Solid Support Oligosaccharide Synthesis: Construction of β-Linked Oligosaccharides by Coupling of Glycal Derived Thioethyl Glycosyl Donors

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A solution to the problem of a solid-phase synthesis of β-(1→4) linked glucosides is described. The method involves conversion of polymer bound glycal to polymer bound thioethyl glucosyl donor bearing an α-oriented pivaloxy group at C2. The latter directs couplings with solution-based glycal acceptors in the β-sense. The ready-reiteratability of the method was demonstrated.

Introduction

Oligosaccharides, in the form of glycoprotein and glycolipid conjugates carry detailed structural information which mediates a variety of important biological events particularly at the level of cell−cell interactions.[1] Investigations into the nature of these signaling processes would be much facilitated by the availability of pure glycoconjugates. A wide range of increasingly powerful glycosylation methods has been developed to meet the demand for chemically synthesized oligosaccharides and glycopeptides.[2] Still, the synthesis of biologically important glycoconjugates remains a complex and time-consuming task.

A particularly desirable goal would be the development of generally applicable methods for the rapid assembly of oligosaccharides on a solid support with a long-term view toward automation.[3] Solid support oligosaccharide synthesis requires the implementation of stereospecific, high-yielding glycosylation methods which allow for a variety of different naturally occurring linkages to be fashioned. A further challenge to be met is the economic management of competing hydroxyl functionalities. Enzymatic approaches to solid support synthesis have bypassed many of the protecting group requirements in a very elegant way.[4] In recent years a number of approaches have aimed at the transfer of powerful glycosyl donors from the solution phase to the solid support synthesis of oligosaccharides.[3]

Our laboratory has been investigating an approach in which glycals are key building blocks for the synthesis of oligosaccharides and glycoconjugates. This approach proved not only highly effective in the solution phase assembly of oligosaccharides, but has also been adapted to the preparation of oligosaccharides and glycopeptides on a solid support.[5] While this methodology allowed for the construction of β-galactosyl linkages with great efficiency even with hindered glycosyl acceptors, the analogous β-glucosidic linkages could not be prepared as efficiently.

This disparity in capability is in turn related to the glycosyl donating performances of two donor structure types. Thus in the galactose series we take advantage of the relative stability of the epoxy donor type **A** to very mild Lewis acids, particularly anhydrous zinc chloride. The stability serves to advantage, in that it allows for galactosylation of even hindered acceptors (such as C4 hydroxyls flanked by protecting groups at C3 and C6). There being at present no analogously constrained glucosyl epoxy donor, we currently make recourse to donor systems of type **B**. These systems, in the presence of zinc chloride, are highly reactive. Unfortunately, with hindered acceptors of the type discussed above, donor deterioration is competitive with glycosylation. Such a destruction of donor can be ill afforded in our approach to polymer-based syntheses, since the polymer bound donor is growing in complexity and value as the synthesis unfolds.

Being mindful of this shortcoming in both solution- and polymer-based work, we recently introduced an approach which allowed for the conversion of glycals into thioethyl glycosyl donors.[6] Thioethyl glycosyl donors constitute a class of extremely powerful glycosylating agents upon activation with thiophilic reagents.[7] The glycal-derived donors were equipped with a C2 pivaloyl neighboring group and coupled to glycal acceptors to fashion a variety of glycosidic linkages with high efficiency.[6]

Having provided a satisfactory and reiteratable protocol for solution work, we wondered about the possibility of its adaptability to solid phase synthesis. Aside from the important goal of solving the problem of building complex oligosaccharide linkages, the study of this technology transfer from the solution to the solid phase would constitute one of the most elaborate schemes conducted in polymer-supported carbohydrate synthesis. We present here the results of an investigation which achieved the effective conversion of support-bound glycals

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(3) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095 and references therein.

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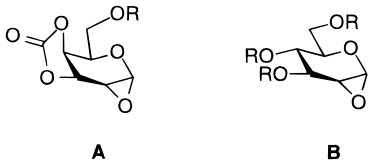
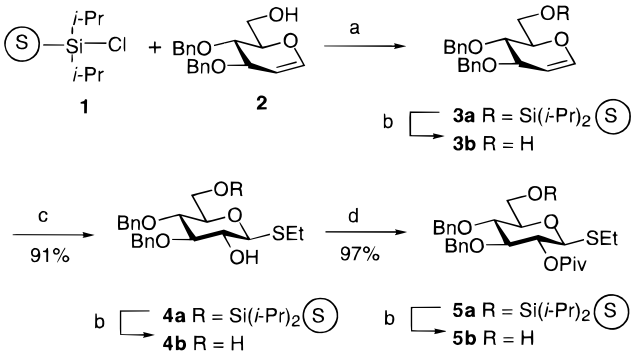


Figure 1.

