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Application of cyclic sulfates in the synthesis of 6-deoxy-D-*manno*-heptopyranose derivatives

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ABSTRACT

6-Deoxy-D-*manno*-heptopyranose was prepared in five steps starting from methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside 4,6-sulfate or methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside 5,6-sulfate. The glycosyl donor ethyl 2,3,4,7-tetra-*O*-benzoyl-6-deoxy-1-thio-α,β-D-*manno*-heptopyranoside was used to synthesise methyl 4-*O*-(6-deoxy-α-D-*manno*-heptopyranosyl)-β-D-galactopyranoside.

INTRODUCTION

L-*glycero*-D-*manno*-Heptopyranose is a component of lipopolysaccharides (LPS) from the cell walls of Gram-negative bacteria[1] and 6-deoxy-D-*manno*-heptopyranose is a component of the LPS from *Yersinia (Pasteurella) pseudotuberculosis*[2]. The LPS of three of the five major serogroups of *Y. pseudotuberculosis* contain[3,4] a disaccharide moiety in which a 6-deoxy-α-D-*manno*-heptopyranosyl unit is 4-linked to a D-galactose moiety.

As part of a programme on the preparation of naturally occurring higher-carbon sugars (*i.e.*, L-*glycero*-D-*manno*-heptopyranose[5,6], 3-deoxy-D-*arabino*-2-heptulosonic acid[7], and 3-deoxy-D-*manno*-2-octulosonic acid[8–10]), we now report syntheses of 6-deoxy-D-*manno*-heptopyranose (**6**) and methyl 4-*O*-(6-deoxy-α-D-*manno*-heptopyranosyl)-β-D-galactopyranoside (**18**).

RESULTS AND DISCUSSION

A route of synthesis to **6** starting from methyl α-D-mannopyranoside has been reported[11], but the overall yield over the nine-step route was low due mainly to the poor yields in the carbon-extension reaction of methyl 2,3,4-tri-*O*-benzyl-α-D-*manno*-hexodialdo-1,5-pyranoside with the Wittig reagent methoxymethyltriphenylphosphonium chloride.

It was anticipated that an improved route to **6** could take advantage of the merits of cyclic sulfate intermediates[7,8,10].

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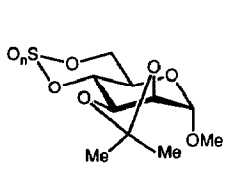

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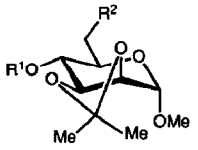
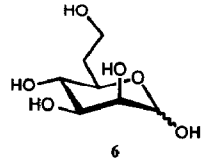


3 $R^1 = SO_3^-$, $R^2 = CH(SMe)_2$
4 $R^1 = H$, $R^2 = CH(SMe)_2$
5 $R^1 = H$, $R^2 = CH_2OH$



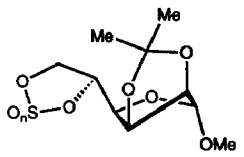
6

Thus, methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside[12] reacted with thionyl chloride–ethyl acetate–pyridine[13] to give the 4,6-cyclic sulfite **1** (*cf.* triethylamine–dichloromethane used originally[14]). Oxidation of **1** with sodium periodate in the presence of the catalyst ruthenium chloride hydrate[14] gave the corresponding 4,6-cyclic sulfate **2** in excellent yield. Treatment of **2** with bis(methylthio)methyl-lithium[15], prepared by treating bis(methylthio)methane with butyl-lithium in tetrahydrofuran containing a small amount of hexamethylphosphoric triamide, for 30 min at −40°, cleaved the cyclic sulfate and gave the 4-sulfate **3**. Mild acid hydrolysis of the sulfate group of **3** gave, after chromatography, homogeneous **4**. Unmasking of the dithioacetal function in **4** with *N*-bromosuccinimide[16] and then borohydride reduction of the exposed aldehyde group afforded the diol **5** (53% from methyl α-D-mannopyranoside). Treatment of **5** with hydrochloric acid in 1,4-dioxane at elevated temperature then gave known[11] 6-deoxy-α,β-D-*manno*-heptopyranose (**6**, 85%).

