n-Pentenyl Glycoside Methodology in the Stereoselective Construction of the Tetrasaccharyl Cap Portion of *Leishmania* Lipophosphoglycan

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Efficient and high yielding stereoselective assembly of the tetrasaccharyl cap region of the lipophosphoglycan from the protozoan parasite *Leishmania* using the *n*-pentenyl glycoside protocol is described in this paper. Both convergent and linear syntheses lead to the protected tetrasaccharide **14**; however, the convergent assembly is more efficient in terms of product recovery. Regioselective reductive cleavage of benzylidene acetal **4** with triethylsilane−trifluoroacetic acid system liberates the required C-4 OH in excellent yield, without affecting the resident chloroacetate functionality.

Introduction

The human disease *Leishmaniasis* is an ancient, widespread, and poorly understood affliction prevalent throughout the tropical and subtropical regions of the world. Protozoan parasites belonging to the genus *Leishmania*, which are the causative agents for this disease, live within the digestive tract of the sandfly and are transferred to the host mammal's bloodstream during feeding. They then cleverly survive the very mechanism which is supposed to destroy them and infection of the host follows.[1] There is evidence that cell surface glycoconjugates play a key role in mediating the interactions which protect the parasite in the host's hydrolytic environment.[2] Insights into the structural assignments of these and related glycoconjugates have poured forth in recent years,[3] and on the basis of reports in the literature, a generic structure of the cell surface lipophosphoglycan (LPG) of *Leishmania* is shown below (Figure 1).[2]

The complex oligosaccharide array may be divided into three components, namely cap, repeating unit, and glycosylphosphatidylinositol (GPI) anchor, interlinked by phosphate residues. Tentative structure−activity relationships have been assigned for each of the three components[2,3] as follows: the cap is thought to attach the parasite to the digestive tract of the sandfly and may also contain the epitope responsible for recognition by the mammalian host macrophage; the repeating unit is presumed to form a macromolecular diffusion barrier, which prevents the binding of host's antibodies to the LPG epitopes; the GPI moiety is implicated in many functions, the most fundamental of which is to anchor the oligosaccharide (or protein) to the plasma membrane.[4]

Synthetic work in the area of membrane-bound glycoconjugates is gaining importance as is evident from contributions from this[5] and other laboratories.[6] However, specific work in the area of *Leishmania* LPG is minimal, including the syntheses of phosphoglycan fragments of *L. donovani*.[7] Herein, we report our work involving the synthesis of the tetrasaccharyl cap moiety of *Leishmania* LPG.

Since their advent,[8] the *n*-pentenyl glycosides (NPGs) have been effectively utilized in synthetic[9] and mechanistic[10] carbohydrate chemistry. The mild conditions required for NPG activation tolerate a wide array of commonly employed protecting groups. The compatibility of the *n*-pentenyl group with a variety of synthetic manipulations enables its installation early on in the synthesis. Coupling reactions are frequently complete even before their progress can be monitored by TLC. On the other hand, the reactivity of the pentenyl group can be erased by dibromination of the olefinic residue. Restoration of the double bond is readily accomplished

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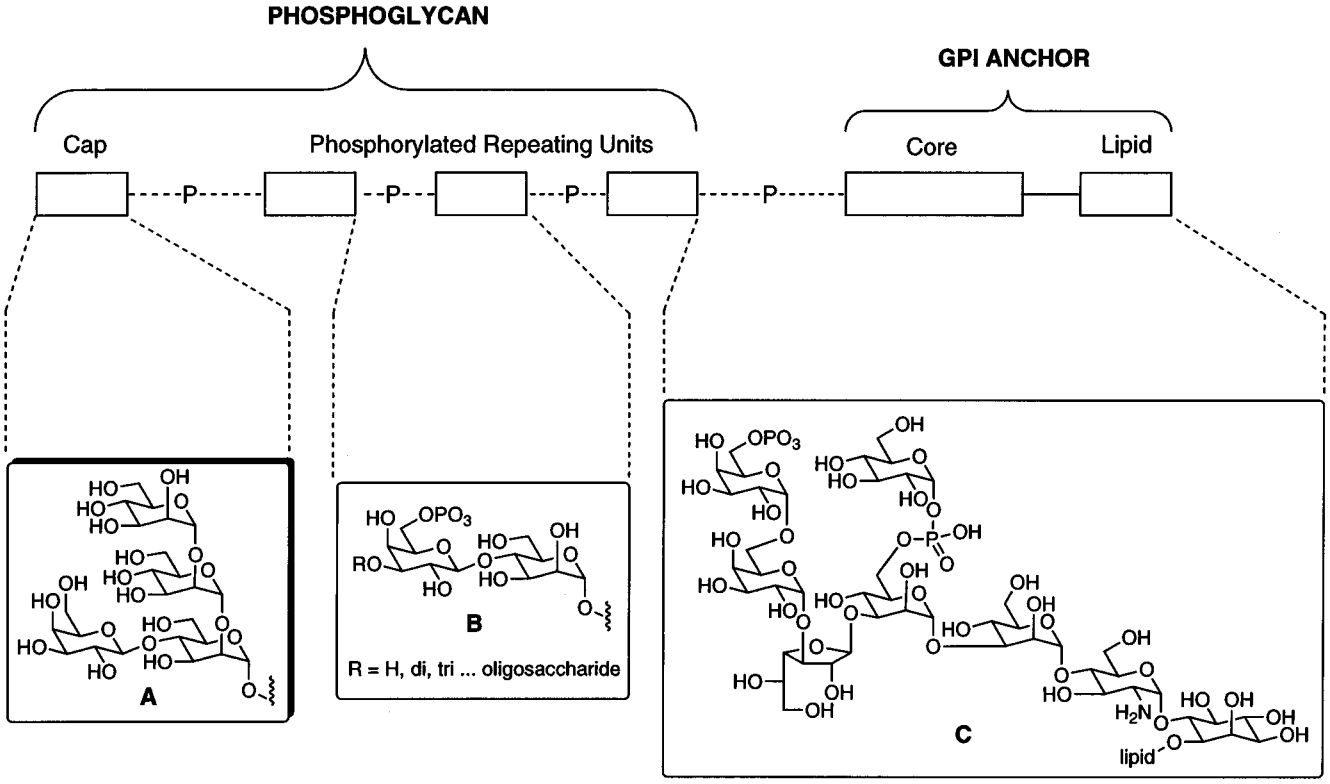