Scheme 1. Synthesis of a Polymer-Bound Thioethyl Glucosyl Donor[a]



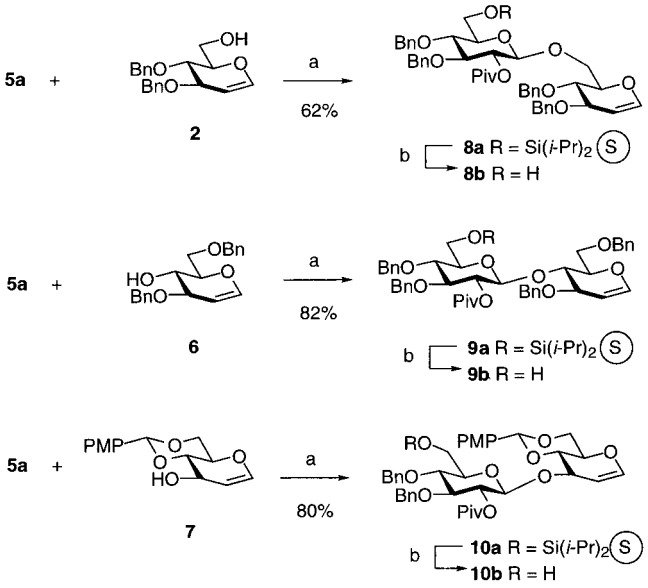
[a] (a) $(i\text{-Pr})_2$NEt, DMAP, CH_2Cl_2, 3 d; (b) TBAF/AcOH (2:1), THF, 40 °C, 18 h; (c) (1) DMDO, CH_2Cl_2, 0 °C, 2.5 h; (2) EtSH, $(CF_3CO)_2O$, −78 °C to rt, CH_2Cl_2; (d) PivCl, DMAP, CH_2Cl_2, rt, 4 h.

into thioethyl glycosyl donors. These donors were subsequently employed in the construction of β-(1→3), β-(1→4), and β-(1→6) glycosidic linkages employing glycal acceptors. Furthermore, this innovative solid phase glycosylation methodology has proven useful in fashioning the synthetically challenging β-(1→2) glycosidic linkage in the preparation of a branched trisaccharide.[8] Finally, the synthesis of a β-(1→4)-linked tetrasaccharide using this methodology has been accomplished. High-resolution magic angle spinning (MAS) NMR was used to rapidly assess the outcome of the transformations.[9]

Results and Discussion

Attachment of protected glycals to polystyrene support via a diisopropyl silyl ether linkage in an efficient manner has provided the basis for the synthesis of oligosaccharides and glycopeptides by our group.[10] While this mode of attachment is stable to all reactions performed, it may be cleaved cleanly and rapidly following established fluoridolysis procedures. Protected glucal **2** was loaded onto silylated polystyrene polymer resin,[11] and the loading was determined at 0.6 mmol/g of resin by cleavage from the solid support. Conversion of **3a** to the protected thioethyl glycosyl donor **5a** closely followed the strategy we recently introduced for the solution phase transformations of glycals into thioethyl glycosyl donors (Scheme 1). Epoxidation with dimethyldioxirane of the support bound glycal **3a** to yield the 1,2 anhydrosugar was

Scheme 2. Synthesis of Disaccharides Using a Polymer-Bound Thioethyl Glucosyl Donor[a]



[a] (a) MeOTf, DTBP, 4 Å MS, CH_2Cl_2, 0 °C to rt 8 h; (b) TBAF/AcOH (2:1), THF, 40 °C, 18 h.

followed by opening of this intermediate by a mixture of ethanethiol and dichloromethane (1:1) in the presence of a trace of trifluoroacetic acid. The thioethyl glycosyl donor **4a** was obtained in 91% yield, which constitutes an improvement over the 78% yield obtained in solution.[6]

