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n-Pentenyl Glycosides in the Efficient Assembly of the Blood Group Substance B Tetrasaccharide

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Dedicated to Professor Gabor Fodor on the occasion of his 75th birthday.

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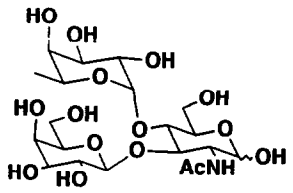
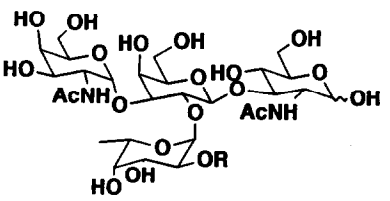
Abstract

The fact that n-pentenyl glycosides (nPGs) are stable to a wide variety of reaction conditions but yet can be chemospecifically activated is advantageous for the efficient, convergent assembly of oligosaccharides. The nPGs are prepared directly from the aldose or by normal glycoside-forming reactions, and by using N-iodosuccinimide/triethylsilyl triflate as the iodonium source, even "disarmed" glycosyl donors react within minutes. The four monosaccharide components of the human blood-group determinant B are prepared with full or partial protection as required. Assembly of the tetrasaccharide then requires only five steps, three to give, in sequence, the disaccharide (68%), trisaccharide (82%), and tetrasaccharide (91%), the other two steps being required to deprotect hydroxyl groups at the di- and tri-saccharide levels for the ensuing coupling reactions.

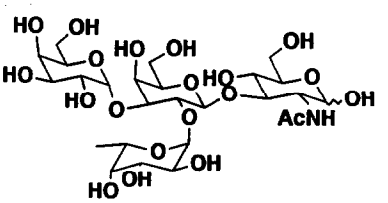
Advances in synthetic oligosaccharide chemistry are key to understanding the biological functions of complex carbohydrates[1] such as cell-surface glycoproteins, glycolipids, and the antigenic determinants of blood-group substances.[2] Within the past 15 years, the latter have attracted considerable attention, synthetic activity having been pioneered by Lemieux and co-workers,[3] and pursued by Paulsen[4] and others.[5,6] Their endeavors, which employed some novel carbohydrate transformations, have culminated in the syntheses of blood-group antigenic determinants such as the lacto-N-biose, **1**, and the blood group substances A and B (**2** and **3**).



1 (lacto-N-biose)



2 (blood group substance A)

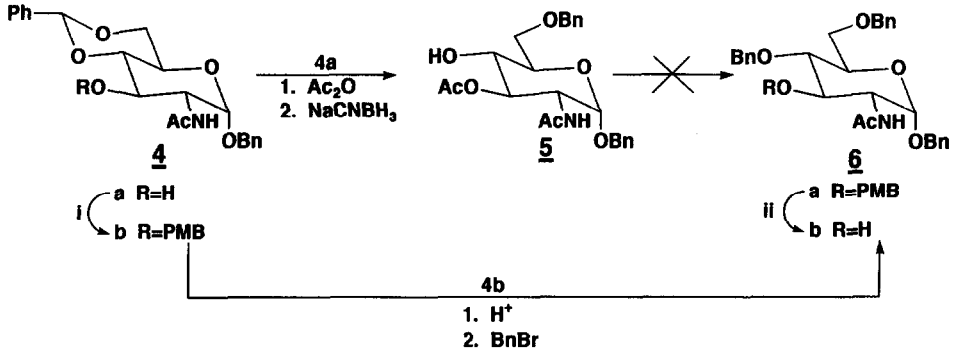


3 (blood group substance B)

We recently showed that n-pentenyl glycosides (nPGs) serve the contrasting functions of excellent protection for, as well as chemospecific liberation of, the anomeric center.[7] Thus the activating group can be attached at the anomeric center of the aldose directly (as in the preparation of **17a**, Scheme 4) or at an early stage, (as in the preparation of **8**, Scheme 2), since it can survive a wide variety of transformations, and yet be activated chemospecifically when required.[8] The use of protecting groups to electronically arm or disarm glycosides, was first demonstrated with nPGs,[8a,8c] and more recently the use of cyclic acetals as agents for obtaining torsionally disarmed substrates was disclosed.[9] However disarmed substrates can be readily activated by use of appropriate promoters,[10] hence coupling strategies of nPGs can be reagent-controlled or substrate-controlled.[11]

In this paper we report the application of nPG technology to a synthesis of the tetrasaccharide unit of the human blood group determinant B,**3**. Our plan was to start with a modified glucosamine unit, and attach it in sequence to the two galactose residues. The fucose moiety would be added subsequently to the central unit of the linear trisaccharide.

Scheme 1



(I) p-$MeOC_6H_4CH_2Br/NaH/nBu_4NI/DMF$; (II) $CAN/CH_2Cl_2/CH_3CN/H_2O$(5:10:1) 93%.

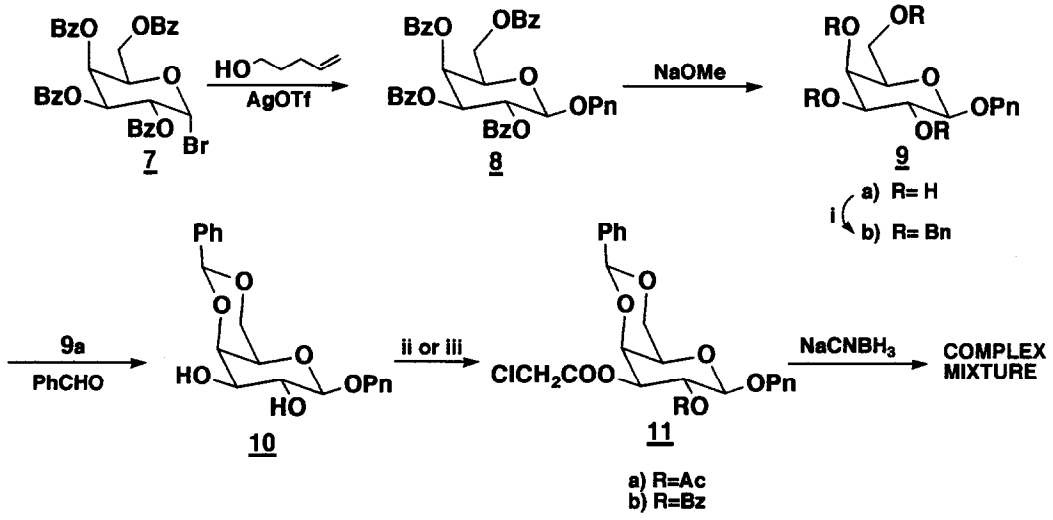
Our first attempts involved the known glucosamine derivative **4a** [14] (Scheme 1) and the benzylidinated pentenyl galactoside **11a** the latter being readily prepared (Scheme 2) from the tetra-O-benzoyl galactopyranosyl bromide, **7**[12], by adaptation of the published method for the corresponding methyl glycoside.[13] Attempts to couple **4a**[14] and **11b** by use of N-iodosuccinimide and triethylsilyltriflate (NIS/Et3SiOTf) led to 10-20% yields of the disaccharide **20** (Scheme 5a). The major product(s) had suffered loss of the benzylidene ring(s). The corresponding 2-O-benzoate **11b** prepared from **10** by the method of Szeja[15] as modified by Krepinsky,[16] fared no better.