Figure 1. Structure of *Leishmania* lipophosphoglycan.

at the appointed time by reductive debromination using zinc dust, sodium iodide, or samarium(II) iodide.[11] Thus, a specific *n*-pentenyl glycoside can be tailored to act as acceptor or donor by employing the bromination−debromination sequence. Finally, arming or disarming the sugar entity for reactivity purposes can be achieved easily by suitable choice of protecting groups. Due to these properties, the *n*-pentenyl methodology has found good use in complex oligosaccharide synthesis.[12]

Retrosynthetic Analysis

Two pathways can be envisioned to the tetrasaccharyl cap moiety of *Leishmania* LPG. Path a leads to disaccharides **I** and **II** (Scheme 1), each of which in turn can be obtained from the monosaccharides **III**−**VI**. By applying the bromination−debromination protocol, both **III** and **IV** could arise from the same precursor **11** (see below), while **V** and **VI** should be available by existing methodologies. The alternative, path b, is linear and leads to the monosaccharide **III** and the trisaccharide **VII**. Further disconnection of the latter gives rise to the previously described saccharides, **II** and **III**. The protected tetrasaccharide has been constructed via both synthetic routes, paths a and b, as described in this paper.

Results and Discussion

Starting from D-mannose, **1**, the known diol **2**[8] was prepared in two steps. Regioselective benzylation of the 3-hydroxyl group via the stannylene acetal[13] intermediate followed by chloroacetylation provided the NPG **4** in 84% yield (Scheme 2). Although cyanoborohydride−HCl combination[14] is widely used for regioselective reductive ring opening of benzylidene acetals, we decided to test the triethylsilane−trifluroacetic acid combination described in a recent report.[15] Thus, treatment of the benzylidene acetal **4** with 5 equiv of triethylsilane−trifluroacetic acid at 0 °C followed by slow warming to room temperature afforded the desired C-4 alcohol **5** in excellent yield. *The survival of the C-2 chloroacetate functionality under these conditions is worthy of special note.* In the final step toward the key acceptor **6**, the reactivity of the pentenyl double bond was obliterated by dibromination using standard conditions.[8]

Initial attempts to obtain disaccharide **9** via Koenigs−Knorr coupling of the acceptor **6** and acetobromogalactose **7** under the agency of silver triflate[16] were unsatisfactory. However upon changing the donor to *n*-pentenyl galactoside **8** and employing the standard NPG conditions (1.3 equiv of NIS and 0.3 equiv of TESOTf), the coupling went smoothly and rapidly at room temperature in dichloromethane to provide the β-linked disaccharide **9** in a very high yield (Scheme 3). Removal of the chloroacetyl group using thiourea in refluxing ethanol resulted in the acceptor **10**, the common intermediate for the convergent and linear syntheses.

The dimannan donor required for the convergent

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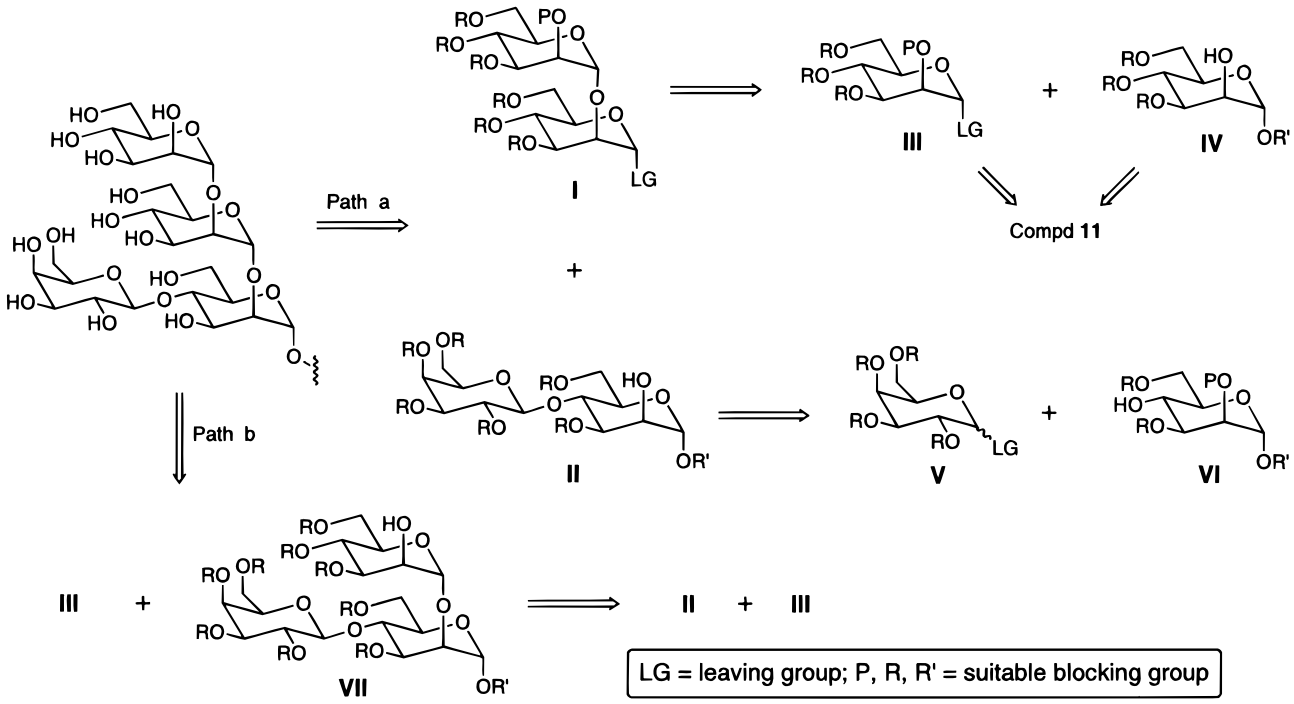
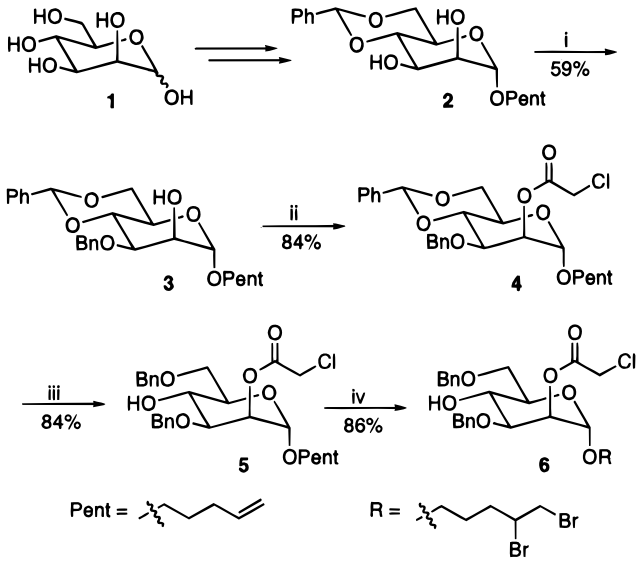
Scheme 1

