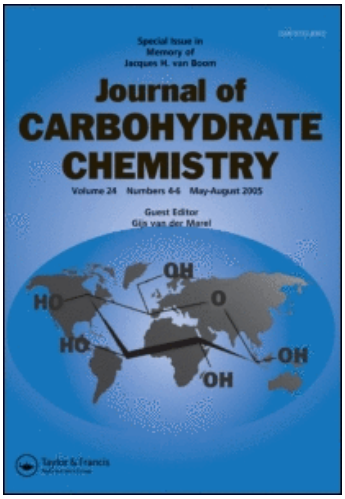

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Synthesis of the C-Glycoside of Methyl α-D-Altropyranosyl-(1→4)-α-D-glucopyranoside†

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ABSTRACT

The C-glycoside of methyl α-D-altropyranosyl-(1→4)-α-D-glucopyranoside **2** was prepared in a convergent fashion, from readily available precursors, 4-*O*-*tert*-butyldiphenylsilyl-1,2-*O*-isopropylidene-D-*erythro*-*S*-phenyl monothiohemiacetal **13** (five steps from D-ribose) and the known acid, methyl 2,3,6-tri-*O*-benzyl-4-*C*-(carboxymethyl)-4-deoxy-α-D-glucopyranoside **17** (seven steps from methyl α-D-glucopyranoside). The key reactions in the synthesis are the oxocarbenium ion cyclization of thioacetal-enol ether **19** to a C1 substituted glycal **20**, and the stereoselective hydroboration of **20** to the α-C-altroside **21**.

Key Words: C-glycoside; Disaccharide; Glycomimetic; Altrose; Allose; Conformation.

INTRODUCTION

Interest in disaccharide analogues as specific inhibitors of glycosidases and glycosyl transferases is based on the notion that they may act as bisubstrate-type transition state mimetics.[1,2] This represents a somewhat oversimplified model because other aspects of the transition state structure such as the involvement of active site residues

†This paper is dedicated to Professor Gérard Decotes on the occasion of his 70th birthday.

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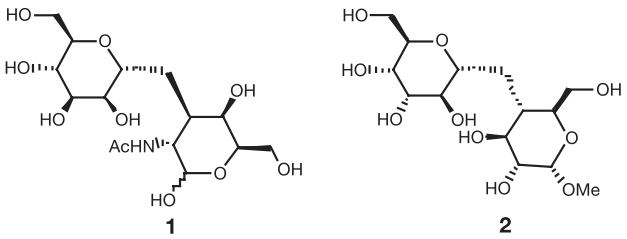

Figure 1.

and sugar nucleotide components, are not incorporated.[3–8]ab Notwithstanding this issue, simple disaccharide probes continue to be popular because of their potential to provide information on the minimal requirements for recognition. In this regard, disaccharide analogues[9–13]c with ''unnatural'' glycone and aglycone substitutes are of interest. C-glycosides have additional appeal because of their hydrolytic stability, and their subtle conformational differences compared with O-glycosides.[12–21] These principles are embodied in a recent investigation on the C-disaccharide of α-D-mannopyranosyl-(1→3)-*N*-acetylgalactosamine **1**.[9]c Compound **1** was found to be a good bisubstrate inhibitor of human α-(1,3)-fucosyltransferase VI (which catalyzes the transfer of GDP-fucose to *N*-acetyllactosamine). Presumably, the α-L-fucopyranosyl and the D-GlcNAc binding sites of the enzyme are homogeneous with the respective binding regions for the C-α-D-mannopyranosyl and the D-GalNAc residues of **1** (Figure 1).

Against this backdrop, we have shown that 1-thio-1,2-*O*-isopropylidene acetals (TIAs) are precursors to β-C-galactodisaccharides.[22,23] Herein, in the preparation of the C-glycoside of methyl α-D-altropyranosyl-(1→4)-α-D-glucopyranoside **2**, we illustrate the suitability of this methodology to the synthesis of C-disaccharides with unusual glycone segments. This investigation is also pertinent to the altromycins, a naturally occurring class of aryl-α-C-altrosides.[24]

Our synthesis of the β-C-galactoside **3** centered on the methyl triflate promoted cyclization of the thioacetal-enol ether **6** to the C1-substituted glycal **4**. This reaction presumably proceeds via a dioxolenium ion intermediate. Notably, the other double bond regioisomer or the acetal stereoisomer was not observed. Hydroboration of **4** led to a single C-glycoside of β-galacto stereochemistry. The cyclization precursor **6** was assembled from the TIA alcohol **7** and the requisite acid **8** over two steps, esterification of **7** and **8** followed by Tebbe olefination of ester **5**. This sequence is convergent from the glycone and aglycone segments and is general for β-C-galactosides. We anticipated that extension of these concepts to diastereomeric TIA alcohol **13**, should lead to the corresponding structures **10** and **9**, thereby constituting a general route to α-C-altrosides (Scheme 1).

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[a]For transferase inhibitors containing glycosyl donor and sugar nucleotide residues, see: Refs. [3–5].
[b]For tricomponent, bisubstrate analogues, see: Refs. [6] and [7].
[c]For a more complex, two component bisubstrate inhibitor of an α-1,3-fucosyltransferase, see: Ref. [10].

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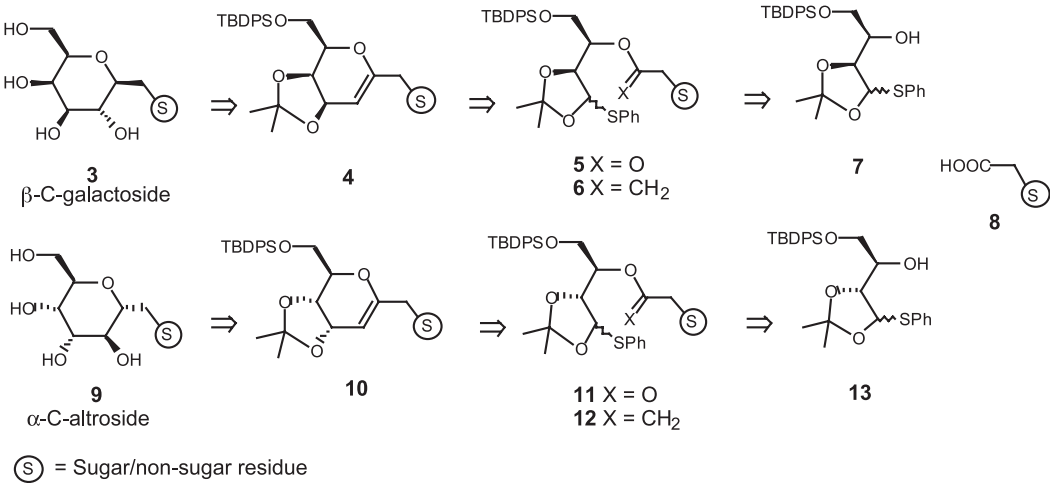
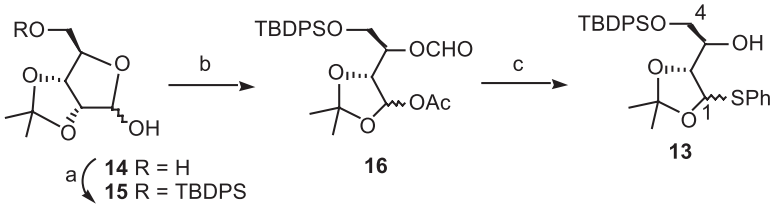