The foregoing results showed that although NIS/Et3SiOTf is a convenient, potent source of iodonium ion,[10] its use in the presence of acid sensitive protecting groups can be

problematic. In addition, in view of the recent observation that acetal protecting groups can be used to disarm glycosyl donors,[9] it was decided to use non-benzylidinated reactants.

The initial plan for preparing the desired glucosamine derivative **6b** involved acetylation of **4a** followed by regioselective reductive cleavage of the benzylidene ring[17] to afford **5** (Scheme 1). However all attempts to benzylate compound **5**, even with silver oxide as promoter[18] or with benzyl trichloroimidate,[19] failed the starting material being recovered unchanged. On the other hand, di-O-benzylation of the 4,6-diol resulting from hydrolytic cleavage of the benzylidene ring of **4b** proceeded smoothly to afford **6a**. Removal of the p-methoxybenzyl group[24] then afforded **6b.**

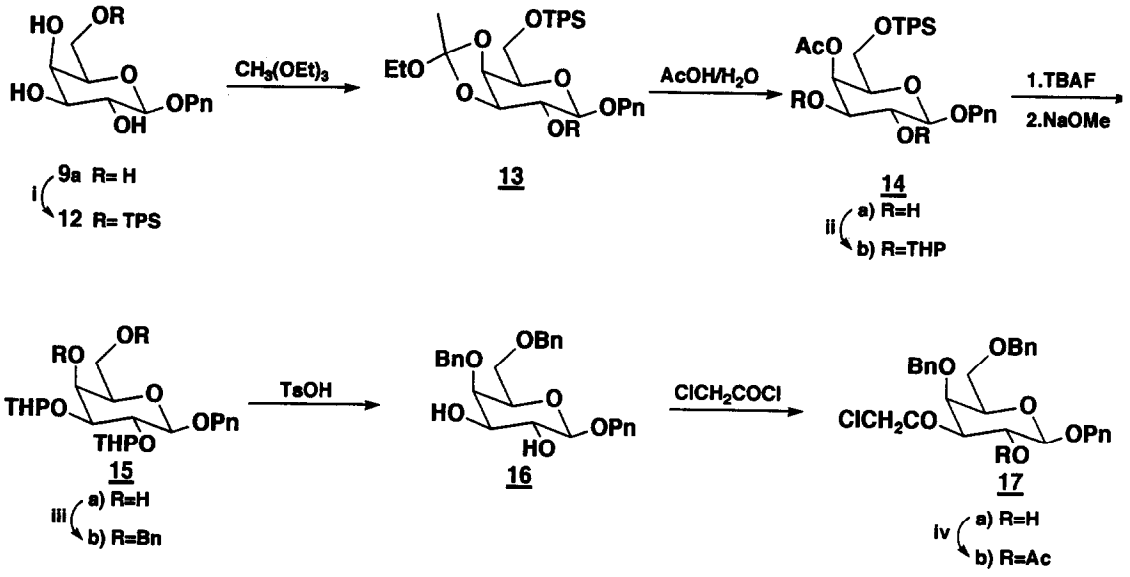
Scheme 2



(i) $PhCH_2Br/NaH/nBu_4NI/DMF$ (90%) (ii) $ClCH_2COCl/Pyridine/CH_2Cl_2/0^0C$; $Ac_2O/DMAP/CH_2Cl_2$(93%) (iii) $PhCOCl/NaOH/nBu_4NHSO_4/CH_2Cl_2/0^0C$; $(ClCH_2CO)_2O/DMAP/CH_2Cl_2$(94%)

Preparation of the non-benzylidinated galactosyl donors proved to be even more involved (Scheme 3). We wished to replace the benzylidene ring of **11** with benzyl groups, but attempts at reductive cleavage with sodium cyanoborohydride[17] produced an intractable mixture. A route to the 4,6-di-O-benzyl derivative **15a** was worked out from the tetrol **9a** by the steps outlined in Scheme 3. Key transformations included the regioselective orthoester rearrangement for converting **13** into **14a**,[20] paving the way to the 4,6-diol **15a**, and subsequent 3-O-chloroacetylation[21] to obtain **17a** and thence the diacyl derivative **17b**.

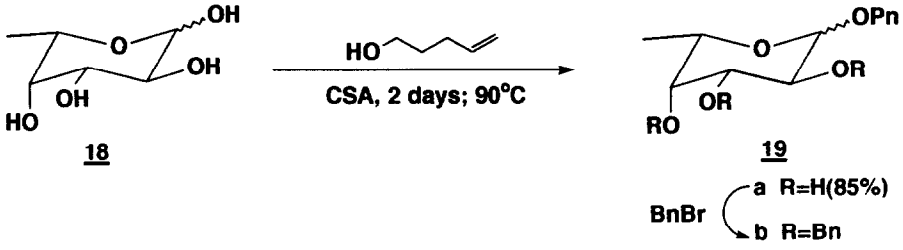
Scheme 3



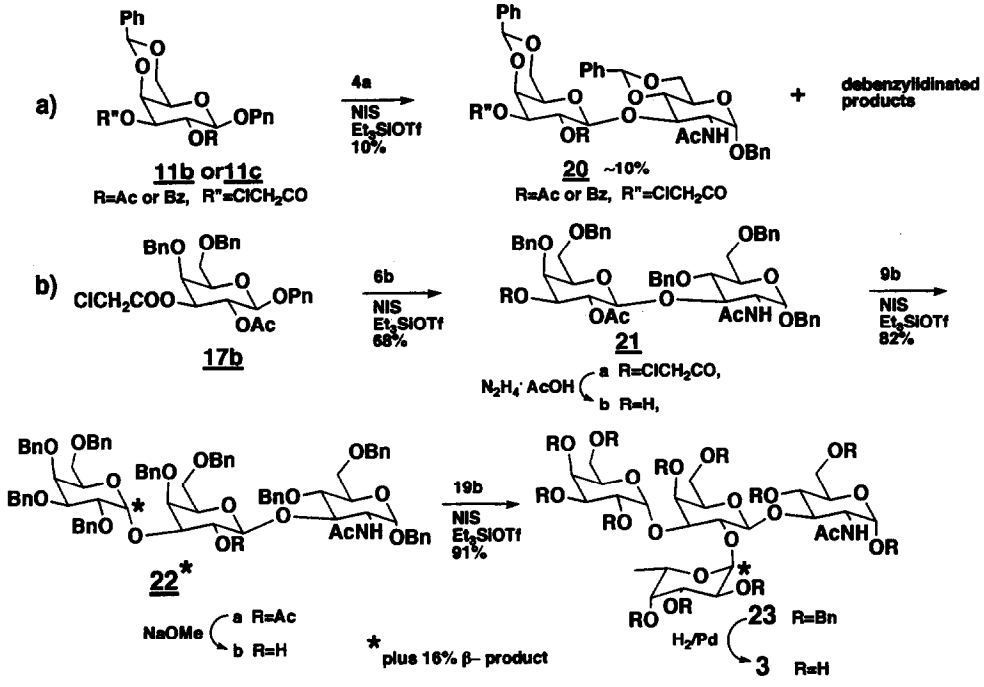
(I) TBDMSCl/Imidazole/THF/r.t./11.5h (87%); (II) DHP/PPTS; (III) $PhCH_2Br/NaH/nBu_4NI/DMF$ (90%); (IV)Ac_2O/ DMAP/CH_2Cl_2(93%)