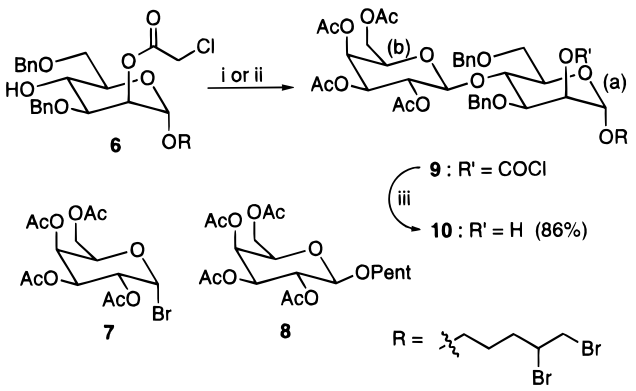


Scheme 2[a]



[a] Key: (i) (a) Bu_2SnO, MeOH, reflux, 1 h; (b) BnBr, DMF, 80−110 °C, 2 h; (ii) $(ClCH_2CO)_2O$, pyr, CH_2Cl_2, 0−10 °C, 30 min; (iii) Et_3SiH, CF_3CO_2H, CH_2Cl_2, 0−20 °C, 2 h; (iv) Et_4NBr, Br_2, CH_2Cl_2, 0 °C.

Scheme 3[a]



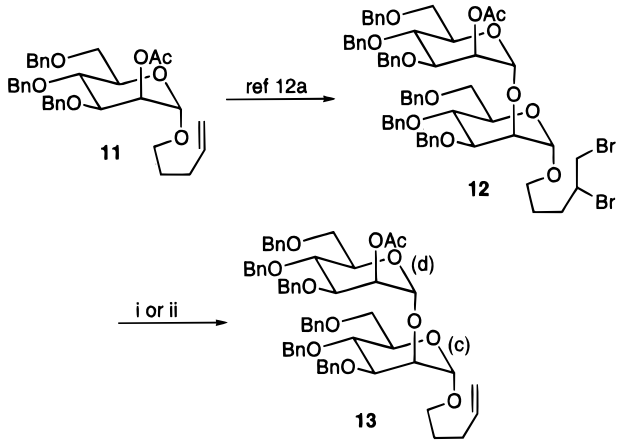
[a] Key: (i) **7**, AgOTf, CH_2Cl_2, 4 Å MS, 1 h (<10% of **9**); (ii) **8**, NIS, TESOTf, CH_2Cl_2 (87% of **9**); (iii) Thiourea, $NaHCO_3$, EtOH/EtOAc, reflux, 2 h.

synthesis was prepared from the known dibromo precursor **12**.[12a] Reductive debromination of **12** was carried out under both zinc dust and sodium iodide conditions (Scheme 4).[11] Though both methods afforded donor **13**, sonication of dibromo compound **12** with freshly activated zinc dust seemed to work better in terms of product recovery.

Coupling of the dimannan donor **13** to the disaccharide acceptor **10** was next investigated under standard NPG coupling conditions. Slow addition of the donor to a mixture of the acceptor **10**, NIS, and catalytic TESOTf in dichloromethane at room temperature under argon atmosphere resulted in instant formation of the tetrasaccharide **14** (Scheme 5), which was isolated in a high yield after column chromatography. The structure was confirmed by NMR (^1H and ^{13}C), mass and combustion analyses.

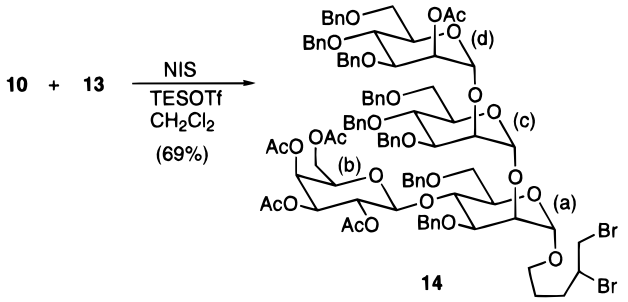
For the linear synthesis, a mannan donor with a suitable protecting group at C-2 was required. Chloroacetate was the obvious choice, and the required donor **15** was obtained from the corresponding acetate **11**[12a] in two simple steps, namely deacylation with potassium carbonate/methanol and reprotection with chloroacetic anhydride and pyridine (Scheme 6). Coupling of the donor **15** to the disaccharide acceptor **10** was carried out as described above. The reaction took place smoothly to afford the trisaccharide **16** in 63% yield (81% based on recovered acceptor) after purification. Deblocking of chloroacetate was accomplished using thiourea and sodium bicarbonate in refluxing ethanol. The final coupling was carried out with the trisaccharide acceptor **17** and mannan donor **11** to provide the previously described tetrasaccharide **14**. However, in this case, TLC analysis of the crude reaction mixture showed the product and

