8 mL), H_2O (8 mL), and 2-methyl-2-butene (3 mL) was stirred at room temperature for 24 h. The mixture was added to 100 mL H_2O and extracted with 5 × 25 mL of EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum to give 329 mg (100%) of **22**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (d, 1 H, J = 7.8 Hz, NH), 5.51 (dd, 1 H, J = 10.6, 9.3 Hz, H-3′), 5.37 (d, 1 H, J = 3.4 Hz, H-4), 5.11 (dd, 1 H, J = 10.0, 8.0 Hz, H-2), 5.08 (d, 1 H, J = 8.3 Hz, H-1′), 5.04 (t, 1 H, J = 9.7 Hz, H-4′), 4.36 (d, 1 H, J = 8.0 Hz, H-1), 4.32 (dd, 1 H, J = 12.3, 2.6 Hz, H-6_a′), 4.16−4.08 (m, 3 H, H-6_a, H-6_b, H-6_b′), 3.88 (dt, 1 H, J = 9.8, 6.1 Hz, one of $GalOCH_2$), 3.84 (dd, 1 H, J = 10.0, 3.6 Hz, H-3), 3.81 (t, 1 H, J = 6.4 Hz, H-5), 3.69 (ddd, 1 H, J = 10.1, 3.8, 2.8 Hz, H-5′), 3.49−3.43 (m, 1 H, one of $GalOCH_2$), 3.32 (dt, 1 H, J = 10.6, 7.9 Hz, H-2′), 2.34 (t, 2 H, J = 7.3 Hz, CH_2CO_2H), 2.12 (s, 3 H, Ac), 2.11 (s, 3 H, Ac), 2.10 (s, 3 H, Ac), 2.022 (s, 3 H, Ac), 2.020 (s, 3 H, Ac), 1.92 (s, 3 H, Ac), 1.70−1.65 (m, 4 H, 2 × CH_2 of aglycon), 1.45−1.35 (m, 2 H, CH_2 of aglycon).

6-[*O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)(1 → 3)-β-D-galactopyranosyl]-oxyhexanoic Acid (23) and the Cesium Salt (3). A solution of **22** (329 mg, 0.436 mmol) and catalytic NaOMe in MeOH was stirred at room temperature for 24 h. Dowex-50 (H^+) was added, and the mixture was stirred for another 2 h. The mixture was filtered through Celite and concentrated under vacuum. The residue was desalted by chromatography on Biogel P-2 (H_2O), and the fractions containing product were again stirred with Dowex-50 (H^+). The Dowex was removed by filtration through Celite, and the filtrate was concentrated to give **23**. The acid **23** was taken up in 3 mL of H_2O and a 0.1 M solution of Cs_2CO_3 (ca. 1.2 mL) was added until the pH was neutral. The resulting solution was lyophilyzed to give the cesium salt **3**. Acid **23**: ^{1}H NMR (500 MHz, D_2O) δ 4.62 (d, 1 H, J = 8.5 Hz), 4.30 (d, 1 H, J = 8.0 Hz), 4.06 (d, 1 H, J = 3.3 Hz), 3.87−3.80 (m, 2 H), 3.72−3.65 (m, 4 H), 3.65−3.56 (m, 4 H), 3.51−3.44 (m, 2 H), 3.41−3.34 (m, 2 H), 2.28 (t, 2 H, J = 7.4 Hz), 1.96 (s, 3 H), 1.60−1.50 (m, 4 H), 1.35−1.29 (m, 2 H).

Esterified CPG 24 and Hydrazide 25. A mixture of **3** (4.5 mg), iodoacetyl controlled pore glass (20 mg, 0.0044 mmol), and DMF (0.4 mL) was shaken for 48 h. The derivatized glass was washed several times each with, sequentially, DMF, H_2O, DMF, and CH_2Cl_2, and was then allowed to dry. To demonstrate that the disaccharide was indeed attached to the solid support, the following procedure was followed. Hydrazine monohydrate (200 μL) was added to ca. 3 mg of **24**, and the mixture was allowed to stand for 24 h. The mixture was filtered through glass wool, and the volatiles were removed under vacuum to give **25**: ^{1}H NMR (500 MHz, D_2O) δ 4.60 (d, 1 H, J = 8.5 Hz), 4.28 (d, 1 H, J = 8.0 Hz), 4.05 (d, 1 H, J = 3.0 Hz), 3.85−3.78 (m, 2 H), 3.71−3.53 (m, 7 H), 3.50−3.42 (m, 2 H), 3.40−3.20 (m, 2 H), 2.13 (t, 2 H, J = 7.5 Hz), 1.95 (s, 3 H), 1.58−1.46 (m, 4 H), 1.30−1.20 (m, 2 H); electrospray positive ion MS (declustering potential = +60 V) calcd for $C_{20}H_{37}N_3O_{12}Na$ (M + Na^+) 534, found 534.