Coupling of **17b** and **6b** using of NIS/Et3SiOTf proceeded smoothly to give a 68% yield of disaccharide **21a** (Scheme 5b). Treatment with hydrazine acetate removed the chloroacetyl group, and coupling of the resulting material, **21b**, to the pentenyl galactopyranoside **9b** afforded an 82% yield (based on recovered **21b**) of trisaccharide **22a**, the α/β ratio being 6:1. The deacetylated material, **22b**, was then coupled to the fucoside **19b**, prepared directly by modified Fischer glycosidation of fucose, **18**[22] (Scheme 4). The tetrasaccharide **23** was thereby obtained in 92% yield based on recovered **22b**, the α/β ratio again being 6:1. Hydrogenolytic debenzylation of **23** then gave **3** whose spectral properties were identical to those reported.[4]

Scheme 4



Scheme 5



Summary

Among the advantages of nPGs for the assembly of oligosaccharides is the fact that the n-pentenyloxy group serves the dual, and divergent roles of protection and activation of the anomeric center. In addition, the group can be installed at the outset (e.g. **18** --> **19a**) or early (e.g. **7** --> **8**) in the synthesis since, being an O-glycoside, it is stable to a wide variety of reaction conditions. Assembly of the oligosaccharide is therefore simplified as illustrated in Scheme 5. Thus once the appropriately protected monosaccharides are prepared, the chemical transformations are restricted to the coupling event (e.g. **17b** + **6b** --> **21a**), followed by liberation of the pertinent hydroxyl group (e.g.**21a** --> **21b**) so that the next stage can proceed. Thus protecting group adjustments in the precious coupled products are kept at minimum.

Acknowledgements

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Experimental Section

General Procedures. Elemental analyses were performed by M-H-W Laboratories, PO Box 15149, Phoenix, AZ 85018. IR spectra were recorded on a Perkin-Elmer Model 297 spectrophotometer with sodium chloride plates for thin films of liquids, syrups, or solids in nujol mulls. Optical rotations were determined at the sodium D line with a Perkin-Elmer 241 polarimeter. ^{1}H NMR spectra were determined on a Varian XL-300 spectrometer. Unless

otherwise stated, the solvent used was $CDCl_3$ with internal tetramethylsilane or $CHCl_3$ as the standard. The coupling constants were verified by homonuclear decoupling experiments. For the purpose of ^1H NMR interpretation, compound structures have been numbered in the schemes. High resolution mass spectra were obtained at the Duke University Medical Center on a VG-705 high resolution magnetic sector instrument operating in the fast atom bombardment (FAB) mode in a glycerol or magic bullet matrix with xenon as the fast atom. The progress of all reactions was monitored by thin-layer chromatography (TLC), which was performed on aluminum plates procoated with silica gel HF-254 (0.2 mm layers) containing fluorescent indicator (Merck, 5554). Detection was first by UV (254 nm), then charring after dipping in either sulfuric acid (70:25:5 H_2O/EtOH/H_2SO_4) or molybdate [(6.25 gm ammonium molybdate 4-hydrate/2.5 gm cerium(IV) sulfate/225 mL H_2O/25 mL conc. H_2SO_4] solution flash chromatography was performed using Kieselgel 60 (230-400 mesh, E. Merck). Pyridine and trithylamine were kept over KOH and then distilled from CaH_2. Acetonitrile and N,N-dimethylformamide (DMF) were distilled from CaH_2. Toluene was distilled from sodium. Dichloromethane (CH_2Cl_2) was distilled from P_2O_5. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium/benzophenone ketyl. Absolute methanol was used as purchased. N-Iodosuccinimide (NIS) was recrystallized from *p*-dioxane/carbon tetrachloride.

Coupling Reaction. The specified amounts of n-pentenyl glycoside and alcohol donor were dissovled in dry toluene, and the solution was evaporated to dryness on a rotary evaporator. This treatment was repeated once, and the residue was dried overnight *in vacuo*. Using the specified amounts of CH_2Cl_2 under argon NIS was added, and the Et3SiOTf was added dropwise for the preparation of **16a** and in one portion for the preparation of **17a** and **18**. After 10 minutes the reaction was checked by tlc, and further portions of NIS and Et3SiOTf were added until the reaction was complete. The solution was then diluted with CH_2Cl_2 and washed successively with 10% aqueous sodium thiosulfate, saturated sodium hydrogen carbonate solution, and brine. The dried (Na_2SO_4) solution was evaporated and the residue flash chromatographed in the specified solvent.