Scheme 4[a]

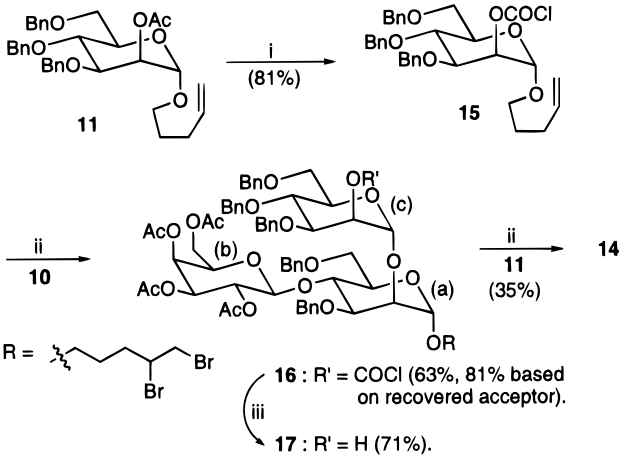


[a] Key: (i) NaI, MEK, reflux, 4 h (73%); (ii) *n*-Bu_4NI, Zn dust, EtOH/EtOAc, sonication, 17 h (86%).

Scheme 5



Scheme 6[a]



[a] Key: (i) (a) K_2CO_3, MeOH, 4 h; (b) $(ClCH_2CO)_2O$, pyr, CH_2Cl_2, 0 °C to RT, 30 min; (ii) NIS, TESOTf, CH_2Cl_2; (iii) Thiourea, $NaHCO_3$, EtOH/EtOAc, reflux, 7 h.

several other unidentified compounds. After repeated column chromatography the tetrasaccharide was isolated in a modest yield of 35%.

In conclusion, the tetrasaccharyl cap portion of *Leishmania* LPG was assembled in an efficient manner using the NPG protocol. Although both the convergent and linear synthetic sequences resulted in the tetrasaccharide **14**, the former is the method of choice in terms of product recovery. The triethylsilane−trifluroacetic acid system provided the required regioselective reductive benzylidene acetal cleavage in an excellent yield, the C-2 chloroacetate functionality being tolerated by the reaction conditions. Work is already in progress towards the construction of the core GPI anchor[17] and will be reported in due course.

Experimental Section

General Methods. All reactions were performed under argon in oven-dried glassware. Dichloromethane was distilled from calcium hydride. NIS was recrystallized from CH_2Cl_2/hexanes. All other solvents and reagents were used as purchased. The carbohydrate derivatives were taken up in a small quantity of toluene and placed under vacuum overnight prior to use. Compounds were visualized on the TLC plate by charring with H_2SO_4/EtOH/H_2O (1/10/10). Flash column chromatography was carried out as described by Still[18] with silica gel 60 (230−400 mesh, Merck). Unless stated otherwise, ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, using $CDCl_3$. Chemical shifts are reported in ppm relative to residual solvent resonance. *J* values are reported in Hz. Spectral assignments were done using COSY and HETCOR experiments. FAB mass spectral data were obtained on a Jeol JMS-SX-102 high-resolution mass spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc.

General Coupling Procedure. To a solution (0.1 M) of the glycosyl acceptor (1.0 equiv) in dry dichloromethane was added *N*-iodosuccinimide (NIS, 1.3 equiv) followed by triethylsilyl trifluoromethanesulfonate (TESOTf, 0.3 equiv). The glycosyl donor was dissolved in dichloromethane (0.4 M solution) which was added dropwise to the reaction mixture at room temperature. The mixture was stirred until it turned into a pale pink homogeneous solution (2−3 min). The reaction was quenched with 10% aqueous sodium thiosulfate and saturated aqueous sodium bicarbonate solutions. The organic layer was separated and the aqueous layer washed with CH_2Cl_2 once. The combined organic layer was dried over sodium sulfate, and solvent was stripped off *in vacuo*. The crude residue was then subjected to flash column chromatography.

Pentenyl 3-*O*-Benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (3). A mixture of the *n*-pentenyl mannoside **2** (2 g, 5.95 mmol, 1.0 equiv) and dibutyltin oxide (1.5 g, 5.95 mmol, 1.0 equiv) was refluxed in methanol (100 mL) until the solution turned completely homogeneous (∼1 h). The solvent was then removed by rotary evaporation. The oily residue was taken up in DMF (20 mL), and benzyl bromide (1.0 mL, 8.33 mmol, 1.4 equiv) was added. The reaction mixture was heated to 80−110 °C for 2 h when TLC analysis indicated complete disappearance of the starting material. DMF was removed *in vacuo*, and the residue was directly subjected to column chromatography using 25/75 EtOAc/petroleum ether. The product **3** (1.5 g, 59%) was isolated as a colorless oil: ^1H NMR δ 1.79−1.88 (m, 2H), 2.24−2.31 (m, 2H), 3.11 (br s, 1H, OH), 3.52−3.59 (m, 1H, OCH_2), 3.80−3.88 (m, 1H, OCH_2), 3.94−4.00 (m, 2H, H-5, H-6), 4.07 (dd, 1H, H-3), 4.14−4.15 (m, 1H, H-2), 4.27 (ap t, 1H, H-4), 4.38−4.45 (m, 1H, H-6), 4.94 (ABq, 2H, $ArCH_2$), 4.96 (s, 1H, H-1), 5.13−5.23 (m, 2H, $=CH_2$), 5.77 (s, 1H, ArCH), 5.89−6.03 (m, 1H, CH=), 7.37−7.68 (m, 10H, ArH); ^{13}C NMR δ 28.40, 30.11, 63.24 (C-5), 66.97 (OCH_2), 68.75 (C-6), 69.86 (C-2), 72.99 ($ArCH_2$), 75.72 (C-3), 78.81 (C-4), 99.95 (C-1), 101.37 (ArCH), 114.95 ($=CH_2$), 125.92−128.32 (ArC's), 137.45 (ipso C), 137.74 (CH=), 137.92 (ipso C); HRMS (FAB) Calcd for $C_{25}H_{30}O_6$ 427.2121 $(M + H)^+$, found 427.2134.