Compound **6** was also accessible from methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside[17] by a sequence of steps similar to that described above. Thus, treatment with thionyl chloride and subsequent oxidation of the resulting 5,6-cyclic sulfite **7** afforded the cyclic sulfate **8**. Regioselective cleavage of the cyclic sulfate in **8** with bis(methylthio)-methyl-lithium (→ **9**) followed by acid hydrolysis furnished **10**. Treatment of **10** with *N*-bromosuccinimide and borohydride reduction of the resulting aldehyde gave **11** (58% from D-mannose). Acid hydrolysis of **11** then afforded α,β-**6** (81%).

In order to assemble the α-linked disaccharide **18**, **6** was converted into the fully acetylated ethyl 1-thioglycoside donor **14**. Thus, acetylation of **6** (→ α,β-**13**) followed by treatment with ethanethiol in the presence of stannic(IV) chloride gave α,β-**14**. Pure α-**13** could be isolated (69% overall yield) after acid hydrolysis of the isopropylidene function from **5**, followed by acetylation, to give methyl 2,3,4,7-tetra-*O*-acetyl-α-D-*manno*-heptopyranoside (**12**), and then acetolysis with sulfuric acid in acetic anhydride[18].

Methyl 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside[19] was glycosylated with α,β-**14** in the presence of *N*-iodosuccinimide and catalytic triflic acid[20] to give, after chromatography, 65% of the disaccharide derivative **16**. The α linkage in **16** was indicated by n.m.r. data ($J_{C\text{-}1,H\text{-}1}$ 170 Hz). Replacement of the acetyl by benzoyl groups in the donor **14** had a beneficial effect[21] on the yield of the glycosylation reaction. Thus, Zemplén *O*-deacetylation of **14** and then benzoylation gave **15** that was used to glycosylate methyl 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside[19] to give 85% of **17**. *O*-Debenzoylation of **17** followed by hydrogenolysis furnished the disaccharide glycoside **18**, the identity of which was established by ^{1}H- and ^{13}C-n.m.r. spectroscopy.



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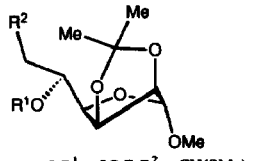
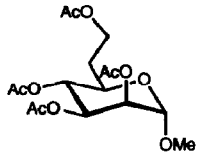


9 $R^1 = SO_3^-$, $R^2 = CH(SMe)_2$
10 $R^1 = H$, $R^2 = CH(SMe)_2$
11 $R^1 = H$, $R^2 = CH_2OH$



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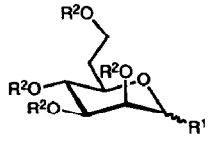
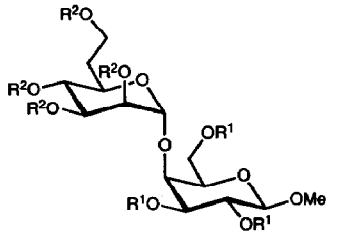


13 $R^1 = OAc$, $R^2 = Ac$
14 $R^1 = SEt$, $R^2 = Ac$
15 $R^1 = SEt$, $R^2 = Bz$



16 $R^1 = Bn$, $R^2 = Ac$
17 $R^1 = Bn$, $R^2 = Bz$
18 $R^1 = R^2 = H$

Thus, 6-deoxy-D-*manno*-heptopyranose (**6**) is accessible readily *via* cyclic sulfate intermediates. Furthermore, compound **6**, its derivatives (*i.e.*, **14** and **15**), and precursors thereof (*e.g.*, **5** or **11**) could be useful for the synthesis of other oligosaccharides containing the heptopyranose moiety **6**.