Benzyl 2-acetamido-4,6-di-O-benzyl-2-deoxy-α-D-glucopyranoside 6b. N,N-Dimethylformamide (15 mL) was added to a cooled (ice bath) mixture of sodium hydride (0.23 g of 60% oil dispersion, 5.7 mmol) and the known alcohol **4a** (1.0 g, 2.5 mmol).[14] After 2 min at 0°C, the reaction mixture was stirred for 20 min at room temperature, recooled to 0°C, and treated with tetra-n-butyl ammonium iodide (92 mg, 0.25 mmol), followed by *p*-methoxybenzyl chloride (0.8 mL, 5.9 mmol).[23] After 1.5 h at room temparature, when tlc (95:5 CH_2Cl_2/MeOH) showed complete consumption of the starting material, the mixture was cooled to 0°C and quenched with MeOH. The mixture was diluted with water and extracted thee times with methylene chloride. The combined extracts were shaken with brine, dried (Na_2SO_4), and concentrated at reduced pressure to afford a white solid, which was washed with 10:1 Et_2O/hexanes to obtain 1.3 g of **4b**. R_f 0.47 (80:20 CH_2Cl_2/EtOAc). ^1H NMR δ 1.87 (s, 3H), 3.36 (m, 1H), 3.67 - 3.95 (m, 6H), 4.25 (m, 2H), 4.47 (d, 1H, J = 11.78 Hz), 4.58 (d, 1H, J = 11.91 Hz), 4.72 (d, 1H, J = 11.91 Hz), 4.86 (d, 1H, J = 11.91 Hz), 4.94 (d, 1H, J = 3.85 Hz, H1), 5.33 (d, 1H, J = 9.03 Hz, NH), 5.60 (s, 1H), 6.85 (d, 2H, J = 8.60 Hz), 6.95 (d, 1H, J = 8.55 Hz), 7.20 - 7.60 (m, 11H). The benzylidene ring was cleaved by treating the material (2.88 g, 5.50 mmol) dissolved in methylene chloride (140 mL) and methanol (100 mL) with 300 mg of *p*-toulenesulfonic acid for 24 h, at which time tlc (95:5 CH_2Cl_2/MeOH) showed complete disappearance of the starting material. The solution was quenched with triethylamine (6 mL) and the resulting colorless solution was evaporated. The residual semi-solid was flash chromatographed on a short column (80:20 CH_2Cl_2/EtOAc --> 95:5 CH_2Cl_2/MeOH) to give 2.1 g of the 4,6-diol. Benzylation was effected as described below for **15b** to give **6a** 1.2 g (40% yield). R_f 0.37 4:1 CH_2Cl_2/EtOAc). ^1H NMR δ 1.84 (s, 3H), 3.60 - 3.88 (m, 9H), 4.27 (m, 1H), 4.40 - 4.86 (m, 7H), 4.90 (d, 1H, J = 3.66 Hz), 5.27 (d, 1H, J = 9.28 Hz), 6.83 (d, 2H, J = 7.50 Hz), 7.13 - 7.40 (m, 17H). A portion of the

material (1.15 g, 1.90 mmol) in 5:10:1 mL of methylene chloride/CH_3CN/H_2O was stirred with ammonium cerium(IV) nitrate[24] (2.07 g, 3.8 mmol) for 0.5 h. The solution was then diluted with methylene chloride and washed with saturated sodium bicarbonate solution and brine. The dried (Na_2SO_4) solution was concentrated at reduced pressure and the residue flash chromatographed (95:5 CH_2Cl_2/MeOH) to afford 0.86 g (93% yield) of **6b**. R_f 0.23 (70:30 pet ether/acetone). $[\alpha]_D^{20}$ +65.39° (c 1.13, $CHCl_3$). ^1H NMR δ 1.98 (s, 3H), 3.54 - 3.90 (m, 5H), 4.16 (dt, 1H, J = 8.86 Hz, 3.50 Hz), 4.44 (d, 1H, J = 11.72 Hz), 4.54 (t, 2H, J = 12.20 Hz), 4.64 (d, 1H, J = 12.20 Hz), 4.73 (d, 1H, J = 11.72 Hz), 4.85 (d, 1H, J = 11.30 Hz), 4.91 (d, 1H, J = 3.80 Hz, H1), 5.79 (d, 1H, J = 8.30 Hz, NH), 7.28 (m, 15H).

Anal. Calcd for $C_{29}H_{33}NO_6$: C, 70.85; H, 6.77; N, 2.85. Found: C, 69.87; H, 6.93; N, 2.76.

Pent-4-enyl 2,3,4,6-tetra-O-benzoyl-β-D-galactopyranoside 8. Silver triflate was rotoevaporated with toluene and then dried under vacuum. 4-Penten-1-ol (6 mL, 69.7 mmol) was added to a mixture of silver triflate (12.62 g, 49.1 mmol) and 9 g of powdered, activated 4Å molecular sieves in 120 mL of dry methylene chloride at -20°C under argon. Tetra-O-benzoyl-D-galactopyranosyl bromide[12] (26.9 g, 40.8 mmol) dissolved in dry methylene chloride (40 mL) was added dropwise *via* a cannula. After 0.5 h at -20°C, the reaction was quenched with saturated aqueous sodium bicarbonate, diluted with methylene chloride and filtered. The filtrate was washed with sodium bicarbonate and brine. The dried (Na_2SO_4) crude product was concentrated and flash chromatographed (85:15 pet ether/EtOAc) to obtain 20 g (74% yield) of **8**. R_f 0.31 (80:20 pet ether/EtOAc). $[\alpha]_D^{20}$ +86.82° (c 1.26, CHCl3). ^1H NMR ($CDCl_3$) δ 2.39 (m, 2H), 2.11 (m, 2H), 3.57 (m, 1H), 3.96 (m, 1H), 4.30 (t, 1H, J = 6.6 Hz), 4.40 (dd, 1H, J = 11.1 Hz, 6.6 Hz), 4.67 (dd, 1H, J = 11.1 Hz, 6.6 Hz), 4.79 (t, 2H, J = 9.3 Hz), 5.56 - 5.70 (m, 3H), 5.77 (dd, 1H, J = 10.3 Hz, 8.1 Hz), 5.97 (d, 1H, J = 3.0 Hz), 7.30 (m, 20H).

Anal. Calcd. for $C_{39}H_{36}O_{10}$: C, 70.47; H, 5.46. Found: C, 70.61; H, 5.27.

Pent-4-enyl β-D-galactopyranoside 9a. The benzoate **8** (20 g, 30.0 mmol) in 100 mL of MeOH was stirred overnight under argon with catalytic amount of NaOMe. The reaction was then concentrated and flash chromatographed (85:15 CH_2Cl_2/MeOH) to obtain 7.2 g (96% yield) of the tetraol **9a**. R_f 0.33 (85:15 CH_2Cl_2/MeOH). $[\alpha]_D^{20}$ -9.02° (c 1.23, H_2O). Anal. Calcd for $C_{11}H_{20}O_6$: C, 53.22; H, 8.12. Found: C, 53.99; H, 7.80.

Pent-4-enyl 2,3,4,6-tetra-O-benzyl-β-D-galactopyranoside 9b: A solution of **9a** (4.1 g, 16.5 mmol) in 10 mL of dry DMF was added dropwise to a slurry of NaH (4 g of 60% oil dispersion, 99.1 mmol, washed with hexane to remove oil before use) in 20 mL of DMF at 0°C under argon. After the addition, the mixture was stirred for 20 min at room temperature Upon recooling to 0°C, nBu_4NI (0.62 g, 1.7 mmol) was added, followed dropwise by benzyl bromide (12.1 mL, 101.7 mmol). The reaction was stirred at room temperature for 2 h before quenching at 0°C with MeOH. Water was added and the mixture extracted three times with Et_2O. The extract was washed with brine. Flash chromatography (95:5 --> 90:10 pet ether/EtOAc) of the dried (Na_2SO_4) and concentrated extract gave 8.8 g (90% yield) of **9b**. R_f 0.56 (90:10 pet ether/EtOAc). $[\alpha]_D^{20}$ -7.01 (c 1.24, $CHCl_3$). ^1H NMR δ 1.72 (m, 2H), 2.10 (m, 2H), 3.49 (m, 4H), 3.80 (t, 1H, J = 10 3 Hz), 3.87 (m, 2H), 4.33 (d, 1H, J = 7.6 Hz), 4.36 (m, 2H), 4.70 (d, 1H, J = 11.7 Hz), 4.68 (m, 4H), 4.90 (m, 4H), 5.77 (m, 1H), 7.25 (m, 20H).