Pentenyl 2-*O*-(Chloroacetyl)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (4). To the mannoside **3** (1.175 g, 2.76 mmol, 1.0 equiv) in dichloromethane (14 mL) at 0 °C was added pyridine (0.45 mL, 5.52 mmol, 2.0 equiv) followed by chloroacetic anhydride (0.472 g, 2.76 mmol, 1.0 equiv) in one bulk. The reaction mixture was slowly warmed to 10 °C over 30 min at which time TLC indicated reaction completion. The reaction was quenched by addition of crushed ice and water. The organic layer was separated and dried over sodium sulfate. The solvent was removed, and the residue was

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chromatographed on silica gel using 15/85 EtOAc/petroleum ether. The product **4** (1.164 g, 84%) was isolated as a colorless oil: ^{1}H NMR δ 1.79−1.88 (m, 2H), 2.24−2.30 (m, 2H), 3.53−3.60 (m, 1H, OCH_2), 3.80−3.87 (m, 1H, OCH_2), 3.94−4.02 (m, 2H, H-5, H-6), 4.13−4.22 (m, 2H, H-3, H-4), 4.31 (s, 2H, CH_2-Cl), 4.39−4.43 (m, 1H, H-6), 4.84 (ABq, 2H, $ArCH_2$), 4.94 (d, 1H, J = 1.5, H-1), 5.11−5.22 (m, 2H, $=CH_2$), 5.58 (dd, 1H, H-2), 5.77 (s, 1H, ArCH), 5.87−5.98 (m, 1H, CH=), 7.37−7.67 (m, 10H, ArH); ^{13}C NMR δ 28.30, 30.06, 40.75 (CH_2Cl), 63.71 (C-5), 67.39 (OCH_2), 68.57 (C-6), 71.57 (C-2), 72.30 ($ArCH_2$), 73.71 (C-3), 78.19 (C-4), 98.23 (C-1), 101.46 (ArCH), 115.13 ($=CH_2$), 125.93−128.86 (ArC's), 137.24 (ipso C), 137.59 (CH=), 137.67 (ipso C), 166.64. Anal. Calcd for $C_{27}H_{31}O_7Cl$: C, 64.47; H, 6.21. Found: C, 64.41; H, 6.29.

Pentenyl 2-*O*-(Chloroacetyl)-3,6-di-*O*-benzyl-α-D-mannopyranoside (5). To the mannoside **4** (0.13 g, 0.26 mmol, 1.0 equiv) in dichloromethane (2 mL) at 0 °C was added triethylsilane (0.21 mL, 1.3 mmol, 5.0 equiv). Trifluoroacetic acid (0.1 mL, 1.3 mmol, 5.0 equiv) was then added dropwise over a period of 2 min. The reaction mixture was slowly brought to 20 °C over 2 h. Careful monitoring by TLC indicated complete disappearance of the starting material at this time. The reaction was diluted with CH_2Cl_2 (10 mL) and quenched with saturated aqueous bicarbonate solution. The organic layer was separated and dried over sodium sulfate and the solvent removed *in vacuo*. Flash chromatography of the crude residue using 20/80 EtOAc/hexanes afforded the product **5** (0.11 g, 84%) as a colorless thick oil: ^{1}H NMR δ 1.76−1.86 (m, 2H), 2.20−2.27 (m, 2H), 2.62 (br s, 1H, OH), 3.52−3.59 (m, 1H, OCH_2), 3.80−3.87 (m, 4H, H-5, H-6, OCH_2), 3.93 (dd, 1H, H-3), 4.01−4.07 (m, 1H, H-4), 4.23 (s, 2H, CH_2Cl), 4.72 (2 × ABq, 4H, $ArCH_2$), 4.97 (d, 1H, J = 1.5, H-1), 5.08−5.18 (m, 2H, $=CH_2$), 5.51 (dd, 1H, H-2), 5.85−5.99 (m, 1H, CH=), 7.37−7.46 (m, 10, ArH); ^{13}C NMR δ 28.37, 30.12, 40.73 (CH_2Cl), 67.04 (C-4), 67.24 (OCH_2), 69.51 (C-6), 69.85 (C-2), 71.12 (C-5), 71.76 ($ArCH_2$), 73.42 ($ArCH_2$), 77.42 (C-3), 97.40 (C-1), 115.01 ($=CH_2$), 127.40−128.45 (ArC's), 137.34 (ipso C), 137.71 (CH=), 138.00 (ipso C), 166.79. Anal. Calcd for $C_{27}H_{33}O_7Cl$: C, 64.21; H, 6.59. Found: C, 64.09; H, 6.63.