In the solution phase, an exhaustive methodology study revealed that thioethyl glycosyl donors with a C2 pivaloyl neighboring group performed superior to other thioethyl glycosyl donors in couplings with glycal acceptors in regard to yield and formation of unwanted side products.[6,12] Accordingly, the thioethyl glycoside **4a** was converted to the pivaloyl-protected thioethyl glycoside **5a** by reaction of pivaloyl chloride in the presence of DMAP in near quantitative yield. The support bound thioglycosides were activated using methyl triflate as a thiophile, while 1 equiv of the nonnucleophilic base di-*tert*-butylpyridine (DTBP) was added to provide stability for the glycal linkage during the coupling experiments. The β-glucosyl (1→4) and β-glucosyl (1→3) linked disaccharides **9a** and **10a** were almost free of contaminating side products and provided the disaccharides in good yields (Scheme 2). Only the formation of the β-glucosyl (1→6)-linked disaccharide **8a** was accompanied by formation of detectable side products. These result almost exclusively from degraded glycosyl donor, but may also contain trace amounts of the undesired α-glycoside linkage. Similar results had previously been obtained in the analogous solution phase systems.[6]

The synthesis of systems with branching from C2 is particularly accessible through this methodology. We demonstrate this facet of the technology in the context of the solid-phase synthesis of **13b**. Thus the C2 pivaloyl neighboring group of the β-glucosyl (1→4)-linked disaccharide **9a** was removed by treatment with DIBAL. The exposed C2 hydroxyl group could now function as the

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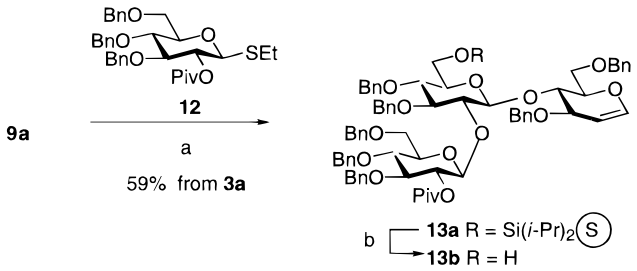
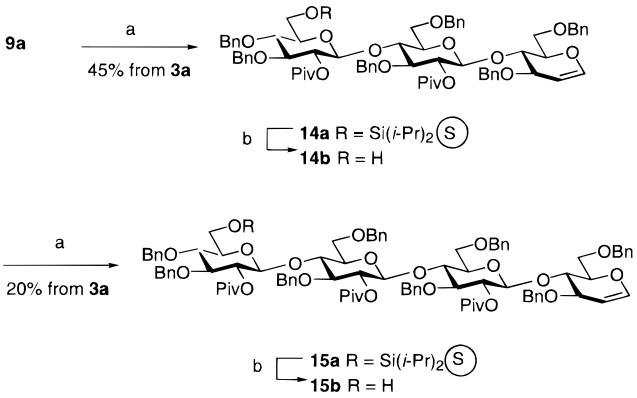
Scheme 3. Synthesis of a Branched Trisaccharide[a]



[a] (a) (1) DIBAL-H, CH_2Cl_2, −78 °C, 5 h; (2) **12**, MeOTf, DTBP, 4 Å MS, CH_2Cl_2, 0 °C → rt, 8 h; (b) TBAF/AcOH (2:1), THF, 40 °C, 18 h.

Scheme 4. Synthesis of a β-(1→4)-Linked Tetrasaccharide[a]



[a] (a) (1) DMDO, CH_2Cl_2, 0 °C; (2) EtSH, $(CF_3CO)_2O$, CH_2Cl_2; (3) PivCl, DMAP, CH_2Cl_2, rt, 4 h; (4) **6**, MeOTf, DTBP, 4 Å MS, CH_2Cl_2, 0 °C to rt 8 h; (b) TBAF/AcOH (2:1), THF, 40 °C, 18 h.

glycosyl acceptor in the synthesis of the branched trisaccharide **13b**. Formation of the synthetically challenging β−(1→2) glycosidic linkage was accomplished in 59% yield when the glycosyl donor **12** was used (Scheme 3).

After an efficient coupling protocol involving support-bound thioethyl glucosyl donors for the synthesis of disaccharides had been established, this methodology was applied to the synthesis of a tetrasaccharide containing exclusively β-(1→4) glucosidic linkages. Transformation of disaccharide glycal **9a** into the C2 pivaloyl thioethyl glycosyl donor was followed by coupling to provide the trisaccharide **14a** in 45% overall yield based on **3a** as determined after cleavage of from the solid support to furnish **14b**. Furthermore, conversion of **14a** to the thioethyl glycosyl donor was followed by coupling to glycal acceptor **6**. The desired tetrasaccharide **15a** was obtained in 20% yield over nine steps from **3a** as determined after cleavage from the support by fluoridolysis. The overall yield corresponds to a yield of 84% per step (Scheme 4).