Anal. Calcd for $C_{39}H_{44}O_6$: C, 76.95; H, 7.28. Found: C, 77.03; H, 7.19.

Pent-4-enyl 2-O-acetyl-4,6-O-benzylidene-3-O-chloroacetyl-β-D-galacto-pyranoside 11a. Following the method of Jansson *et .al.*,[13] the tetraol **9a** (6.6 g, 26.6 mmol) was stirred with benzaldehyde (11.8 mL) and formic acid (11.8 mL) for 2 h at room temperature, at which time most of the starting material was consumed. The mixture was then diluted with

dichloromethane and washed with ice-cold water, saturated aqueous sodium bicarbonate, and brine. The organic solution was dried (Na_2SO_4) and concentrated at diminished pressure. The residue was diluted with cold hexane. The precipitated solid was collected and washed with hexane. Flash chromatography (70:30 --> 50:50 pet ether/EtOAc) gave 4 g (44% yield) of **10**. Rf 0.30 (70:30 CH_2Cl_2/EtOAc). ^1H NMR δ 1.76 (m, 2H), 2.15 (m, 2H), 2.56 (br s, 2H), 3.47 - 3.58 (m, 2H), 3.72 (m, 2H), 3.98 (m, 1H), 4.08 (dd, 1H, J = 12.45 Hz, 1.65 Hz), 4.21 (m, 1H), 4.28 (d, 1H, J = 7.13 Hz), 4.34 (dd, 1H, J = 12.45 Hz, 1.65 Hz), 5.02 (m, 2H), 5.55 (s, 1H), 5.84 (m, 1H), 7.35 (m, 3H), 7.50 (m, 2H). A solution of **10** (1.0 g, 3.0 mmol) in methylene chloride (15 mL) and pyridine (7 mL) at 0°C was treated dropwise under argon with chloroacetyl chloride (0.14 mL, 5.1 mmol) at 0°C the mixture was stirred at 0°C for ~ 20 min until the starting material could no longer be detected by tlc (90:10 CH_2Cl_2/EtOAc). The reaction was then quenched with brine and diluted with methylene chloride. The aqueous layer was extracted with methylene chloride, and the combined organic extracts were dried (Na_2SO_4) and concentrated at reduced pressure. The residual oil was flash chromatographed (90:10 CH_2Cl_2/EtOAc) to afford 729 mg (60% yield) of the 3-O-chloroacetate, Rf 0.69 (90:10 CH_2Cl_2/EtOAc). ^1H NMR δ 1.75 (m, 2H), 2.15 (m, 2H), 4.17 (d, 2H, J = 3.15 Hz), 4.32 (d, 1H, J = 1.41 Hz), 4.34 (d, 1H, J = 7.70 Hz, H1), 4.43 (d, 1H, J = 3.67 Hz, H4), 4.93 (dd, 1H, J = 10.21 Hz, 3.72 Hz, H3), 5.04 (m, 2H), 5.50 (s, 1H), 5.83 (m, 1H), 7.35 (m, 3H), 7.50 (m, 2H). A portion of this material (689 mg, 1.66 mmol) in methylene chloride containing a catalytic amount of 4-dimethylamino pyridine was acetylated with excess Ac_2O to obtain, after flash chromatography (98:2 CH_2Cl_2/EtOAc), 712 mg (93% yield) of **11a**. Rf 0.49 (98:2 CH_2Cl_2/EtOAc). $[\alpha]_D^{20}$ +65.58° (c 1.29, $CHCl_3$). ^1H NMR δ 1.69 (m, 2H), 2.06 (s, 3H), 2.08 (m, 2H), 3.44 - 3.55 (m, 3H), 3.96 (td, 1H, J = 9.54 Hz, 6.11 Hz), 4.04 - 4.10 (m, 3H), 4.36 (dd, 1H, J = 12.47 Hz, 1.22 Hz), 4.42 (d, 1H, J = 3.72 Hz, H4), 4.51 (d, 1H, J = 7.89 Hz, H1), 4.96 - 5.06 (m, 3H, H3 + olefinic H), 5.41 (dd, 1H, J = 10.34 Hz, 7.87 Hz, H2), 5.50 (s, 1H), 5.80 (m, 1H), 7.37 (m, 3H), 7.51 (m, 2H). Partial ^{13}C NMR 100.71, 100.90, 114.85, 166.87, 169.06 ppm.

Anal. Calcd. for $C_{22}H_{27}ClO_8$: C, 58.09; H, 5.98; Cl, 7.79. Found: C, 57.95; H, 6.05; Cl, 8.00.

Pent-4-enyl 2-O-benzoyl-4,6-O-benzylidene-3-O-chloroacetyl-β-D-galactopyranoside 11b

The 2-O-benzoate of **10** was prepared by the method of Szeja[15] as modified by Krepinsky.[13] The diol **10** (1.4 g, 4.16 mmol) in methylene chloride (26 mL) was cooled to 0°C and treated sequentially with tetra-n-butyl ammonium hydrogen sulphate (70 mg, 0.21 mmol), 40% aqueous sodium hydroxide (3.8 mL), and benzoyl chloride (0.56 mL, 4.8 mmol, dropwise). The reaction was stirred for 10 min. at 0°C before diluting with methylene chloride. The organic layer was separated, washed with water until neutral, and then with brine. Drying (Na_2SO_4) and concentration at diminished pressure, afforded a white solid consisting of a mixture of C-2 and C-3 benzoates (Rf 0.29 and 0.64, respectively, 60:40 pet ether/EtOAc). To migrate the C-3 benzoate to C-2,[25] the solid was taken up in 75 mL of acetone and cooled to 0°C. Ice-cold 0.05 M aqueous sodium hydroxide solution (75 mL) was added giving a white precipitate. After 10 min at 0°C, the mixture was diluted with ice-water and quickly suction-filtered. The solid was air-dried for a few minutes and then taken up in methylene chloride. The dried (Na_2SO_4) and concentrated solution was flash chromatographed through a short column, eluting first with 70:30 pet ether/EtOAc to collect 370 mg of the C-3 benzoate and then with 4:1 CH_2Cl_2/EtOAc to afford 0.37 g of the C-2 benzoate. Repetition of this benzoate-migration procedure with the 370 mg of C-3 benzoate led to a total of 0.93 g of the C-2 benzoate which was dissolved in 10 mL of methylene chloride containing catalytic amount of 4-dimethylaminopyridine, and stirred with chloroacetic anhydride (0.44 g, 2.57 mmol) until all the starting material was consumed. The reaction mixture was then evaporated and the residue was flash chromatographed (70:30 pet ether/EtOAc) to yield 1.03 g (94% yield) of **11b**. Rf 0.47 (70:30 pet ether/EtOAc). $[\alpha]_D^{20}$ +69.39° (c 1.32, $CHCl_3$). ^1H NMR δ 1.60 (m, 2H), 1.95 (m, 2H), 3.49 (m, 1H), 3.58 (br s, 1H), 3.94 (m, 1H), 4.00 (d, 2H, J = 10.99 Hz), 4.10 (dd, 1H, J = 12.40 Hz, 1.71 Hz, H6), 4.38 (dd, 1H, J = 12.40 Hz, 1.30