Scheme 1.

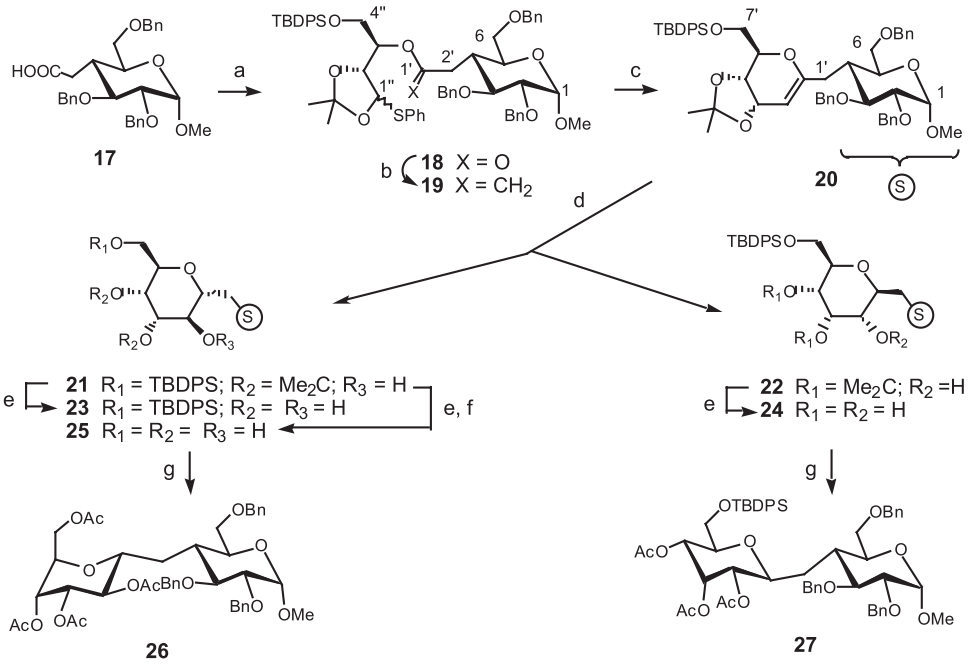
RESULTS AND DISCUSSION

The TIA segment **13** for the C-altroside synthesis was obtained through the identical methodology that was used for the TIA in the C-galactoside series.[23] Thus 2,3-*O*-isopropylidene-D-ribofuranose **14**[25] was converted to the silyl ether **15**, and this material treated with diacetoxyiodosobenzene and iodine, according to the Suarez protocol.[26] The resulting 1-*O*-acetyl-1,2-*O*-isopropylidene **16** was exposed to thiophenol and $BF_3 \cdot OEt_2$ at $-78^{\circ}C$, and the crude reaction mixture subjected to basic hydrolysis of the formate ester. This sequence provided TIA alcohol **13** in 81% yield from **16**. The configuration of the acetal carbon in **13** was not determined (Scheme 2).

The aglycone segment **17** for the title C-altroside, was obtained by hydrolysis of the known ethyl ester derivative.[27,28] DCC mediated esterification of alcohol **13** and acid **17** afforded ester **18**, which was transformed to enol ether **19** by treatment with the Tebbe reagent (Scheme 3). The key cyclization step on **19** was promoted by methyl triflate in the presence of 2,6-di-*tert*-butyl-4-methylpyridine, and led to C1 substituted glycal **20** in 70% yield. Hydroboration of **20** provided an approximately 5:1 ratio of two stereoisomers **21** and **22**, in a combined yield of 84%. Chromatography of this mixture

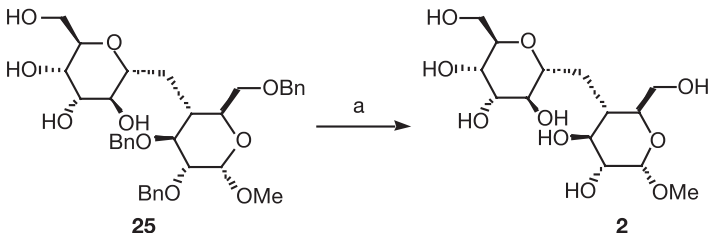


Scheme 2. (a) TBDPSCl, DMF, imidazole, 87%; (b) diacetoxyiodoso-benzene, I_2, cyclohexane, 77%; (c) (i) PhSH, CH_2Cl_2, $BF_3 \cdot OEt_2$, $-78^{\circ}C$; (ii) NaOMe, MeOH, 88%.



Scheme 3. (a) **13**, DCC, DMAP, PhH, 85%; (b) Tebbe, 60%; (c) MeOTf, DTBMP, CH_2Cl_2, 70%; (d) $BH_3 \cdot DMS$ then Na_2O_2, 63%; (e) HCl, MeOH; (f) Bu_4NF, THF; (g) Ac_2O, DMAP, EtOAc.

provided partial separation, giving a sample of pure **21** and an unseparated mixture of **21** and **22**. The stereochemistry of **21** was determined by ^1H NMR analysis of tetraacetate **26**. Compound **26** was obtained by sequential removal of isopropylidene and silyl ether protecting groups in **21**, followed by acetylation of the derived tetraol **25**. The J values ($J_{2',3'} = J_{3',4'} = 8.5$, $J_{4',5'} = 2.5$, $J_{5',6'} < 2.0$ Hz) for **26** were in agreement with an α-C-altroside in primarily the $^1C_4$ conformation.[29] The minor product **22**, was characterized as the triacetate **27**. Thus, acid hydrolysis of the mixture of hydroboration products **21** and **22**, provided an easily separable mixture of the corresponding triols **23** and **24**. Acetylation of **24** provided **27**. The data for **27** ($J_{2',3'} = 9.5$, $J_{3',4'} = J_{4',5'} = 2.0$, $J_{5',6'} = 9.9$ Hz) supported a β-alloside in the $^4C_1$ conformation,[30] a result that is consistent with the stereochemistry of the hydroboration reaction.