Dibromopentanyl 2-*O*-(Chloroacetyl)-3,6-di-*O*-benzyl-α-D-mannopyranoside (6). The pentenyl mannoside **5** (0.71 g, 1.41 mmol, 1.0 equiv) was dissolved in dichloromethane (8 mL), and tetraethylammonium bromide (0.15 g, 0.71 mmol, 0.5 equiv) was added in one portion. Bromine (73 μL, 1.41 mmol, 1.0 equiv) was then added dropwise, and when the brown color persisted, the reaction was quenched with 10% aqueous sodium thiosulfate solution. The organic phase was separated and dried over sodium sulfate and the solvent removed by rotary evaporation. Silica gel chromatography provided the dibromide (0.8 g, 86%) as a thick oil: ^{1}H NMR δ 1.82−2.04 (m, 3H), 2.32−2.41 (m, 1H), 2.60 (br s, 1H, OH), 3.58−3.63 (m, 1H, OCH_2), 3.72 (ap t, 1H, CH_2Br), 3.84−4.03 (m, 7H, H-3 to H-6, OCH_2, CH_2Br), 4.23 (s, 2H, CH_2Cl), 4.24−4.30 (m, 1H, CHBr), 4.72 (2 × ABq, 4H, $ArCH_2$), 4.98 (d, 1H, J = 1.6, H-1), 5.50 (ap d, 1H, H-2), 7.37−7.46 (m, 10H, ArH); ^{13}C NMR δ 26.52, 32.63, 35.93 (CH_2Br), 40.67 (CH_2Cl), 52.13 (CHBr), 66.72 (OCH_2), 66.87, 69.43 (C-6), 69.72, 71.30, 71.67 ($ArCH_2$), 73.38 ($ArCH_2$), 77.17, 97.38 (C-1), 127.39−128.43 (ArC's), 137.23 (ipso C), 137.91 (ipso C), 166.70; HRMS (FAB) calcd for $C_{27}H_{33}O_7Br_2Cl$ 661.0203 $(M - H)^+$, found 661.0228. Anal. Calcd: C, 48.78; H, 5.00. Found: C, 48.84; H, 5.07.

Dibromopentanyl *O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2-*O*-(chloroacetyl)-3,6-di-*O*-benzyl-α-D-mannopyranoside (9). The acceptor **6** (0.86 g, 1.30 mmol, 1.0 equiv) and donor **8** (0.704 g, 1.69 mmol, 1.3 equiv) were coupled using the general procedure described above. The crude product was chromatographed using 25/75 EtOAc/petroleum ether to provide 1.122 g (87%) of the disaccharide **9**: ^{1}H NMR δ 1.75−2.02 (m, 3H), 2.02 (s, 3H), 2.06 (s, 6H), 2.21 (3, 3H), 2.25−2.40 (m, 1H), 3.54−4.28 (m, 15 H), 4.57−4.90 (5H, $H\text{-}1_b$, 2 × $ArCH_2$), 4.91−4.95 (m, 2H, $H\text{-}1_a$, $H\text{-}3_b$), 5.21 (dd, 1H, $H\text{-}2_b$), 5.36 (d, 1H, $H\text{-}4_b$), 5.43 (ap t, 1H, $H\text{-}2_a$), 7.37−7.46 (m, 10H, ArH); ^{13}C NMR δ 20.53, 20.58, 20.64, 20.75, 26.59, 32.65, 35.94 (CH_2Br), 40.70 (CH_2Cl), 52.21 (CHBr), 66.67 ($C\text{-}4_b$), 67.11 ($C\text{-}6_{a\ or\ b}$), 67.86 ($C\text{-}6_{a\ or\ b}$), 69.47 ($C\text{-}2_b$), 70.68 ($C\text{-}2_a$), 70.73, 70.92 ($C\text{-}3_b$), 71.14, 71.77 ($ArCH_2$), 73.60 ($ArCH_2$), 74.25, 75.81, 97.20 ($C\text{-}1_a$), 100.53 ($C\text{-}1_b$), 127.05−128.53 (ArC's), 137.96 (ipso C), 138.01 (ipso C), 166.61, 169.25, 169.95, 170.00, 170.06. Anal. Calcd for $C_{41}H_{51}O_{16}Br_2Cl$: C, 49.49; H, 5.17. Found: C, 49.57; H, 5.24.

Dibromopentanyl *O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-3,6-di-*O*-benzyl-α-D-mannopyranoside (10). The disaccharide **9** (1.012 g, 1.02 mmol, 1.0 equiv) was taken up in EtOH (22 mL), and a minimum amount of EtOAc (3 mL) was added to effect dissolution. Sodium bicarbonate (0.171 g, 2.04 mmol, 2.0 equiv) and thiourea (0.093 g, 1.22 mmol, 1.2 equiv) were added, and the mixture was refluxed for 2 h. The solvent was then removed by rotary evaporation and the residue taken in dichloromethane. The dichloromethane layer was washed with water once and dried over sodium sulfate, and solvent was removed. Flash column chromatography of the crude product using 40/60 EtOAc/petroleum ether resulted in 0.802 g (86%) of the disaccharide acceptor **10**: ^{1}H NMR δ 1.79−2.02 (m, 3H), 2.04 (s, 3H), 2.06 (s, 3H), 2.09 (s, 3H), 2.19 (s, 3H), 2.22-2.35 (m, 1H), 2.73 (br, 1H, OH), 3.54−3.59 (m, 1H, OCH_2), 3.68−3.87 (m, 7H), 3.92−3.98 (ddd, 1H, $H\text{-}2_a$), 4.01−4.30 (m, 5H), 4.55−4.92 (m, 6H, $H\text{-}1_b$, $H\text{-}3_b$, 2 × $ArCH_2$), 4.95 (s, 1H, $H\text{-}1_a$), 5.21 (dd, 1H, $H\text{-}2_b$), 5.39 (d, 1H, $H\text{-}4_b$), 7.46−7.49 (m, 10 H, ArH); ^{13}C NMR δ 20.50, 20.53, 20.58, 20.65, 26.67, 32.78, 36.05 (CH_2Br), 52.30 (CHBr), 60.72, 66.63 (OCH_2), 66.77 ($C\text{-}4_b$), 67.91, 68.81 ($C\text{-}2_a$), 69.47 ($C\text{-}2_b$), 70.30, 70.77 ($C\text{-}3_b$), 70.94, 72.42 ($ArCH_2$), 73.56 ($ArCH_2$), 74.12, 77.76, 99.07 ($C\text{-}1_a$), 100.48 ($C\text{-}1_b$), 127.18−128.38 (ArC's), 137.96 (ipso C), 138.17 (ipso C), 169.23, 169.95, 170.09. Anal. Calcd for $C_{39}H_{50}O_{15}Br_2$: C, 50.99; H, 5.49. Found: C, 51.10; H, 5.44.