EXPERIMENTAL

General procedures. — Reactions were performed at ambient temperature unless noted otherwise. Column chromatography was performed on Silica Gel 60 (Merck, 70–230 mesh) and t.l.c. on DC Fertigfolien (Schleicher & Schüll F1500 LS254) with detection by charring with H_2SO_4. Optical rotations were determined with a Perkin–Elmer Model 241 polarimeter, for solutions in $CHCl_3$ unless stated otherwise. ^{13}C-N.m.r. spectra (50.1 MHz) were recorded with a Jeol JNM-FX200 spectrometer and ^1H-n.m.r. spectra with a Bruker WM-300 spectrometer equipped with an ASPECT 2000 computer. Chemical shifts are given relative to that of internal Me_4Si, unless stated otherwise.

Methyl 2,3-O-isopropylidene-α-D-mannopyranoside 4,6-sulfate (**2**). — To a solution of methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside[12] (936 mg, 4 mmol) and thionyl chloride (0.31 mL, 4.2 mmol) in EtOAc (20 mL) was added a solution of pyridine (0.68 mL, 8.4 mmol) in EtOAc (4 mL). The mixture was stirred and the temperature was kept below 20°. When t.l.c. 3:97 acetone–CH_2Cl_2 showed complete conversion of the starting material into cyclic sulfite **1**, the mixture was diluted with EtOAc (100 mL), washed with water (20 mL), dried ($NaSO_4$), and concentrated. To a solution of the residue in CH_2Cl_2 (8 mL), acetonitrile (8 mL), and water (12 mL) were added sodium periodate (1.71 g, 8 mmol) and $RuCl_3 \cdot H_2O$ (5 mg). The mixture was stirred for 1 h, then

filtered, and diluted with CH_2Cl_2 (75 mL). The organic layer was washed with water (15 mL), dried ($MgSO_4$), and concentrated. Column chromatography (97:3 CH_2Cl_2–acetone) of the residue gave **2** (1.05 g, 89%), $[\alpha]_D^{20}$ +10° (*c* 1). N.m.r. data ($CDCl_3$): ^1H, δ 1.37, 1.57 (2 s, 6 H, CMe_2), 3.42 (s, 3 H, OMe), 4.03 (m, 1 H, H-5), 4.23 (d, 1 H, $J_{2,3}$ 5.6 Hz, H-2), 4.32 (dd, 1 H, $J_{3,4}$ 7.8 Hz, H-3), 4.53 (dd, 1 H, $J_{5,6a}$ 5.5, $J_{6a,6b}$ 10.6 Hz, H-6a), 4.60 (dd, 1 H, $J_{4,5}$ 10.3 Hz, H-4), 4.64 (t, 1 H, $J_{5,6b}$ 10.6 Hz, H-6b), 4.99 (s, 1 H, H-1); ^{13}C, δ 26.0, 27.8 [$(CH_3)_2C$], 55.7 (OCH_3), 58.4 (C-4), 71.9 (C-6), 73.1, 75.8, 84.0 (C-2,3,5), 98.9 (C-1), 110.6 [$(CH_3)_2C$].

Anal. Calc. for $C_{10}H_{16}O_8S$: C, 40.54; H, 5.44. Found: C, 40.56; H, 5.41.

*Methyl 6-deoxy-2,3-*O*-isopropylidene-α-*D*-manno-heptadialdo-1,5-pyranoside 7-(dimethyl dithioacetal)* (**4**). — To a solution of bis(methylthio)methane (0.4 mL, 3.9 mmol) in dry tetrahydrofuran (7.8 mL) and hexamethylphosphoric triamide (2.4 mL) at −60° was added 1.6M butyl-lithium in hexane (2.43 mL). The mixture was stirred for 0.5 h at −40°, a solution of **2** (0.89 g, 3 mmol) in tetrahydrofuran (3 mL) was added, and stirring was continued for 1 h, when t.l.c. (95:5 CH_2Cl_2–MeOH) showed complete conversion of **2** into **3**. Conc. H_2SO_4 (150 μL) and water (54 μL) were added, and the mixture was stirred for 2 h at 50°, then diluted with EtOAc (50 mL), washed with 0.9M $NaHCO_3$ (2 × 15 mL) and water (15 mL), dried (Na_2SO_4), and concentrated. Column chromatography [1:1 light petroleum (b.p. 40–60°)–ether] of the residue gave **4** (0.85 g, 87%), $[\alpha]_D^{20}$ +32° (*c* 1). ^{13}C-N.m.r. data ($CDCl_3$): δ 10.9, 13.0 [$(SCH_3)_2$], 26.0, 27.8 [$(CH_3)_2C$], 36.4 (C-6), 49.9 (C-7), 54.2 (OCH_3), 66.5, 72.5, 75.4, 78.4 (C-2,3,4,5), 97.9 (C-1), 109.2 [$(CH_3)_2C$].