Scheme 4. (a) H_2, Pd/C, MeOH, 80%.

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The targeted *altro*-α-C-disaccharide **2** was obtained by the straightforward processing of the major component **21** from the mixture of hydroboration products (Scheme 4). Thus, hydrogenolysis of the aforementioned tetraol **25**, provided **2**. The structure of **2** was confirmed by ^{1}H and ^{13}C NMR and HRMS data. The stereochemical integrity of **2** resides in the assignment of the aforementioned tetraacetate derivative **26**. Unfortunately, poor signal resolution in the ^{1}H NMR of **2** did not allow for conformational analysis of the altropyranoside residue.

In summary, the synthesis of **2**, taken together with earlier studies, illustrates that the TIA C-glycoside methodology may be used for the stereoselective synthesis of β-C-*galacto*- and α-C-*altro*-disaccharides. An attractive feature is the convergent nature of this strategy, which allows for incorporation of different aglycone subunits. Elaboration of the intermediate disaccharide glycal intermediates provides additional possibilities for variation of the glycone segment. These attributes are especially relevant to the synthesis of libraries of C-disaccharides with unusual substitution patterns.

EXPERIMENTAL

General methods. Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere in oven-dried glassware using standard syringe and septa technique. Diethyl ether and THF were distilled from sodium or potassium/benzophenone ketyl under N_2 immediately prior to use. Dry CH_2Cl_2 was obtained by distilling over P_2O_5. Dry DMF was distilled from $CaSO_4$ under reduced pressure. Anhydrous benzene and toluene were obtained by azeotropic removal of water.

^{1}H and ^{13}C NMR spectra were obtained using a GE QE 300 (300 MHz) or Varian Unity Plus 500 (500 MHz) spectrometer. Chemical shifts are relative to the deuterated solvent peak or the tetramethylsilane (TMS) peak at (δ 0.00) and are in parts per million (ppm). The ^{1}H and ^{13}C NMR spectra were recorded at either 300 or 500 MHz and 75 MHz, respectively. Assignments for selected nuclei were determined from ^{1}H COSY experiments. The assignments for signals that are marked with an asterisk (*) are interchangeable.

High resolution mass spectroscopy was performed at the Mass Spectrometry Facility at University of Illinois, Urbana. Infrared (IR) spectra were recorded for neat films or $CHCl_3$ solutions on a Perkin-Elmer 710B spectrometer and are reported in cm^{-1}. Thin-layer chromatography (TLC) was done on 0.25 mm thick precoated silica gel HF_{254} (Whatman) aluminum sheets. The chromatograms were observed under UV light and/or were visualized by heating plates that were dipped in ammonium molybdate solution. Flash column chromatography (FCC) was performed using silica gel 60 (230–400 mesh) and employed a stepwise solvent polarity gradient, correlated with TLC mobility.

2,3-*O*-Isopropylidene-5-*O*-*tert*-butyldiphenylsilyl-α/β-D-ribofuranose (15). A solution of 2,3-*O*-isopropylidene-D-ribofuranose **14**[25] (7.86 g, 41.0 mmol), TBDPSCl (11.4 mL, 41.0 mmol), and imidazole (5.64 g, 85.0 mmol) in anhydrous DMF (100 mL) was stirred at 50°C for 1.5 h. The reaction mixture was then diluted with water and extracted with ether. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by FCC to give an inseparable mixture **15α/β** (15.2 g, 87%) as a colorless oil; R_f = 0.42 (20% EtOAc/petroleum ether); IR (neat) 3423 cm^{-1}. Compound **15β** had ^{1}H

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NMR (300 MHz, $CDCl_3$) δ 1.06 [s, 9H, $(CH_3)_3CSi$], 1.33, 1.48 [both s, 3H ea, $C(CH_3)_2$], 3.66 (dd, J = 2.6, 11.4 Hz, 1H, H-5a), 3.83 (dd, J = 2.6, 11.4 Hz, 1H, H-5b), 4.29 (bs, 1H, H-4), 4.54 (d, J = 10.6 Hz, D_2O ex, 1H, OH), 4.61 (d, J = 6.2 Hz, 1H, H-3), 4.72 (d, J = 5.9 Hz, 1H, H-2), 5.38 (d, J = 10.3 Hz, 1H, H-1), 7.43–7.80 (m, 10H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 26.8 [$C(CH_3)_2$], 27.2 $(CH_3)_3CSi$], 65.8, 82.0, 87.4, 87.5 (4C, C-2, 3, 4, 5), 103.6 (C-1), 112.3 [$C(CH_3)_2$], 128.0–135.9 (Ph). Compound **15α** had ^1H NMR (300 MHz, $CDCl_3$) δ (selected signals) 1.06 [s, 9H, $(CH_3)_3CSi$], 1.41, 1.56 [both s, 3H ea, $C(CH_3)_2$], 3.94 (d, J = 11.4 Hz, 1H, D_2O ex, OH), 4.16 (bs, 1H, H-4), 5.67 (dd, J = 4.0, 11.4 Hz, 1H, H-1). ^{13}C NMR δ 25.1, 26.5 [$C(CH_3)_2$], 27.2 $(CH_3)_3CSi$], 66.2, 79.8, 81.6, 82.2 (4C, C-2, 3, 4, 5), 98.2 (C-1), 113.3 [$C(CH_3)_2$]. Mixture **15α/β** had HRMS(EI) *m/z* calcd for $C_{23}H_{29}O_5Si$ (M-CH_3) 413.1784. Found 413.1777.