Pentenyl *O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (13) via Zn Dust Method. To the dibromide **12** (0.077 g, 0.067 mmol, 1.0 equiv) was added EtOH (2 mL) and drops of EtOAc to effect dissolution. Tetra-*n*-butylammonium iodide (0.025 g, 0.067 mmol, 1.0 equiv) and freshly activated Zn dust (0.022 g, 0.33 mmol, 5.0 equiv) were added, and the reaction mixture was sonicated overnight (17 h) under argon atmosphere. The reaction mixture was diluted with EtOAc and filtered through a pad of Celite. The solvent was removed *in vacuo*, and the residue was subjected to flash chromatography using 25/75 EtOAc/petroleum ether to afford 0.57 g (86%) of the donor **13**. **Via NaI method.** To a solution of the dibromide **12** (0.05 g, 0.043 mmol, 1.0 equiv) in methyl ethyl ketone (MEK, 2 mL) was added dry sodium iodide (0.007 g, 0.43 mmol, 10.0 equiv), and the mixture was refluxed for 4 h. The solvent was removed by rotary evaporation, and the residue was dissolved in dichloromethane and washed with 10% aqueous sodium thiosulfate solution. The organic phase was dried over sodium sulfate and the solvent stripped off *in vacuo*. Flash column chromatography using 30/70 EtOAc/petroleum ether provided 0.31 g (73%) of the donor **13**: ^{1}H NMR δ 1.69−1.79 (m, 2H), 2.15−2.22 (m, 2H), 2.27 (s, 3H), 3.39−3.47 (m, 1H, OCH_2), 3.72−3.80 (m, 1H, OCH_2), 3.83−4.16 (m, 11H), 4.53−4.88 (m, 10H, 5 × $ArCH_2$), 4.98−5.02 (m, 3H, $H\text{-}1_c$, $ArCH_2$), 5.06−5.17 (m, 2H, $=CH_2$), 5.24 (d, 1H, J = 1.4, $H\text{-}1_d$), 5.70 (dd, 1H, $H\text{-}2_d$), 5.84−6.15 (m, 1H, CH=), 7.41−7.49 (m, 30H, ArH); ^{13}C NMR δ 21.12, 28.56, 30.21, 66.92 (OCH_2), 68.63 ($C\text{-}2_d$), 98.61 ($C\text{-}1_c$), 99.49 ($C\text{-}1_d$), 114.82 ($=CH_2$), 170.10; HRMS (FAB) calcd for $C_{61}H_{68}O_{12}$ 991.4633 $(M - H)^+$, found 991.4584. Anal. Calcd: C, 73.77; H, 6.90. Found: C, 73.58; H, 6.92.

Pentenyl 2-*O*-(Chloroacetyl)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (15). The pentenyl mannoside **11** (0.6 g, 1.07 mmol, 1.0 equiv) was dissolved in MeOH (12 mL), and anhydrous potassium carbonate (0.06 g) was added. The mixture was stirred at room temperature for 4 h. The solvent was removed, and dichloromethane was added to the oily residue. The organic phase was washed with water once and dried over sodium sulfate and the solvent removed by rotary evaporation. The residue was dissolved in dichloromethane (5 mL) and cooled to 0 °C. Pyridine (0.34 mL, 4.28 mmol, 4.0 equiv) was added followed by chloroacetic anhydride (0.366 g, 2.14 mmol, 2.0 equiv) in two portions. The reaction was warmed to 20 °C over 30 min, diluted with dichloromethane, and quenched with crushed ice and water. The organic layer

was separated and dried over sodium sulfate, and the solvent was removed *in vacuo*. Column chromatography using 15/85 EtOAc/petroleum ether resulted in 0.515 g (81%) of **15** as a colorless thick oil: ^{1}H NMR δ 1.78−1.87 (m, 2H), 2.22−2.29 (m, 2H), 3.55−3.62 (m, 1H, OCH_2), 3.82−4.06 (m, 5H, H-4, H-5, H-6, OCH_2), 4.17 (dd, 1H, H-3), 4.31 (s, 2H, CH_2Cl), 4.61−4.98 (m, 6H, 3 × $ArCH_2$), 5.02 (d, 1H, J = 1.9, H-1), 5.10−5.22 (m, 2H, $=CH_2$), 5,80 (dd, 1H, H-2), 5.88−5.99 (m, 1H, CH=), 7.30−7.52 (m, 15H, ArH); ^{13}C NMR δ 28.39, 30.10, 40.87 (CH_2Cl), 67.22 (OCH_2), 68.59 (C-6), 70.59 (C-2), 71.26 (C-5), 71.93 ($ArCH_2$), 73.32 ($ArCH_2$), 74.03 (C-4), 75.15 ($ArCH_2$), 78.02 (C-3), 97.26 (C-1), 114.98 ($=CH_2$), 127.50−128.27 (ArC's), 137.60 (ipso C), 137.70 (CH=), 138.03 (ipso C), 138.10 (ipso C), 166.86; HRMS (FAB) calcd for $C_{34}H_{39}O_7Cl$ 593.2306 $(M - H)^+$, found: 593.2307. Anal. Calcd: C, 68.62; H, 6.60. Found: C, 68.39; H, 6.64.