High resolution magic angle spinning (HR-MAS) NMR proved again to be extremely useful to characterize the solid support bound intermediates of this nine-step synthesis without loss of polymer-bound material.[8] Examination of the ^{1}H HR-MAS NMR spectra provided quick and reliable information about the success of the couplings en route to trisaccharide **14a**. The spectra show the absence of any significant levels of contaminating side products in the support bound "crude products". To further characterize the support bound structures at every step, an analytical amount of each compound was cleaved from the polymeric support, purified by column chromatography, and analyzed by NMR and MS. The yields of all reactions were determined exclusively based on the recovery of purified product in respect to the loading determined at the outset of the synthesis. While connection of the glycosyl acceptor to the solid support allows for the use of excess glycosyl donor (the more fragile reactant), it does require a capping step to prevent the formation of deletion sequences. Even more importantly, the acceptor-bound synthetic strategy does not provide direct synthetic access to glycoconjugates such as glycolipids and glycopeptides. The synthetic logic outlined here results in a terminal glycal which may be further elaborated into glycopeptides[13] or other glycoconjugates. It thereby opens synthetic entry to a variety of target structures of biological importance. These results also clearly demonstrate an important advantage, at least in certian instances, of the use of a support-bound glycosyl donor, namely the absence of deletion sequences. Since any side products stemming from degraded donor are nonreactive in the next glycosylation, a capping step is not needed, and the final purification remains manageable due to the absence of $n - 1$ structures.

In conclusion, a novel protocol for the preparation of thioethyl glycosyl donors from solid support bound glycals has been developed. Coupling of these glycosyl donors to glycal acceptors proceeded in good yields and high stereoselectivity due to the use of a C2 pivaloyl protecting group. This methodological advance now expands the range of glycosidic linkages which may be fashioned using glycal acceptors on a solid support to glucosyl donors. The previously difficultly accessible β-(1→4) glucosydic linkages can now be repeatedly installed as shown by the synthesis of tetrasaccharide **15b**. The methodology seems to be broadly applicable to the generation of powerful solid support bound thioethyl galactosyl and mannosyl donors.[8c] The application of these glycosyl donors in different glycosylation reactions is currently under investigation and will be reported in due course.

Experimental Section

General Methods. All chemicals used were reagent grade and used as supplied except where noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under N_2. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride under N_2. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm). Compounds were visualized by dipping the plates in a cerium sulfate−ammonium molybdate solution followed by heating. Liquid column chromatography was performed using forced flow of the indicated solvent on Sigma H-type silica (10−40 μm). High-resolution magic angle spinning (MAS) NMR spectra were obtained on a Bruker DRX 500 spectrometer equipped with a 4 mm Bruker CCA HR-MAS probe as described before.[8]

Retrieval of Glycals from the Solid Support. General Procedure A. Polymer-bound glucal **3** (60 mg) was suspended in 1 mL of THF before adding 0.2 mL of 1.0 M AcOH in THF and 0.4 mL of 1.0 M TBAF in THF. The mixture was stirred at 40 °C for 18 h, and the polymer was washed using CH_2Cl_2 (2 × 5 mL) and THF (2 × 5 mL). The combined washes were concentrated and purified by column chromatography on silica gel (3:7 EtOAc:hexanes) to give **2** as a colorless gum (12

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mg). The loading of this batch of polymer-bound glycal was determined to be 0.61 mmol of **2** per gram of resin.

Synthesis of Polymer-Bound Ethyl 3,4-Di-*O*-benzyl-1-thio-*β*-D-glucopyranoside 4a. Polymer-bound glycal **3** (1.0 g) was placed in a solid-phase synthesis flask and suspended in anhydrous CH_2Cl_2 (20 mL) under N_2. The suspension was cooled to 0 °C, and 50 mL of dimethyldioxirane solution (ca. 0.1 M in acetone) was added, stirred at 0 °C for 90 min, and filtered. This procedure was repeated, and the polymer was dried for 2 h. The polymer-bound epoxide was suspended in CH_2Cl_2 (10 mL) and EtSH (10 mL) and cooled to −78 °C before being treated with trifluoroacetic anhydride (100 μL), and the mixture was allowed to slowly warm to room temperature over 8 h. The polymer was washed, using THF (4 × 20 mL), and dried in vacuo to give **4a** as a colorless powder. IR (KBr) 3446, 3027, 2926, 1945, 1874, 1793, 1744, 1666, 1599, 1491, 1452, 1362, 1208, 1068, 888 cm^{-1}.