1-*O*-Acetyl-4-*O*-*tert*-buty1diphenylsilyl-3-*O*-formyl-1,2-*O*-isopropylidene-D-*erythro*-hemiacetal (16). A solution of compound **15** (5.82 g, 13.6 mmol) in anhydrous cyclohexane (90 mL) containing diacetoxyiodosobenzene (4.39 g, 15.2 mmol) and iodine (3.45 g, 13.5 mmol) was stirred under an atmosphere of argon at rt for 4 h. The reaction mixture was then diluted with water and extracted with ether. The organic phase was washed with aq $Na_2S_2O_3$ and brine, then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was separated by FCC to give major (4.00 g, 61%) and minor (1.08 g, 16%) isomers of **16**. The major isomer was isolated as a white solid; R_f = 0.23 (5% EtOAc/petroleum ether); IR (film) 1732, 1752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 9H, $(CH_3)_3CSi$], 1.41, 1.50 [both s, 3H ea, $C(CH_3)_2$], 2.04 (s, 3H, CH_3CO), 3.91 (m, 2H, H-4a, 4b), 4.52 (dd, J = 1.8, 5.9 Hz, 1H, H-2), 5.18 (q, J = 4.8 Hz, 1H, H-3), 6.27 (d, J = 1.8 Hz, 1H, H-1), 7.38-7.70 (m 10H, Ph), 8.02 (s, 1H, HCO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9 (CH_3CO), 27.5, $(CH_3)_3CSi$, $C(CH_3)_2$,1C], 28.1 [$C(CH_3)_2$,1C), 62.9, 73.4, 81.2 (3C, C-2, 3, 4), 96.8 (C-1), 113.6 [$C(CH_3)_2$], 128.4, 130.4, 133.6, 136.2 (Ph), 160.3 (HCO), 170.2 (CH_3CO). HRMS (EI) *m/z* calcd for $C_{24}H_{31}O_5Si$ (M–$C_2H_3O_2$) 427.1941. Found 427.1932.

The minor isomer was isolated as a colorless oil; R_f = 0.28 (5% EtOAc/petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.42, 1.51 [both s, 3H ea, $C(CH_3)_2$], 2.04 (s, 3H, CH_3CO), 3.98 (m, 2H, H-4a,b), 4.54 (dd, J = 3.3, 9.2 Hz, 1H, H-2), 5.33 (m, 1H, H-3), 6.33 (d, J = 3.3 Hz, 1H, H-1), 7.40–7.70 (m 10H, Ph), 7.91 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3 (CH_3CO), 26.3 [$C(CH_3)_2$, 1C], 27.1 $(CH_3)_3CSi$], 28.4 [$C(CH_3)_2$, 1C], 63.4, 71.3, 76.0 (3C, C-2, 3, 4), 93.5 (C-1), 112.7 [$C(CH_3)_2$], 127.8, 129.9, 133.3, 135.7 (Ph), 159.5 (HC = O), 170.0 (CH_3C = O). ESMS m/z 504.3 $[M + NH_4]^+$.

4-*O*-*tert*-Butyldiphenylsilyl-1,2-*O*-isopropylidene-D-*erythro*-*S*-phenyl monothiohemiacetal (13). $BF_3 \cdot OEt_2$ (1.60 mL, 12.7 mmol) was slowly added to a solution of **16** (4.10 g, 8.4 mmol) and thiophenol (2.16 mL, 21.1 mmol) in anhydrous CH_2Cl_2 (40 mL) at −78°C under an atmosphere of argon. The reaction was warmed to −40°C and stirred at this temperature for 1 h, or until TLC indicated complete disappearance of the starting material. Triethylamine (6.0 mL) was then added, and the reaction mixture was diluted with satd aq $NaHCO_3$ and extracted with ether. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was dissolved in methanol (50 mL) and treated with a solution of NaOMe in methanol at rt for 30 min. Most of the solvent was then removed under reduced pressure. FCC of the residue provided **13** (3.49 g, 81%) as a colorless oil; R_f = 0.42 (10% EtOAc/petroleum ether); IR (neat) 3485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9H,

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$(CH_3)_3CSi$], 1.40, 1.53 [both s, 3H ea, $C(CH_3)_2$], 2.55 (d, J = 4.4 Hz, 1H, D_2O ex, OH), 3.81 (m, 3H, H-4a, 4b, H-3), 4.18 (t, J = 5.7 Hz, 1H, H-2), 5.58 (d, J = 5.5 Hz, 1H, H-1), 7.26–7.71 (m, 15H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3 [$C(CH_3)_2$, 1C], 26.8 $(CH_3)_3CSi$), 27.1 ($CH_3)_3CSi$), 27.8 [$C(CH_3)_2$, 1C], 64.6, 72.4, 81.2 (3C, C-2, 3, 4), 86.0 (C-1), 111.7 [$C(CH_3)_2$], 127.2–135.6 (Ph). HRMS(EI) *m/z* calcd for $C_{23}H_{31}O_4Si$ (M–SPh) 399.1992. Found 399.1996.

Methyl 2,3,6-tri-*O*-benzyl-4-*C*-(carboxymethyl)-4-deoxy-α-D-glucopyranoside (17). The ethyl ester of **17**[27] (7.20 g, 10.0 mmol) was treated with a 1:1 mixture of aq 3N NaOH:ethanol (120 mL). After 4 h most of the ethanol was removed under reduced pressure. The resulting mixture was acidified with concentrated HCl to pH 4-5 and extracted with ethyl acetate. The combined organic layer was concentrated in vacuo. The residue was purified by FCC to give unreacted starting material and acid **17** (3.63g, 86% based on recovered starting material) as a colorless oil; R_f = 0.49 (40% EtOAc/petroleum ether); IR (film) 2500–3200 (br), 1707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.03 (m, 2H, H-4, H-2′a), 2.57 (dd, J = 5.5, 16.5 Hz, 1H, H-2′b), 3.38 (s, 3H, OCH_3), 3.61, 3.83 (both m, 3H, 2H resp, H-2, 3, 5, 6a, 6b), 4.47 (d, J = 11.7 Hz, 1H, PhC*H*), 4.57–4.81 (m, 5H, H-1, 4 × PhC*H*), 5.02 (d, J = 11.0 Hz, 1H, PhC*H*), 7.20–7.35 (m, 15H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.9, 41.2 (C-4, 2′), 56.1 (OCH_3), 70.4, 70.9, 73.7, 74.2, 76.0, 78.6, 82.4 (7C, C-2, 3, 5, 6, PhCH_2), 99.2 (C-1), 128.2–139.3 (Ph), 178.7 (C = O). HRMS(FAB) *m/z* calcd for $C_{30}H_{34}O_7Na$ $[M + Na]^+$ 529.2201. Found 529.2202.