Hz, H6), 4.46 (d, 1H, J = 3.66 Hz, H4), 4.65 (d, 1H, J = 8.01 Hz, H1), 4.79 (m, 2H), 5.22 (dd, 1H, J = 10.3 Hz, 3.66 Hz, H3), 5.53 (s, 1H), 5.62 (m, 1H), 5.66 (dd, 1H, J = 10.37 Hz, 8.10 Hz, H2), 7.30 - 7.60 (m, 8H), 8.01 (m, 2H). Partial ^{13}C NMR 100.98, 114.65, 165.00, 167.49 ppm.

Anal. Calcd. for $C_{27}H_{29}ClO_8$: C, 62.73; H, 5.65; Cl, 6.86. Found: C, 62.73; H, 5.69; Cl, 6.87.

Pent-4-enyl 6-O-tert-butyldiphenylsilyl-β-D-galactopyranoside 12. A solution of **9a** (8.8 g, 35.4 mmol) in dry THF (80 mL) was treated under argon with imidazole (3.14 g, 46.1 mmol), followed by dropwise addition of *tert*-butylchlorodiphenylsilane (11 mL, 42.3 mmol). The mixture was stirred for 11.5 h at room temperature before quenching with saturated sodium bicarbonate solution. THF was then removed at diminished pressure, and the residue was taken up in methylene chloride (150 mL) and washed twice with sodium bicarbonate solution and once with brine. The dried (Na_2SO_4) and concentrated crude product was flash chromatographed (95:5 --> 90:10 CH_2Cl_2/MeOH) to obtain 14.93 g (87% yield) of **12**. R_f 0.55 (90:10 CH_2Cl_2/MeOH). $[\alpha]_D^{20}$ -17.98 (c 1.24, $CHCl_3$).

Anal. Calcd. for $C_{27}H_{38}O_6Si$: C, 66.63; H, 7.87. Found: C, 66.43; H, 7.33.

Pent-4-enyl 4,6-di-O-benzyl-β-D-galactopyranoside 16. Following a literature precedent,[20] *p*-toluenesulfonic acid monohydrate (42 mg, 0.22 mmol) was added to a solution of the triol **12** (14.7 g, 30.2 mmol) and triethyl orthoacetate (28 mL, 152.7 mmol) in dry toluene (105 mL). The reaction mixture was stirred for 1 h at room temperature and then quench with triethylamine (2 mL). The solution was then washed with water and brine and dried over sodium sulfate. Flash chromatography (75:25 pet ether/EtOAc) of the syruppy product gave 14.2 g (84% yield) of the 3,4-O-orthoester,**13** (R_f 0.41, 75:25 pet ether/EtOAc), which was then stirred for 1 h with 4:1 HOAc/H_2O mixture (100 mL). Coevaporation with toluene yielded **14a** quantitatively. A portion of the material (2.5 g, 4.7 mmol) in dry methylene chloride (6 mL) was treated with 3,4-dihydro-2H-pyran (2.5 mL, 27.4 mmol), followed by 100 mg pyridinium *p*-toluenesulfonate (100 mg, 0.4 mmol).[26] The mixture was stirred at room temperature for 23 h and then diluted with CH_2Cl_2, washed with brine and dried (Na_2SO_4) to provide **14b** (3.45 g, R_f 0.69 and 0.76, 80:20 pet ether/EtOAc), which was dissolved in dry THF (12 mL) and treated with nBu_4NF (8 mL of 1M THF solution, 1.5 equiv.) at 0°C under argon for 9 h at room temperature. The reaction mixture was concentrated at reduced pressure and flash chromatography (80:20 pet ether/EtOAc --> 95:5 CH_2Cl_2/MeOH) of the residual oil gave 2.45 g of material (R_f 0.52 and 0.60, 95:5 CH_2Cl_2/MeOH), which was deacetylated with a catalytic amount of sodium methoxide in methanol (10 mL) for 2 h, affording 2.19 g of the diol **15a** (R_f 0.30, 95:5 CH_2Cl_2/MeOH). Benzylation was effected by dissolving in DMF (6 mL) and adding dropwise to a slurry of NaH (0.84 g, 21.0 mmol, 4 equiv.) in DMF (5 mL) at 0°C under argon. The mixture was stirred for 15 min. at room temperature, recooled to 0°C, and tetra-n-butyl ammonium iodide (0.19 g, 0.5 mmol) was added, followed dropwise by benzyl bromide (2.5 mL, 21.0 mmol). After 4 h at room temperature, the reaction was quenched at 0°C with MeOH, and the residue from evaporation at reduced pressure was taken up in methylene chloride and washed with water and brine. Flash chromatography (90:10 --> 85:15 pet ether/EtOAc) of the dried (Na_2SO_4) and concentrated solution gave 2.5 g of the dibenzyl ether **15b** (R_f 0.30 and 0.42, 85:15 pet ether/EtOAc). The tetrahydropyranyl groups were removed by stirring in methanol (10 mL) with catalytic amount of *p*-TsOH for 3h. The solution was evaporated under reduced pressure, and the residual solid material was taken up in methylene chloride and washed with saturated aqueous sodium bicarbonate solution and brine. The dried (Na_2SO_4) solution was concentrated to yield a solid which was washed with pentane to remove pyran by-products, giving 1.7 g of the diol **16** (84% yield from **14a**). R_f 0.38 (50:50 pet ether/EtOAc). ^1H NMR δ 1.73 (m, 2H), 2.12 (m, 2H), 2.25 (d, 1H, J = 6.6 Hz), 2.40 (br s, 1H), 3.00 (m, 1H), 3.14 (m, 5H), 3.90 (m,

2H), 4.20 (d, 1H, J = 7.1 Hz), 4.50 (dd, 2H, J = 16.6 Hz, 11.7 Hz), 4.70 (s, 1H), 5.00 (m, 2H), 5.80 (m, 1H), 7.33 (m, 10H).