Polymer-bound monosaccharide **4a** (53 mg) was cleaved from the solid support by general procedure A to yield desired product **4b** (11.7 mg, 91.2% from **3a**). R_f = 0.5 (1:1 EtOAc:hexanes); $[\alpha]^{23}_D = -27.1°$ (*c* 0.48, CH_2Cl_2); IR (thin film) 3353, 1453, 1357, 1220, 1127, 1087, 1029 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46−7.26 (m, 10H), 4.95 (d, *J* = 11.3 Hz, 1H), 4.89 (d, *J* = 11.0 Hz, 1H), 4.88 (d, *J* = 11.3 Hz, 1H), 4.66 (d, *J* = 10.9 Hz, 1H), 4.36 (d, *J* = 9.7 Hz, 1H), 3.89−3.86 (m, 1H), 3.71−3.7 (m, 1H), 3.63−3.55 (m, 2H), 3.52−3.50 (m, 1H), 3.42−3.40 (m, 1H), 2.76−2.71 (m, 2H), 2.40 (d, *J* = 1.8 Hz, 1H), 1.31 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.5, 137.9, 128.5, 128.1, 128.0, 127.8, 86.3, 85.8, 79.6, 75.2, 75.1, 73.4, 62.1, 24.6, 15.4; MS (ES^+): 427.3 ($M^+ + Na^+$); (ES^-): 439.2 ($M^- + Cl^-$).

Synthesis of Polymer-Bound Ethyl 3,4-Di-*O*-benzyl-2-*O*-pivaloyl-1-thio-*β*-D-glucopyranoside 5a. Polymer-bound monosaccharide **4a** (1.00 g, 0.56 mmol) was suspended in 10 mL of CH_2Cl_2, and DMAP (0.68 g, 5.6 mmol) and pivaloyl chloride (0.35 mL, 2.8 mmol) were added. The mixture was stirred at room temperature for 4 h. The polymer was filtered, washed using acetone (4 × 20 mL) and THF (3 × 20 mL), and dried in vacuo to give **5a** as colorless powder. IR (KBr) 3459, 3060, 3027, 2925, 2864, 1945, 1874, 1798, 1739, 1600, 1490, 1453, 1364, 1323, 1278, 1138 (br), 883, 793, 697 cm^{-1}.

Compound **5a** (72 mg) was cleaved from the solid support by general procedure A to yield desired product **5b** (18.7 mg, 97.2% yield from **4a**) R_f = 0.4 (3:7 EtOAc:hexanes); $[\alpha]^{23}_D = -33.2°$ (*c* 0.94, CH_2Cl_2): IR (thin film) 3493, 2968, 2927, 2871, 1735, 1454, 1277, 1133, 1036 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34−7.25 (m, 11H), 5.07 (dd, *J* = 9.2, 9.9 Hz, 1H), 4.80 (t, *J* = 10.8 Hz, 2H), 4.72 (d, *J* = 11.0 Hz, 1H), 4.63 (d, *J* = 10.9 Hz, 1H), 4.44 (d, *J* = 10.1 Hz, 1H), 3.91−3.87 (m, 1H), 3.75−3.63 (m, 1H), 3.45 (m, 1H), 2.72−2.65 (m, 2H), 1.94 (t, *J* = 7.3 Hz, 1H), 1.24 (t, *J* = 7.4 Hz, 3H), 1.22 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 176.8, 138.0, 137.8, 128.5, 128.4, 128.04, 127.95, 127.6, 127.3, 84.5, 83.7, 79.6, 77.5, 75.2, 75.1, 71.5, 62.0, 38.7, 27.1, 23.9, 14.9; MS (ES^+): 511.3 ($M^+ + Na^+$); (ES^-): 523.2 ($M^- + Cl^-$). HRMS (FAB) calcd for $C_{27}H_{36}O_6S$: 511.2130, found: 511.2111.

Synthesis of Disaccharides. General Procedure B. Polymer-bound thioethyl glycosyl donor **5a** (200 mg, 0.12 mmol), glycosyl acceptor (5 equiv, 0.6 mmol), and DTBP (20 equiv) were stirred over 200 mg 4 Å molecular sieves in CH_2Cl_2 (10 mL) for 10 min at room temperature. The mixture was cooled to 0 °C, and MeOTf (20 equiv) was added dropwise. The mixture was stirred for 2 h at 0 °C and then slowly warmed to room temperature and stirred for 8 h. Triethylamine (1 mL) was added, and the polymer was filtered. The polymer was suspended in acetone (3 × 20 mL), stirred for several minutes, and then allowed to settle to remove the molecular sieves. The polymer was further washed with DMSO (2 × 20 mL), CH_2Cl_2 (2 × 20 mL), and THF (2 × 20 mL) and dried *in vacuo*. Analytical samples (50−80 mg of polymer) were cleaved from the solid support following general procedure A.