CPG-Trisaccharide Conjugate 26 and 6-[*O*-(β-D-Galactopyranosyl)(1 → 4)-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)(1 → 3)-β-D-galactopyranosyl]-oxyhexanoyl Hydrazide (27). A mixture of derivatized CPG **24** (0.0044 mmol, ca. 20 mg), UDP-Gal (8 mg), DTT (1 mg), and β-1,4-galactosyltransferase (1 U) in HEPES buffer (200 μL, 50 mM, pH 7.2), containing 5 mM $MnCl_2$, was vigorously shaken for 48 h. After this reaction period, the supernatant solution was decanted and the resin was washed with 5 × 1 mL of H_2O. About 3 mg of the trisaccharide-resin conjugate **26** was suspended in hydrazine monohydrate (0.2 mL) and allowed to stand at room temperature for 24 h. The mixture was filtered through glass wool to remove the solid support, and the filtrate was concentrated under vacuum. The residue was purified on BioGel P2 (H_2O as eluant) to give the trisaccharide **27**, with none of **28** being detected: ^{1}H NMR (500 MHz, D_2O) δ 4.63 (d, 1 H, J = 8.6 Hz), 4.39 (d, 1 H, J = 7.8 Hz), 4.29 (d, 1 H, J = 8.0 Hz), 4.06 (d, 1 H, J = 3.2 Hz), 3.90−3.54 (m, 17 H), 3.53−3.48 (m, 1 H), 3.46 (dd, 1 H, J = 9.9, 7.9 Hz), 2.14 (t, 2 H, J = 7.4 Hz), 1.95 (s, 3 H), 1.60−1.50 (m, 4 H), 1.22 (m, 2 H).

6-[*O*-(β-D-Galactopyranosyl)(1 → 4)-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)(1 → 3)-β-D-galactopyranosyl]oxyhexanoic acid (28). Synthesized from **3** in the standard manner: ^{1}H NMR (500 MHz, D_2O) δ 4.64 (d, 1 H, J = 8.3 Hz), 4.40 (d, 1 H, J = 7.8 Hz), 4.29 (d, 1 H, J = 8.0 Hz), 4.06 (d, 1 H, J = 3.2 Hz), 3.90−3.81 (m, 3 H), 3.71−3.57 (m, 13 H), 3.53−3.48 (m, 1 H), 3.45 (dd, 1 H, J = 9.7, 8.1 Hz), 3.41 (t, 1 H, J = 5.8 Hz), 2.11 (t, 2 H, J = 7.4 Hz), 1.96 (s, 3 H), 1.59−1.46 (m, 4 H), 1.32−1.25 (m, 2 H).

CPG-Tetrasaccharide Conjugate 29 and 6-[*O*-(5-Acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonic acid)(2 → 3)-*O*-(β-D-galactopyranosyl)(1 → 4)-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)(1 → 3)-β-D-galactopyranosyl]oxyhexanoyl Hydrazide (30). A mixture of solid supported trisaccharide **26** (0.002 mmol, ca. 10 mg), CMP-NeuAc (2.5 mg), DTT (0.15 mg), and α-2,3-sialyltransferase (5 mU), Triton-X (1.25 μL), alkaline phosphatase (1.25 U), and BSA (0.15 mg) in sodium cacodylate buffer (200 μL, 50 mM, pH 7.5), was vigorously shaken for 48 h. After this reaction period, the supernatant solution was decanted and the resin was washed with 5 × 1 mL of H_2O. The tetrasaccharide-resin conjugate **29** was suspended in hydrazine monohydrate (0.5 mL) and allowed to stand at room temperature for 24 h. The mixture was filtered through glass wool to remove the solid support, and the filtrate was concentrated under vacuum. The residue was purified on BioGel P2 (H_2O as eluant) to give the tetrasaccharide **30**: ^{1}H NMR (500 MHz, D_2O) δ 4.53 (d, 1 H, J = 8.5 Hz), 4.38 (d, 1 H, J = 8 Hz), 4.19 (d, 1 H, J = 8.0 Hz), 3.96 (d, 1 H, J = 3.0 Hz), 3.94 (dd, 1 H, J = 9.8, 3.0 Hz), 3.78−3.35 (m, 25 H), 2.58 (dd, 1 H, J = 12.5, 4.7 Hz), 2.04 (t, 2 H, J = 7.5 Hz), 1.85 (s, 6 H), 1.62 (t, 1 H, J = 12.2 Hz), 1.43−1.45 (m, 4 H), 1.20−1.23 (m, 2 H); electrospray negative ion MS (declustering potential = −80 V) calcd for $C_{37}H_{63}N_4O_{25}$ ($M - H^+$) 963, found 963.

Supplementary Material Available: NMR spectra for compounds **5b−8b**, **11**, **13a**, **13b**, **15b**, **16−23**, **25**, **27**, **28**, and **30** (20 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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