Methyl 2,3,6-tri-*O*-benzyl-[(4-*C*-(4-*O*-*tert*-buty1diphenylsilyl-1,2-*O*-isopropylidene-D-*erythro*-*S*-phenyl monothiohemiacetal)-2-ethanoate]-4-deoxy-α-D-glucopyranoside (18). DCC (2.71 g, 13.15 mmol) was added at 0°C to a solution of alcohol **13** (2.67 g, 5.26 mmol), acid **17**, (3.63 g, 7.17 mmol), and DMAP (128 mg, 1.05 mmol) in anhydrous benzene (50 mL). The reaction was warmed to rt and stirred for 2 h. The mixture was then diluted with ether (20 mL) and filtered. The filtrate was washed with 0.1 N aq HCl and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by FCC to give **18** (4.47 g, 85%) as a colorless oil; R_f = 0.42 (20% EtOAc/petroleum ether); IR (neat) 1734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.00 [s, 9H, $(CH_3)_3CSi$], 1.31, 1.42 [both s, 3H ea, $C(CH_3)_2$], 2.26 (m, 2H, H-4, 2′a), 2.55 (m, 1H, H-2′b), 3.10 (s, 3H, OCH_3), 3.33 (m, 1H, H-1), 3.52 (m, 2H, H-6a, 6b), 3.79 (m, 4H, H-3, 5, 4a, 4b), 4.31 (t, J = 6.0 Hz, 1H, H-2″), 4.39 (d, J = 12.0 Hz, 1H, PhC*H*), 4.51 (m, 3H, 3 × PhC*H*), 4.61 (d, J = 11.0 Hz, 1H, PhC*H*), 4.62 (d, J = 4.0 Hz, 1H, H-1), 4.89 (m, 1H, H-3″), 4.91 (d, J = 11.0 Hz, 1H, PhC*H*), 5.37 (d, J = 6.5 Hz, 1H, H-1″), 7.10–7.70 (m, 30 H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7 [$C(CH_3)_2$, 1C], 27.6 ($CH_3)_3CSi$), 28.1 [$C(CH_3)_2$, 1C], 33.5 (C-2′), 41.2 (C-4), 55.9 (OCH_3), 62.8 (C-4″), 70.6, 71.1, 73.5, 74.1, 74.4, 75.9, 78.9, 79.5, 82.5 (9C, C-2, 3, 5, 6, 2″, 3″, PhCH_2), 85.6 (C-1″), 99.1 (C-1), 112.2 [$C(CH_3)_2$], 127.8–139.3 (Ph), 171.6 (C = O). HRMS (FAB) *m/z* calcd for $C_{59}H_{68}O_{10}SSiNa$ $[M + Na]^+$ 1019.4203. Found 1019.4200.

Methyl 2,3,6-tri-*O*-benzyl-4-*C*-[(4-*O*-*tert*-buty1diphenylsilyl-1,2-*O*-isopropylidene-D-*erythro*-*S*-phenyl monothiohemiacetal)-2-propene]-4-deoxy-α-D-glucopyranoside (19). A solution of Tebbe reagent[31,32]d in THF (9.3 mL, 0.5 M, 4.7 mmol),

[d]The Tebbe reagent used in this research was purchased from Sigma-Aldrich Inc.

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was added dropwise, under an atmosphere of argon at −78°C, to ester **18** (1.82 g, 1.86 mmol) and pyridine (0.15 mL) in anhydrous 3:1 toluene/THF (20 mL). The reaction mixture was warmed to rt, stirred for 2 h, and then slowly poured into a solution of 1 N aq NaOH at 0°C. The resulting suspension was extracted with ether, and the organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by FCC on basic alumina (Brockmann I, 150 mesh) to give enol ether **18** (1.09 g, 60%) as a colorless oil, R_f = 0.61 (15% EtOAc/petroleum ether); ^{1}H NMR (300 MHz, C_6D_6) δ 1.10 [s, 9H, $(CH_3)_3CSi$], 1.47, 1.62 [both s, 3H ea, $C(CH_3)_2$], 2.30 (dd, J = 4.8, 14.5 Hz, 1H, H-2′a), 2.40 (m, 1H, H-4), 2.69 (dd, J = 3.6, 14.5 Hz, 1H, H-2′b), 3.16 (s, 3H, OCH_3), 3.54 (dd, J = 3.5, 9.7 Hz, 1H, H-2), 3.75–4.15, 4.28 (both m, 8H, 1H, resp, H-3, 5, 6a, 6b. 3″, 4″a, 4″b, $=CH_2$), 4.30–4.65 (m, 4H, 2 × $PhCH_2$), 4.74 (m, 2H, H-1, PhC*H*), 4.88 (bt, J = 5.0 Hz, 1H, H-2″), 5.19 (d, J = 11.2 Hz, 1H, PhC*H*), 6.10 (d, J = 6.2 Hz, 1H, H-1″), 6.94–7.84 (m, 30H, Ph); ^{13}C NMR (75 MHz, C_6D_6) δ 26.8 [$C(CH_3)_2$, 1C], 27.6 ($CH_3)_3CSi$], 28.2 [$C(CH_3)_2$, 1C], 33.8 (C-2′), 42.1 (C-4), 55.2 (OCH_3), 62.3 (C-4″), 71.5, 71.9, 72.7, 74.1, 75.2, 77.4, 78.6, 81.4, 83.8, 85.7 (10C, C-2, 3, 5, 6, 2″, 3″, $=CH_2$, $PhCH_2$) 86.1 (C-1″), 98.7 (C-1), 112.4 [$C(CH_3)_2$], 127.5–140.7 (Ph), 160.1 ($OC=CH_2$). HRMS (FAB) *m/z* calcd for $C_{60}H_{71}O_9SSiH$ $[M + H]^+$ 995.4587. Found 995.4588.