(3,4-Di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranosyl)-(1→6)-1,5-anhydro-2-deoxy-3,4-di-*O*-benzyl-D-*arabino*-hex-1-enitol 8b (62%). R_f = 0.35 (3:7 EtOAc:hexanes); $[\alpha]^{23}_D$ −21.2° (*c* 0.25, CH_2Cl_2); IR (thin film) 3511, 3031, 2872, 1737, 1647, 1454, 1362, 1237, 1086, 739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33−7.25 (m, 20H), 6.36 (d, *J* = 6.2 Hz, 1H), 5.05 (t, *J* = 8.5 Hz, 1H), 4.90−4.89 (m, 1H), 4.81−4.60 (m, 9H), 4.52−4.49 (m, 2H), 4.13 (m, 1H), 4.08 (m, 1H), 4.00 (dd, *J* = 5.8, 2.5 Hz, 1H), 3.83−3.80 (m, 1H), 3.73−3.63 (m, 4H), 3.38 (m, 1H), 1.92 (m, 1H), 1.19 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 176.8, 144.2, 138.2, 138.02, 137.97, 137.8, 128.48, 128.45, 128.43, 128.36, 128.03, 127.93, 127.87, 127.84, 127.71, 127.68, 127.63, 127.4, 101.5, 99.7, 83.0, 77.5, 76.3, 75.4, 75.0, 74.9, 73.8, 72.98, 72.95, 70.3, 68.3, 61.9, 38.8, 27.1; MS (ES^+): 775.5 ($M^+ + Na^+$), (ES^-): 787.5 ($M^- + Cl^-$). HRMS (FAB) calcd for $C_{45}H_{52}O_{10}$: 775.3458; found: 775.3497.

(3,4-Di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranosyl)-(1→4)-1,5-anhydro-2-deoxy-3,6-di-*O*-benzyl-D-*arabino*-hex-1-enitol 9b (82%). R_f = 0.30 (3:7 EtOAc:hexanes); $[\alpha]^{23}_D$ −23.96° (*c* 0.69, CH_2Cl_2); IR (thin film) 3425, 3030, 2964, 2871, 1738, 1649, 1454, 1395, 1277, 1243, 1085, 898, 822 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36−7.25 (m, 20H), 6.39 (d, *J* = 6.1 Hz), 5.02 (t, *J* = 7.9 Hz, 1H), 4.85−4.83 (m, 1H), 4.78−4.72 (m, 2H), 4.67−4.59 (m, 6H), 4.53−4.51 (d, *J* = 12 Hz, 1H), 4.13−4.12 (m, 2H), 4.05 (m, 1H), 3.80−3.56 (m, 7H), 3.30 (m, 1H), 1.15 (s, 9H); ^{13}C NMR δ 176.7, 144.6, 138.5, 138.0, 137.8, 128.5, 128.45, 128.41, 128.35, 127.95, 127.90, 127.86, 127.61, 127.36, 127.3, 99.9, 99.3, 82.9, 77.6, 77.3, 76.7, 75.9, 75.2, 74.9, 74.8, 73.6, 73.0, 73.0, 72.8, 70.4, 67.9, 61.7, 38.8, 27.2; MS (ES^+): 775.6 ($M^+ + Na^+$), (ES^-): 787.5 ($M^- + Cl^-$). HRMS (FAB) calcd for $C_{45}H_{52}O_{10}$: 775.3458, found: 775.3468.