Pent-4-enyl 2-O-acetyl-4,6-di-O-benzyl-3-O-chloroacetyl-β-D-galacto-pyranoside 17b. The diol **16** (1.28 g, 3.00 mmol) in a solution of methylene chloride (15 mL) and pyridine (7 mL) was treated dropwise at 0°C under argon with chloroacetyl chloride (0.58 mL, 7.28 mmol). After ~ 10 min at 0°C all of the starting material was consumed (tlc, 95:5 CH_2Cl_2/EtOAc). The yellow solution was then washed with brine, and concentrated to an oil. Flash chromatography (95:5 CH_2Cl_2/EtOAc) gave 412 mg of **17a**, along with 313 mg of a mixture of 2-O-monochloroacetate and the 2,3-di-O-chloroacetates. For compound **17a**. R_f 0.57 (90:10 CH_2Cl_2/EtOAc). ^1H NMR δ 1.70 (m, 2H), 2.10 (m, 2H), 2.24 (d, 1H, J = 2.2 Hz), 3.48 (m, 1H), 3.59 (m, 2H), 3.67 (m, 1H), 3.76 (d, 1H, J = 14.95 Hz), 3.90 (m, 1H), 3.98 (d, 2H, J = 14.9 Hz), 4.01 (m, 1H), 4.26 (d, 1H, J = 7.62 Hz), 4.46 (q, 1H, J = 11.85 Hz, 6.41 Hz), 4.57 (s, 2H), 4.89 (dd, 1H, J = 10.27 Hz, 3.20 Hz), 4.97 (m, 2H), 5.80 (m, 1H), 7.30 (m, 10H). Compound **17a** was acetylated in the usual way with excess acetic anhydride in methylene chloride containing a catalytic amount of 4-dimethylaminopyridine. Flash chromatography (80:20 pet ether/EtOAc) of the concentrated reaction gave **17b**. R_f 0.60 (80:20 pet ether/EtOAc). ^1H NMR δ 1.65 (m, 2H), 2.03 (s, 3H), 2.08 (m, 2H), 3.45 (m, 1H), 3.59 - 3.74 (m, 3H), 3.66 (d, 1H, J = 14.71 Hz), 3.84 (d, 1H, J = 14.71 Hz), 3.88 (m, 1H), 4.03 (d, 1H, J = 3.17 Hz, H4), 4.42 (d, 1H, J = 7.92 Hz, H1), 4.50 (q, 2H, J = 11.72 Hz, 4.88 Hz), 4.59 (s, 2H), 4.92 - 5.04 (m, 3H, H3 + olefinic H), 5.35 (dd, 1H, J = 10.3 Hz, 7.90 Hz, H2), 5.80 (m, 1H), 7.30 (m, 10H). Partial ^{13}C NMR 101.05, 114.90, 166.88, 169.37 ppm.

Benzyl-2-acetamido-3-O-(2-O-acetyl-4,6-di-O-benzyl-3-O-chloroacetyl-β-D-galacto-pyranosyl)-4,6-di-O-benzyl-2-deoxy-α-D-glucopyranoside 21a. Using the general procedure for the *Coupling Reaction* the pentenyl glycoside **17b** (0.45 g, 0.84 mmol), alcohol **6b** (0.54 g, 1.1 mmol) were coupled using methylene chloride (13 mL) NIS (217 mg, 0.96 mmol), and Et_3SiOTf (0.22 mL, 0.96 mmol). After 5-10 min, when tlc (70:30 pet ether/acetone) showed that most of **17b** had been consumed, the solution was processed as described and the crude product was flash chromatographed (80:20 --> 70:30 pet ether/acetone) affording 0.55 g (68% yield) of **21a**. R_f 0.50 (70:30 pet ether/acetone). $[\alpha]_D^{20}$ +45.36° (c 1.38, $CHCl_3$). ^1H NMR δ 1.93 (s, 3H), 2.08 (s, 3H), 3.38 (dd, 1H, J = 8.39 Hz, 5.60 Hz), 3.48 (t, 1H, J = 8.80 Hz), 3.58 (m, 2H), 3.64 (d, 1H, J = 10.00 Hz), 3.69 (d, 2H, J = 14.80 Hz), 3.75 (d, 1H, J = 10.01 Hz), 3.82 (d, 2H, J = 14.70 Hz), 3.94 (m, 1H), 3.99 (d, 1H, J = 2.93 Hz, H4'), 4.22 (d, 1H, J = 11.78 Hz), 4.28 - 4.39 (m, 4H), 4.51 (dd, 2H, J = 11.93 Hz, 4.00 Hz), 4.57 (d, 1H, J = 9.20 Hz, H1'), 4.62 (dd, 2H, J = 11.60 Hz, 8.66 Hz), 4.79 (d, 1H, J = 3.67 Hz, H1), 4.88 (dd, 1H, J = 10.50 Hz, 3.17 Hz, H3'), 4.94 (d, 1H, J = 10.01 Hz), 5.32 (dd, 1H, J = 10.47 Hz, 7.80 Hz, H2'), 5.49 (d, 1H, 10.07 Hz, NH), 7.00 - 7.36 (m, 25H). Partial ^{13}C NMR 99.14, 100.72 ppm.

Anal. Calcd. for $C_{53}H_{58}ClNO_{13}$; C, 66.83; H, 6.14; Cl, 3.72; N, 1.47. Found: C, 66.71; H, 6.11; Cl, 3.70; N, 1.47.

Benzyl O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside-(1-->3)-O-(2-O-acetyl-4,6-di-O-benzyl-β-D-galactopyranosyl)-(1-->3)-2-acetamido-4,6-di-O-benzyl-2-deoxy-α-D-glucopyranoside 22a. The chloroacetate **21a** (310 mg, 0.32 mmol) in 5 mL of dry methylene chloride was treated under argon with 2.5 mL (15 equiv.) of a 2M solution of hydrazine acetate (from 0.38 mL of 98% hydrazine monohydrate + 0.45 mL of glacial acetic acid in 3.91 mL of MeOH at 0°C). Three drops of acetic acid were added, and the mixture was stirred for 12 h at room temperature. The residue from evaporation under reduced pressure was taken up in methylene chloride and washed with water and brine. The dried (Na_2SO_4) extract was concentrated and flash chromatographed (80:20 methylene chloride/acetone) yielding 210 mg (74% yield) of **21b**. R_f 0.27 (80:20 methylene chloride/acetone). ^1H NMR δ 1.97 (s, 3H), 2.16 (s, 3H), 2.35 (m, 1H, OH), 3.40 -