Methyl 4-*C*-(2,6-anhydro-7-*O*-*tert*-butyldiphenylsilyl-4,5-*O*-isopropylidene-1,3-dideoxy-D-*ribo*-hept-2-enitol-1-*C*-yl)-2,3,6-tri-*O*-benzyl-4-deoxy-α-D-glucopyranoside (20). A mixture of enol ether **19** (740 mg, 0.08 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (1.54 g, 7.51 mmol), and freshly activated, powdered 4 Å molecular sieves (300 mg) in anhydrous CH_2Cl_2 (25 mL) was stirred for 15 min at rt under an argon atmosphere, then cooled to 0°C. Methyl triflate (1.0 mL, 7.55 mmol) was introduced, and the mixture was warmed to rt and stirred for an additional 18 h, or until all the starting material had disappeared, at which time triethylamine (2.5 mL) was added. The mixture was diluted with ether, washed with satd aq $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by FCC over basic alumina (Brockmann I, 150 mesh) to give **20** (460 mg, 70%) as a clear oil, R_f = 0.60 (20% EtOAc/petroleum ether); IR (film) 1647 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 1.24 [s, 9H, $(CH_3)_3CSi$], 1.31, 1.37 [both s, 3H ea, $C(CH_3)_2$], 2.40 (dd, J = 5.7, 14.4 Hz, 1H, H-1′a), 2.56 (m, 2H, H1′b, 4), 3.24 (s, 3H, OCH_3), 3.70 (m, 2H, H-2, 7′a), 3.85 4.00–4.20 (both m, 2H, 5H resp., H-3, 5, 6a, 6b, 3′, 6′, 7′b), 4.27 (t, J = 5.0 Hz, 1H, H-5′), 4.60 (m, 4H, 2 × $PhCH_2$), 4.83 (m, 2H, H-1, PhC*H*), 4.93 (d, J = 5.6 Hz, 1H, H-4′), 5.27 (d, J = 11.7 Hz, 1H, PhC*H*), 7.11–7.46 and 7.90 (both m, 25H, Ph); ^{13}C NMR (75 MHz, C_6D_6) δ 26.8 [$C(CH_3)_2$, 1C], 27.7 ($CH_3)_3CSi$], 28.2 [$C(CH_3)_2$, 1C], 33.9 (C-1′), 42.2 (C-4), 55.3 (OCH_3), 62.4 (C-7′), 71.6, 72.0, 72.8, 74.2, 75.3, 77.5, 78.7, 81.6, 83.9, 85.7, 86.2 (11C, C2, 3, 5, 6, 3′, 4′, 5′, 6′, 3 × $PhCH_2$), 100.0 (C-1), 112.5 [$C(CH_3)_2$], 128.0–140.8 (Ph), 160.2 (C-2′). HRMS (FAB) *m/z* calcd for $C_{54}H_{65}O_9Si$ $[M + H]^+$ 885.4399. Found 885.4398.

Methyl 4-*C*-(2,6-anhydro-4,5-*O*-isopropylidene-7-*O*-*tert*-butyldiphenylsilyl-1-deoxy-D-*glycero*-D-*manno*-heptitol-1-*C*-yl)-2,3,6-tri-*O*-benzyl-4-deoxy-α-D-glucopyranoside (21) and Methyl 4-*C*-(2,6-anhydro-4,5-*O*-isopropylidene-7-*O*-*tert*-butyldiphenylsilyl-1-deoxy-D-*glycero*-D-*allo*-heptitol-1-*C*-yl)-2,3,6-tri-*O*-benzyl-4-deoxy-α-D-glucopyranoside (22). $BH_3 \cdot Me_2S$ (2.7 mL of 1 M solution in CH_2Cl_2, 2.7 mmol) was added at 0°C to a solution of the glycal **20** (340 mg, 0.39 mmol) in anhydrous

THF (15 mL) under an atmosphere of argon. The mixture was warmed to rt and stirred for an additional 1 h. At that time the solution was cooled to 0°C and treated with a mixture of 3N NaOH (2.5 mL) and 30% aqueous H_2O_2 (2.5 mL) for 30 min. The mixture was diluted with ether, washed with satd aq $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. FCC of the residue afforded a mixture of **21** and **22** (264 mg, ca. ratio 5:1, 84%) which had identical TLC mobilities (R_f = 0.25, 10% EtOAc/petroleum ether). For characterization purposes, a pure sample of **21** was obtained by resubjecting this material to a second chromatography and collection of a later eluting fraction. Compound **21** was isolated as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 [s, 9H, $(CH_3)_3CSi$], 1.29, 1.46 [both s, 3H ea, $C(CH_3)_2$], 1.51 (m, 1H, H-1′a), 1.75 (m, 1H, H-1′b), 2.05 (m, 1H, H-4), 3.00 (bs, 1H, D_2O ex), 3.32 (m, 1H), 3.37 (s, 3H), 3.41 (m, 1H), 3.55 (m, 2H), 3.60–3.95 (m, 7H), 4.12 (m, 1H), 4.44 (s, 2H), 4.65–4.85 (m, 4H), 5.03 (d, J = 12.0 Hz, 1H), 7.26–7.78 (m, 25H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.7 ($CH_3)_3CSi$, $C(CH_3)_2$, 1C), 28.8 [$C(CH_3)_2$, 1C], 33.1 (C-1′), 40.5 (C-4), 55.9 (OCH_3), 65.4 (C-7′), 71.4, 72.4, 73.5, 74.0, 74.6, 75.5, 76.6, 78.8, 81.2, 82.6 (12C, C-2, 3, 5, 6, 2′, 3′, 4′, 5′ 6′, 3 × PhCH_2), 99.0 (C-1), 109.5 [$C(CH_3)_2$], 128.1–139.1 (Ph). HRMS (FAB) *m/z* calcd for $C_{54}H_{66}O_{10}SiNa$ $[M + Na]^+$ 925.4321. Found 925.4323. Compound **22** was characterized as triol **24** and triacetate **26** (vide infra).