(3,4-Di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranosyl)-(1→3)-1,5-anhydro-2-deoxy-4,6-*O*-(4-methoxybenzylidene)-D-*arabino*-hex-1-enitol 10b (80%). R_f = 0.40 (3:7 EtOAc:hexanes); $[\alpha]^{23}_D$: −56.52° (*c* 0.85, CH_2Cl_2); IR (thin film) 3497, 2966, 2872, 1737, 1644, 1614, 1517, 1457, 1367, 1306, 1172, 1089, 831 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41 (d, *J* = 8.7 Hz, 2H), 7.31−7.22 (m, 11H), 6.89 (dd, *J* = 6.8, 1.9 Hz, 2H), 6.35 (dd, *J* = 6.1, 1.4 Hz, 1H), 5.55 (s, 1H), 5.03 (t, *J* = 8.0 Hz, 1H), 4.76−4.73 (m, 2H), 4.68−4.66 (m, 2H), 4.63 (d, *J* = 7.9 Hz, 1H), 4.57 (d, *J* = 10.9 Hz, 1H), 4.43 (m, 1H), 4.33 (m, 1H), 3.97 (m, 1H), 3.83−3.52 (m, 9H), 3.25 (m, 1H), 1.90 (m, 1H), 1.20 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 176.7, 160.21, 145.0, 138.0, 137.7, 129.6, 128.5, 128.3, 128.1, 127.9, 127.6, 127.4, 113.7, 101.6, 101.1, 100.2, 82.9, 78.7, 77.5, 75.2, 75.1, 74.9, 74.4, 73.3, 68.7, 68.2, 61.8, 55.3, 38.8, 27.2; MS (ES^+): 713.3 ($M^+ + Na^+$), (ES^-): 725.4 ($M^- + Cl^-$). HRMS (FAB) calcd for $C_{39}H_{46}O_{11}$: 713.2938, found: 713.2909.

Synthesis of 3,4-Di-*O*-benzyl-*β*-D-glucopyranosyl-(1→2)-[3,4,6-tri-*O*-benzyl-*β*-D-glucopyranosyl-(1→4)]-1,5-anhydro-2-deoxy-3,6-di-*O*-benzyl-D-*arabino*-hex-1-enitol 14. In a solid-phase synthesis flask **9a** (217 mg, 0.14 mmol) was suspended in anhydrous CH_2Cl_2 (15 mL), cooled to −78 °C, and treated with DIBAL in toluene (0.7 mL, 5 equiv). The mixture was stirred at −78 °C for 5 h, quenched with saturated sodium potassium tartarate, and filtered. The polymer was washed with H_2O (2 × 20 mL), acetone (4 × 15 mL), and CH_2Cl_2 (4 × 15 mL) and dried in vacuo for 2 h. To the polymer-bound alcohol were added 4 Å molecular sieves (450 mg) and a solution of **12** (470 mg, 0.81 mmol, 5 equiv) in CH_2Cl_2 (20 mL). The suspension was cooled to 0 °C before being treated with MeOTf (460 μL, 5 equiv) and DTBP (912 μL, 5 equiv), and the mixture was allowed to slowly warm to room temperature and stirred for 8 h. The reaction was quenched with Et_3N and filtered. The polymer was suspended in acetone (3 × 20 mL), stirred for several minutes, and allowed to settle in order to remove the molecular sieves. The acetone was decanted, and the polymer was washed with DMSO (2 × 20 mL), CH_2Cl_2 (2 × 20 mL), and THF (2 × 20 mL) and dried in vacuo for 2 h to give **13a** as a colorless powder. The polymer **13a** was treated according to general procedure A to provide **13b** (81% from **9a**). R_f = 0.35 (3:7 EtOAc:hexanes); $[\alpha]^{23}_D$ −11.67° (*c* 0.60, CH_2Cl_2); IR (thin film) 3453, 3062, 3030, 2922, 2869, 1737, 1649, 1454, 1362, 1208, 1081, 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37−7.23 (m, 41H), 7.17−7.15 (m, 2H), 6.35 (d, *J* = 6.1 Hz, 1H), 5.16 (t, *J* = 9.2 Hz, 1H), 5.02 (d, *J* = 8.0 Hz, 1H), 4.83 (m, 3H), 4.74−4.49 (m, 15H), 4.16−4.06 (m, 3H), 3.92 (m, 2H), 3.83−3.42 (m, 11H), 3.18−3.16 (m, 1H), 1.85 (m, 1H), 1.15 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 176.7, 144.0, 138.8, 138.5, 138.1, 137.8, 137.7, 138.5, 138.3, 138.1, 137.85, 137.78, 128.57,

128.51, 128.44, 128.40, 128.35, 128.32, 128.06, 127.91, 127.81, 127.63, 127.57, 127.43, 127.15, 127.12, 101.25, 100.16, 85.6, 83.2, 78.2, 77.3, 76.7, 75.5, 75.0, 74.8, 73.8, 72.8, 69.8, 38.8, 27.3; MS (ES^+): 1207.7 ($M^+ + Na^+$), (ES^-): 1219.6 ($M^- + Cl^-$). HRMS (FAB) calcd for $C_{72}H_{80}O_{15}$: 1207.5395; found: 1207.5381.