Dibromopentanyl *O*-[2-*O*-(Chloroacetyl)-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl]-(1→2)-*O*-[(2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl)-(1→4)]-3,6-di-*O*-benzyl-α-D-mannopyranoside (16). The acceptor **10** (0.244 g, 0.266 mmol, 1.0 equiv) and donor **15** (0.206 g, 0.346 mmol, 1.3 equiv) were coupled using the general procedure described above. Flash chromatography using 20/70 to 50/50 EtOAc/petroleum ether provided 0.237 g (63%) of the product **16** and 0.056 g of unreacted acceptor **10**. Thus, the yield based on recovered acceptor was 81%: ^{1}H NMR δ 2.05 (s, 6H), 2.07 (s, 3H), 2.19 (s, 3H), 4.87−4.91 (m, 3H, H-1_b, $ArCH_2$), 4.95 (s, 1H, H-1_a), 5.03 (dd, 1H, H-3_b), 5.08 (s, 1H, H-1_c), 5.26 (dd, 1H, H-2_b), 5.39 (d, 1H, H-4_b), 5.67 (dd, 1H, H-2_c); ^{13}C NMR δ 20.56, 20.80, 26.69, 32.76, 36.08 (CH_2Br), 40.84 (CH_2Cl), 52.34 (CHBr), 60.67, 66.66 (OCH_2), 66.73 (C-4_b), 68.26, 68.83, 69.59 (C-2_b), 70.21 (C-2_c), 70.41, 71.06, 71.34, 71.76, 71.97, 72.09, 73.40, 73.58, 74.04, 74.33, 75.04, 75.14, 77.98, 78.16, 98.43 (C-1_a), 98.93 (C-1_c), 101.06 (C-1_b), 126.62−128.30 (ArC's), 137.62 (ipso C), 137.94 (ipso C), 138.08 (ipso C), 138.31 (ipso C), 138.40 (ipso C), 166.48, 169.55, 170.03, 170.19; HRMS (FAB) calcd for $C_{68}H_{79}O_{21}Br_2Cl$ 1423.3091 $(M - H)^+$, found 1423.3082. Anal. Calcd: C, 57.21; H, 5.58. Found: C, 57.18; H, 5.66.

Dibromopentanyl *O*-(3,4,6-Tri-*O*-benzyl-α-D-mannopyranosyl)-(1→2)-*O*-[(2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl)-(1→4)]-3,6-di-*O*-benzyl-α-D-mannopyranoside (17). Dechloroacylation of the trisaccharide **16** (0.192 g, 0.134 mmol) was carried out using the procedure described for **10**. Column chromatography of the crude residue afforded 0.129 g (71%) of the trisaccharide acceptor **17** as a foam: ^{1}H NMR δ 2.05 (s, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 2.23 (s, 3H), 4.56−4.93 (m, 11H, H-1b, 5 × $ArCH_2$), 5.02−5.05 (m, 2H, H-1_a, H-3_b), 5.14 (s, 1H, H-1_c), 5.27 (dd, 1H, H-2_b), 5.40 (d, 1H, H-4_b); ^{13}C NMR δ 20.54, 20.61, 20.79, 26.72, 32.75, 36.10, 52.41 (CHBr), 60.74, 66.67 (OCH_2), 66.77 (C-4_b), 68.29, 68.38, 69.20, 69.57 (C-2_b), 70.32, 71.04 (C-3_b), 71.37, 71.48, 72.03, 73.35, 73.55, 74.35, 74.96, 77.81, 79.96, 98.61 (C-1_a), 100.92 (C-1_c), 101.01 (C-1_b), 126.82−127.79 (ArC's), 137.86 (ipso C), 138.07 (ipso C), 138.12 (ipso C), 138.45 (ipso C), 138.50 (ipso C), 169.47, 170.06, 170.09, 170.18; HRMS (FAB) calcd for $C_{66}H_{78}O_{20}Br_2$ 1349.3531 $(M - H)^+$, found 1349.3473. Anal. Calcd: C, 58.67; H, 5.82. Found: C, 58.57; H, 5.78.

Dibromopentanyl *O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→2)-*O*-(3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→2)-*O*-[(2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl)-(1→4)]-3,6-di-*O*-benzyl-α-D-mannopyranoside (14) via Convergent Synthesis. Coupling of the disaccharide acceptor **10** (0.235 g, 0.255 mmol, 1.0 equiv) to the disaccharide donor **13** (0.33 g, 0.332 mmol, 1.3 equiv) was performed using the general procedure described above. Standard chromatography of the crude residue using 20/80 to 30/70 EtOAc/petroleum ether provided 0.319 g (69%) of the tetrasaccharide **14**. **Via Linear Synthesis.** The trisaccharide acceptor **17** (0.074 g, 0.055 mmol, 1.0 equiv) and mannan donor **15** (0.04 g, 0.072 mmol, 1.3 equiv) were coupled by the procedure described above. The crude product was subjected to flash column chromatography to provide 0.035 g (35%) of the tetrasaccharide **14**: ^{1}H NMR (500 MHz) δ 4.76−4.84 (m, 3H, H-1_b), 4.90 (dd, 1H, H-3_b), 4.97 (s, 1H, H-$1_{a\ or\ c}$), 4.99 (d, 1H, J = 1, H-1_d), 5.03 (s, 1H, H-$1_{a\ or\ c}$), 5.15 (ap d, 1H, H-2_b), 5.26 (d, 1H, H-4_b), 5.50 (dd, 1H, H-2_d); ^{13}C NMR δ 20.47, 20.54, 20.75, 21.04, 26.69, 32.67, 36.04 (CH_2Br), 52.36 (CHBr), 60.30, 66.56, 66.60 (C-4_b), 66.67, 68.22, 68.45 (C-2_d), 68.57, 69.53 (C-2_b), 70.15, 71.00 (C-3_b), 71.10, 71.69, 71.79, 71.92, 72.05, 73.07, 73.15, 73.52, 74.01, 74.58, 74.68, 74.82, 74.94, 75.01, 75.78, 77.82, 79.42, 98.39 (C-$1_{a\ or\ c}$), 99.17 (C-1_d), 100.76 (C-1_b), 101.03 (C-$1_{a\ or\ c}$), 126.75−128.18 (ArC's), 137.83, 138.14, 138.20, 138.26, 138.33, 138.39, 138.47, 169.44, 169.83, 169.99, 170.04, 170.11; HRMS (FAB) calcd for $C_{95}H_{108}O_{26}Br_2$ 1821.5417 $(M - H)^+$, found 1821.5505. Anal. Calcd: C, 62.50; H, 5.96. Found: C, 63.17; H, 5.94.

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