Methyl 4-*C*-(2,6-anhydro-7-*O*-*tert*-butyldiphenylsilyl-1-deoxy-D-*glycero*-D-*manno*-heptitol-1-*C*-yl)-2,3,6-tri-*O*-benzyl-4-deoxy-α-D-glucopyranoside (23) and Methyl 4-*C*-(2,6-anhydro-7-*O*-*tert*-butyldiphenylsilyl-1-deoxy-D-*glycero*-D-*allo*-heptitol-1-*C*-yl)-2,3,6-tri-*O*-benzyl-4-deoxy-α-D-glucopyranoside (24). To a portion of the mixture of **21** and **22** from the previous step (103 mg, 0.11 mmol) in dry methanol was added a 1 M solution of HCl in ether (0.7 mL). The reaction was stirred for 1.5 h and then neutralized with a solution of NaOMe in methanol. Removal of the volatiles followed by FCC of the residue provided triols **23** (65 mg, 66%) and **24** (12 mg, 12%). Compound **23** was isolated as a clear gum; R_f = 0.50 (50% EtOAc/petroleum ether); ^{1}H NMR (300 MHz, C_6D_6) δ 1.18 [s, 9H, $(CH_3)_3CSi$], 1.82 (m, 1H, H-1′a), 1.98 (m, 1H, H-1′b), 2.32 (m, 1H, H-4), 2.75 (s, 1H, D_2O ex, OH), 2.92 (s, 1H, D_2O ex, OH), 3.22 (s, 3H, OCH_3), 3.51 (s, 1H, D_2O ex, OH), 3.52 (dd, J = 3.3, 9.9 Hz, partially hidden by s at δ 3.51, 1H), 3.60 (dd, J = 2.6, 8.4 Hz, 1H), 3.72 (m, 2H), 3.82 (m, 4H), 3.93 (dd, J = 6.3, 9.3 Hz, 1H), 4.01 (t, J = 9.6 Hz, 1H), 4.09 (bs, 1H), 4.26 (t, J = 6.2 Hz, 1H), 4.44 (ABq, Δδ = 0.06 ppm, J = 11.7 Hz, 1H), 4.49 (ABq, Δδ = 0.05 ppm, J = 12.4 Hz, 1H), 4.74 (d, J = 3.3 Hz, 1H, H-1), 4.87 (ABq, Δδ = 0.41 ppm, J = 10.6 Hz, 1H), 7.10–7.76 (m, 25H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.2 $(CH_3)_3CSi$], 33.4 (C-1′), 40.0 (C-4), 55.4 (OCH_3), 62.9 (C-7′), 69.0, 69.1, 70.8, 72.0, 72.9, 73.6, 73.7, 73.8, 74.4, 76.5, 81.3, 82.2, (12C, C-2, 3, 5, 6, 2′, 3′, 4′ 5′ 6′, 3 × PhCH_2), 98.4 (C-1), 127.6–138.4 (Ph). HRMS (FAB) *m/z* calcd for $C_{51}H_{62}O_{10}NaSi$ $[M + N]^+$ 885.4010. Found 885.4013.

Compound **24** was isolated as a clear gum; R_f = 0.64 (50% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.16 [s, 9H, $(CH_3)_3CSi$], 1.68 (m, 1H, H-1′a), 2.20 (m, 1H, H-1′b), 2.42 (m, 1H, H-4), 2.44 (bs, 1H, D_2O ex, OH), 2.58 (d, J = 7.5 Hz, 1H, D_2O ex, OH), 2.93 (d, J = 5.5 Hz, 1H, D_2O ex, OH), 3.07 (t, J = 7.3 Hz, 1H), 3.18 (s, 3H, OCH_3), 3.60 (m, 3H), 3.80 (m, 3H), 3.88–4.00 (m, 4H), 4.04 (dd, J = 4.5, 11.0 Hz, 1H), 4.42 (ABq, J = 12.0 Hz, Δδ = 0.05 ppm, 2H, PhCH_2), 4.48 (ABq, Δδ = 0.04 ppm, J = 12.0 Hz, 2H, PhCH_2), 4.76 (d, J = 3.0 Hz, 1H, H-1), 4.89 (ABq, Δδ = 0.44 ppm,

J = 11.0 Hz, 2H, PhCH_2), 7.05–7.82 (m, 25H); HRMS (FAB) *m/z* calcd for $C_{51}H_{62}O_{10}NaSi$ $[M + Na]^+$ 885.4010. Found 885.4030.

Methyl 4-*C*-(2,6-anhydro-1-deoxy-D-*glycero*-D-*manno*-heptitol-1-*C*-yl)-2,3,6-tri-*O*-benzyl-4-deoxy-α-D-glucopyranoside (25). A solution of HCl in ether (0.3 mL of ca.1M) was added to **21** (419 mg, 0.49 mmol) in dry methanol (30 mL). The reaction was stirred at rt for approximately 4 h, then neutralized with a solution of NaOMe in methanol. Addition of Bu_4NF (2.8 mL of a 1 M solution in THF, 2.8 mmol) to the reaction mixture, followed by stirring for an additional 1 h, then removal of the volatiles under reduced pressure, and FCC of the residue, provided **25** (164 mg, 58%) as a colorless oil; R_f = 0.37, (20% acetone/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (m, 1H, H-1′a), 1.77 (m, 1H, H-1′b), 2.07 (m, 1H, H-4), 2.86 (bs, 1H, D_2O ex, OH), 3.29 (m, 2H), 3.38 (s, 3H, OCH_3), 3.43–3.67 (m, 8H), 3.85 (m, 2H), 4.50–4.76 (m, 6H, H-1, 5 × PhC*H*), 5.03 (d, J = 10.6 Hz, 1H, PhC*H*), 7.24–7.37 (m, 15H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.3 (C-1′), 39.4 (C-4), 55.5 (OCH_3), 59.4 (C-7′), 68.6, 70.6, 71.5, 72.3, 72.5, 73.0, 73.4, 73.6, 76.3, 77.5, 81.6, 82.0 (12C, C-2, 3, 5, 6, 2′, 3′, 4′, 5′, 6′, 3 × Ph*C*H_2), 98.3 (C-1), 127.7–138.2 (Ph). HRMS (FAB) *m/z* calcd for $C_{35}H_{44}O_{10}Na$ $[M + Na]^+$ 647.2832. Found 647.2834.

Methyl 4-*C*-(2,6-anhydro-3,4,5,7-tetra-*O*-acetyl-1-deoxy-D-*glycero*-D-*manno*-heptitol-1-*C*-yl)-2,3,6-tri-*O*-benzyl-4-deoxy-α-D-glucopyranoside (26). A solution of tetraol **25** (25.5 mg, 0.04 mmol), DMAP (1.00 mg, 4 μmol), and acetic anhydride (0.04 mL, 0.40 mmol) in ethyl acetate (3.0 mL), was stirred at rt for 20 min. Methanol was then added and the reaction mixture concentrated under reduced pressure. The residue was purified by FCC to give **26** (26.7 mg, 82%) as a colorless oil; R_f = 0.66 (40% EtOAc/petroleum ether); $[\alpha]_D$ + 23° (*c* 1.3 $CHCl_3$); IR (film) 1743 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 1.59 (s, 3H, CH_3CO), 1.64, (m, buried under s at δ 1.64, 1H, H-1′a) 1.64, 1.69, 1.78 (all s, 3H ea, 3 × CH_3CO), 2.12 (t, J = 10.5 Hz, 1H, H-1′b), 2.23 (apparent q, J = 7.5 Hz, 1H, H-4), 3.25 (s, 3H, OCH_3), 3.56 (bd, J = 9.0 Hz, 1H, H-2), 3.62 (m, 1H, H-6a), 3.70 (bd, J = 10.5 Hz, 1H, H-6b), 3.81 (bd, J = 10.5 Hz, 1H, H-5), 3.89 (bd, J = 11.0 Hz, 1H, H-7′a), 4.06 (m, 2H, H-3, 6′), 4.28 (m, 2H, H-2′, 7′b), 4.43 (m. 4H, 2 × PhCH_2), 4.74 (bs, 1H, H-1), 4.94 (ABq, Δδ = 0.49 ppm, J = 10.5 Hz, 2H, PhCH_2), 5.33 (t, J = 8.5 Hz, 1H, H-3′), 5.43 (dd, J = 2.5, 8.5 Hz, 1H, H-4′), 5,49 (d, J = 2.5 Hz, 1H, H-5′), 7.10-7.51 (m, 15H, Ph); ^{13}C NMR (75 MHz, C_6D_6) δ 20.7, 20.8, 20.9 (*C*H_3CO, 4C), 31.8 (C-1′), 41.1 (C-4), 55.5 (OCH_3), 62.3, 69.5, 70.6, 71.7, 72.0, 72.3, 72.9, 73.3 (2C), 74.2, 75.8, 81.4, 83.5 (13C, C-2, 3, 5, 6, 2′, 3′, 4′, 5′, 6′, 7′, 3 x Ph*C*H_2), 99.0 (C-1) 128.0-130.0 (Ph), 169.6, 169.7, 169.8, 170.1 (CH_3*C*O). HRMS (FAB) *m/z* calcd for $C_{43}H_{52}O_{14}Na$ $[M + Na]^+$ 815.8355. Found 815.3256.