(3,4-Di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranosyl-(1→4)-(3,6-di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranosyl)-(1→4)-1,5-anhydro-2-deoxy-3,6-di-*O*-benzyl-D-*arabino*-hex-1-enitol 14b (45% from 3a). $R_f = 0.40$ (3:7 EtOAc:hexanes); $[\alpha]^{23}_D$ −36.13° (*c* 0.32, CH_2Cl_2); IR (thin film) 3030, 2964, 2924, 2869, 1738, 1650, 1455, 1364, 1276, 1135, 1084, 738; ^{1}H NMR ($CDCl_3$) δ 7.34−7.19 (m, 35H), 6.38 (d, $J = 6.1$ Hz, 1H), 5.01−4.93 (m, 3H), 4.83−4.75 (m, 2H), 4.69−4.49 (m, 11H), 4.39−4.31 (m, 2H), 4.14−4.03 (m, 4H), 3.84−3.81 (m, 1H), 3.72−3.68 (m, 2H), 3.62 (d, $J = 12$ Hz, 1H), 3.56−3.37 (m, 4H), 3.25−3.11 (m, 3H), 1.14 (s, 9H), 1.12 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 176.7, 176.6, 144.0, 138.9, 138.7, 138.0, 137.9, 137.81, 137.77, 128.60, 128.41, 128.37, 128.29, 128.17, 128.09, 127.97, 127.80, 127.59, 127.42, 127.4, 127.1, 126.3, 100.2, 99.5, 82.8, 80.6, 77.9, 77.3, 77.0, 76.7, 75.8, 75.2, 75.0, 74.9, 74.7, 74.4, 73.7, 73.3, 73.0, 72.4, 70.7, 68.0, 67.6, 61.4, 38.8, 38.7, 29.7, 27.3, 27.2; MS (ES^+): 1201.8 ($M^+ + Na^+$), (ES^-): 1213.8 ($M^- + Cl^-$). HRMS (FAB) calcd for $C_{70}H_{82}O_{16}$: 1201.5501, found: 1201.5487.

(3,4-Di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranosyl-(1→4)-(3,6-di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranosyl-(1→4)-(3,6-di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranosyl-(1→4)-1,5-anhydro-2-deoxy-3,6-di-*O*-benzyl-D-*arabino*-hex-1-enitol 15b (20% from 3a). $R_f = 0.45$ (3:7 EtOAc:hexanes); $[\alpha]^{23}_D$ −50.0° (*c* 0.30, CH_2Cl_2); IR (thin film) 2965, 1738, 1651, 1456, 1364, 1276, 1135, 1086, 803 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34−7.13 (m, 49H), 6.37 (d, $J = 6.1$ Hz, 1H), 5.16 (d, $J = 11.9$ Hz, 1H), 5.02 (t, $J = 11.2$ Hz, 1H), 4.97−4.92 (m, 3H), 4.80 (m, 1H), 4.75 (d, $J = 11.5$ Hz, 1H), 4.69−4.46 (m, 12 H), 4.35−4.24 (m, 4H), 4.15−4.03 (m, 5H), 3.99−3.93 (m, 2H), 3.82 (m, 1H), 3.77−3.65 (m, 5H), 3.62−3.58 (m, 2H), 3.52−3.40 (m, 6H), 3.26−3.05 (m, 5H), 1.11 (s, 18 H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 176.8, 176.59, 176.56, 144.4, 139.1, 138.8, 138.73, 138.02, 137.95, 137.88, 137.77, 137.6, 128.7, 128.54, 128.46, 128.41, 128.37, 128.33, 128.27, 128.2, 128.04, 128.0, 127.9, 127.77. 127.7. 127.6, 127.5, 127.35, 127.1, 126.7, 126.0, 100.1, 99.52, 99.47, 99.4, 82.8, 81.2, 80.4, 77.9, 76.7, 75.8, 75.5, 75.4, 75.1, 75.0, 74.9, 74.7, 74.4, 74.3, 73.7, 73.6, 73.3, 73.3, 72.8, 72.8, 72.5, 72.2, 70.6, 67.9, 67.5, 67.4, 61.4, 38.8, 38.7, 38.6, 27.3, 27.2, 27.0; MS (ES^+): 1629.1 ($M^+ + Na^+$), (ES^-): 1641.1 ($M^- + Cl^-$). HRMS (FAB) calcd for $C_{95}H_{112}O_{22}$: 1627.7543; found: 1627.7626.

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Supporting Information Available: NMR spectra for compounds **4b**, **5a**, **5b**, **8b**, **9a**, **9b**, **10b**, **13b**, **14a**, **14b**, **15b** (19 pages). This material is contained in 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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