3.90 (m, 9H), 4.00 (dd, 1H, J = 10.47 Hz, 8.75 Hz), 4.25 (d, 1H, J = 11.72 Hz), 4.29 - 4.45 (m, 4H), 4.49 - 4.79 (m, 6H), 4.83 (d, 1H, J = 3.67 Hz, H1), 4.99 (m, 2H, H2' + benzyl proton), 5.54 (d, 1H, J = 10.02 Hz, NH), 7.06 - 7.50 (m, 25H). Using the general procedure for the *Coupling Reaction* a portion of the material **21b**, (198 mg, 0.22 mmol) and the pentenyl glycoside **9b** (204 mg, 0.33 mmol) were coupled, using dry methylene chloride (7 mL), NIS (74 mg, 0.33 mmol), and followed by Et_3SiOTf (0.074 mL, 0.32 mmol). After 15 min at room temperature, the reaction was worked up as described above, and the residue was flash chromatographed, eluting first with 80:20 pet ether/acetone to give 169 mg of **22a**. (R_f 0.42, 75:25 pet ether/acetone) and 27.8 mg of the corresponding β-coupling product (R_f 0.32, 75:25 pet ether/acetone). The solvent was then changed to 50:50 methylene chloride/acetone, giving 49.7 mg of unconverted alcohol **21b**. The total yield of the trisaccharide was 82% (6:1 α/β) based on recovered alcohol **21b**. For compound **22a**: $[\alpha]_D^{20}$ +55.08° (c 1.18, $CHCl_3$). ^1H NMR δ 1.90 (s, 3H), 2.12 (s, 3H), 3.40 - 4.20 (m, 16H), 4.24 (d, 1H, J = 11.91 Hz), 4.30 - 4.80 (m, 15 H), 4.90 (m, 2H), 4.97 (d, 1H, J = 6.59 Hz), 5.01 - 5.13 (m, 3H), 5.43 (dd, 1H, J = 10.01 Hz, 7.75 Hz), 5.61 (d, 1H, J = 9.77 Hz), 7.05 - 7.50 (m, 45H). Partial ^{13}C NMR 96.99, 98.84, 100.81 ppm.

Anal. Calcd. for $C_{85}H_{91}NO_{17}$: C, 72.99; H, 6.56; N, 1.00. Found: C, 73.11; H, 6.61; N, 0.97. For **22a**: Partial ^{13}C NMR 96.99, 100.38, 105.28 ppm.

Pent-4-enyl 2,3,4-tri-O-benzyl-α-L-fucopyranoside 19b. To a mixture of L-fucose **18**, (1 g) and pentenyl alcohol (5 mL), was added a catalytic amount of camphor sulphonic acid (~ 20 mg) and the mixture was heated at 90°C for two days. The reaction mixture was cooled, neutralized with triethylamine, and then excess of pentenyl alcohol was removed under vacuum. The residue was purified by flash chromatography using the mixture of dichloromethane and methanol (95:5-->90:10) to obtain pentenyl fucoside **19a** (1.25 g, 85% yield), which was benzylated to give compound **19b** (following the same procedure as **9b**) in a quantitative yield. This mixture of anomers was separated by flash chromatography using pet-ether and ethyl acetate (9:1). For **19bα**: $[\alpha]_D^{21}$ -39.30 (c 1.3, $CHCl_3$. ^1H NMR δ 1.10 (d, 3H), 1.70 (m, 2H), 2.14 (m, 2H), 3.4-3.7 (m, 3H), 3.85-4.10 (m, 3H), 4.60-5.10 (m, 9H), 5.74-5.90 (m, 1H), 7.2-7.5 (m, 15H).

Anal. Calcd for $C_{32}H_{38}O_5$: C, 76.46; H, 7.62. Found C,76.37, H,7.64.

Benzyl O-(2,3,4,6-tetra-O-Benzyl-α-D-galactopyranosyl)-(1-->3)-O-[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)-(1-->2)]-O-(4,6-di-O-benzyl-β-D-galactopyranosyl)-(1-->3)-2-acetamido-4,6-di-O-benzyl-2-deoxy-α-D-glucopyranoside 23. The acetate **22a** (149 mg, 0.11 mmol) in a solution of methylene chloride (0.4 mL) and MeOH (6 mL) was stirred for 5 h under argon with catalytic amount of NaOMe. The solution was then concentrated at diminished pressure and the residual oil was flash chromatographed (70:30 pet ether/acetone) to obtain 140 mg (97% yield) of **22b**. R_f 0.38 (70:30 pet ether/acetone). ^1H NMR δ 1.94 (s, 3H), 3.21 (m, 1H), 3.53 (m, 5H), 3.70 - 4.34 (m, 14H), 4.37 - 4.88 (m, 14H), 4.96 (d, 1H, J = 11.72 Hz), 5.04 (d, 1H, J = 11.47 Hz), 5.13 (m, 3H), 5.25 (d, 1H, J = 3.42 Hz), 6.60 (d, 1H, J = 7.03Hz). 7.10 - 7.55 (m, 45H). Using the general procedure for the *Coupling Reaction* the pentenyl fucoside **19bα** (102 mg, 0.20 mmol) and the alcohol **22b** (168 mg, 0.12 mmol) were coupled using methylene chloride (4 mL), NIS (40 mg, 0.18 mmol), and Et_3SiOTf (0.04 mL, 0.17 mmol). Work up as described gave an oil which was flash chromatographed (85:15 --> 80:20 pet ether/acetone) to yield 145.4 mg of **23** (R_f 0.34, 80:20 pet ether/acetone), 22.7 mg of the β-coupled product (R_f 0.27, 80:20 pet ether/acetone), and 27.6 mg of unconsumed alcohol **22b**. The total yield of **23** was 91% (6.1:1 α/β) based on recovered alcohol **22b**. For compound **18**: $[\alpha]_D^{20}$ +24.39° (c 1.16, $CHCl_3$). ^1H NMR δ 1.90 (s, 3H), 3.37 - 5.18 (m, 51H), 5.43 (d, 1H, J = 2.93 Hz), 5.69 (d, 1H, J = 3.72 Hz), 5.84 (d, 1H, J = 8.36 Hz), 6.95 - 7.60 (m, 60H). Partial ^{13}C NMR 96.25, 96.75, 97.91, 101.45 ppm.

Anal. Calcd. for $C_{110}H_{117}NO_{20}$: C, 74.51; H, 6.65; N, 0.79. Found: C, 74.65; H, 6.76; N, 0.77.

O-(α-D-Galactopyranosyl)-(1-->3)-O-[α-L-fucopyranosyl-(1-->2)]-O-(β-D-galactopyranosyl)-(1-->3)-2-acetamido-2-deoxy-D-glucopyranose 3. Compound **23** (70 mg, 0.04 mmol) in 10 mL of MeOH containing 10 drops of glacial acetic acid was hydrogenated for 4 days at 55 PSI of hydrogen over Pd-C (10%). The reaction was then filtered through a bed of celite. The filtrate was concentrated to obtain 25.3 mg (92% yield) of **3**. $[\alpha]_D^{20}$ +34.00° (c 1.05, MeOH) [Lit.[4] $[\alpha]_D^{20}$ +33.3° (c 1.0, MeOH)]. Anal. Calcd. for $C_{26}H_{45}NO_{20}$: C, 45.15; H, 6.56; N, 2.03. Found: C, 44.36; H, 6.50; N, 1.36.

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