Methyl 4-*C*-(2,6-anhydro-7-*O*-*tert*-butyldiphenylsilyl-3,4,5-tri-*O*-acetyl-1-deoxy-D-*glycero*-D-*allo*-heptitol-1-*C*-yl)-2,3,6-tri-*O*-benzyl-4-deoxy-α-D-glucopyranoside (27). Triol **24** (4.0 mg, 0.005 mmol) was subjected to the identical acetylation procedure that was described for the preparation of **26**. FCC of the crude reaction product provided **27** (4.2 mg, 91%) as a clear gum; R_f = 0.50 (30% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.72 [s, 9H, $(CH_3)_3CSi$], 1.50, 1.63, 1.64 (all s, 3H ea, CH_3CO), 1.75 (m, 1H, H-1′a), 2.15 (bdd, J = 4.5, 14.0 Hz, 1H, H-1′b), 2.62 (m, 1H, H-4), 3.16 (s, 3H, OCH_3), 3.70 (dd, J = 3.0, 8.8 Hz, 1H, H-2), 3.76 (dd, J = 3.5, 11.5

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Hz, 1H, H-7′a), 3.84 (m, 2H, H-6a, 6′), 3.88 (bd, J = 11.5 Hz, 1H, H-7′b), 3.98 (dd, J = 3.5, 11.0 Hz, 1H, H-6b), 4.12, (t, J = 10.5 Hz, 1H, H-3), 4.23 (m, 2H, H-5, H-2′), 4.44 (ABq, $\Delta\delta$ = 0.03 ppm, J = 12.0 Hz, 2H, PhCH_2), 4.54 (ABq, $\Delta\delta$ = 0.07 ppm, J = 12.0 Hz, 2H, PhCH_2), 4.81, (d, J = 3.0 Hz, 1H, H-1), 4.90 (dd, J = 2.0, 9.5 Hz, 1H, H-3′), 4.99 (ABq, $\Delta\delta$ = 0.55 ppm, J = 11.5 Hz, 2H, PhCH_2), 5.43 (dd, J = 2.0, 9.9 Hz, 1H, H-5′), 6.20 (bt, J = 2.0 Hz, 1H, H-4′), 7.20, 7.80 (both m, 25H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 20.8, 20.9 (CH_3CO), 27.2, 27.6 ($CH_3)_3CSi$], 30.0 (C-1′), 40.4 (C-4), 55.3 (OCH_3), 63.1, 64.5, 66.8, 68.8, 70.3, 70.7, 71.0, 71.8, 73.1, 73.8, 74.7, 75.0, 82.5 (13C, C-2, 3, 5, 6, 2′, 3′, 4′, 5′, 6′, 7′, 3 × PhCH_2), 98.6 (C-1), 127.4-139.3 (Ph), 168.9, 169.3, 169.9 (CH_3CO). ESMS *m/z* 1006.5 $[M + NH_4]^+$.

Methyl 4-*C*-(2,6-anhydro-1-deoxy-D-*glycero*-D-*manno*-heptitol-1-*C*-yl)-4-deoxy-α-D-glucopyranoside (2). A mixture of **25** (124 mg, 0.20 mmol), 20% Pd on carbon (400 mg), formic acid (0.35 mL) and methanol (7.0 mL) was stirred under an atmosphere of hydrogen (balloon), for 12 h. The reaction mixture was purged with argon and filtered through a bed of Celite. The filtrate was concentrated in vacuo, and the residue was purified by FCC to provide **2** (55.0 mg, 83%) as a white solid; R_f = 0.68 (50% MeOH/$CHCl_3$); $[\alpha]_D$ + 93° (*c* 0.54 MeOH); ^{1}H NMR (500 MHz, D_2O, 50°C) δ 1.83 (ddd, J = 2.5, 10.0, 13.5 Hz, 1H, H-1′a), 1.93 (m, 1H, H-4), 2.08 (dd, J = 6.0, 13.5 Hz, 1H, H-1′b), 3.53 (s, 3H, OCH_3), 3.61 (bd, J = 9.5 Hz, 1H, H-7′a), 3.64 (dd, J = 4.0, 9.0 Hz, 1H, H-2), 3.79–3.86 (m, 4H, H-5, 2′, 3′, 6′), 3.92* (m, 3H, H-4′, 7′a, 7′b), 4.01* (bdd, J = 8.0, 11.5 Hz, H-6a), 4.08* (m, 2H, H-6b, 5′), 4.95 (d, J = 3.5 Hz, H-1); ^{13}C NMR (75 MHz, D_2O) δ 33.8 (C-1′), 42.8 (C-4), 58.6 (OCH_3), 62.1, 65.3 (C-6, 7′), 72.2, 74.7, 75.2, 75.5, 76.1, 76.2, 76.6, 81.8 (8C, C-2, 3, 5, 2′, 3′, 4′, 5′, 6′), 103.2 (C-1). HRMS (FAB) *m/z* calcd for $C_{14}H_{27}O_{10}Na$ $[M + Na]^+$ 355.1604. Found 355.1602.

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