Anal. Calc. for $C_{13}H_{24}O_5S_2$: C, 48.12; H, 7.46. Found: C, 48.09; H, 7.49.

*Methyl 6-deoxy-2,3-*O*-isopropylidene-α-*D*-manno-heptopyranoside* (**5**). — To a solution of **4** (0.65 g, 2 mmol) in acetonitrile (16 mL) and triethylammonium hydrogencarbonate (4 mL) at 0° was added *N*-bromosuccinimide (1.42 g, 8 mmol). The mixture was stirred for 5 min, then poured into aq. 10% $NaHCO_3$ and Na_2SO_3 (1:1, 50 mL), and diluted with CH_2Cl_2 (75 mL). The organic phase was washed with water (15 mL), dried ($MgSO_4$), and concentrated. To a solution of the residue in EtOH (25 mL) was added sodium borohydride (0.76 g, 20 mmol), the mixture was stirred for 6 h, acetone (4 mL) was added, and the mixture was concentrated. Column chromatography (95:5 CH_2Cl_2–MeOH) of the residue gave **5** (456 mg, 92%), $[\alpha]_D^{20}$ +40° (*c* 1). ^{13}C-N.m.r. data ($CDCl_3$): δ 26.1, 27.9 [$(CH_3)_2C$], 34.3 (C-6), 54.9 (OCH_3), 59.7 (C-7), 68.3, 72.6, 75.4, 78.2 (C-2,3,4,5), 98.0 (C-1), 109.4 [$(CH_3)_2C$].

Anal. Calc. for $C_{11}H_{20}O_6$: C, 53.22; H, 8.12. Found: C, 53.30; H, 8.15.

*6-Deoxy-*D*-manno-heptopyranose* (**6**). — A mixture of **5** (372 mg, 1.5 mmol), 1,4-dioxane (48 mL), and 2M HCl (12 mL) was boiled under reflux for 15 min, then neutralised with Amberlite IRA-400 (HO^-) resin, filtered, and concentrated. The residue was eluted from a column (1.5 × 80 cm) of Sephadex LH-20 with 1:1 MeOH–water to give **6** (247 mg, 85%).

Compound **6** (81%), prepared from **11** using the above conditions, had $[\alpha]_D^{20}$ +24° (*c* 1, water); lit.[11] $[\alpha]_D$ +25° (water). N.m.r. data (D_2O): ^1H, δ 1.65–1.74 (m, 2 H, H-6aα and H-6aβ), 2.05–2.13 (m, 2 H, H-6bα and H-6bβ), 3.33–3.86 (m, 10 H, H-3,4,5,7a,7b),

3.91–3.93 (m, 2 H, H-2α and H-2β), 4.85 (d, 1 H, $J_{1,2}$ 1.0 Hz, H-1β), 5.11 (d, 1 H, $J_{1,2}$ 1.7 Hz, H-1α); ^{13}C, δ 33.7 (C-6), 58.5, 58.7 (C-7), 69.4, 70.6, 70.9, 71.0, 71.5, 73.1, 73.3 (C-2,3,4,5), 94.0 (C-1β, $J_{C\text{-}1,H\text{-}1}$ 161 Hz), 94.3 (C-1α, $J_{C\text{-}1,H\text{-}1}$ 170 Hz).

*Methyl 2,3-*O*-isopropylidene-α-*D*-mannofuranoside 5,6-sulfate* (**8**). — Prepared from methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside[17], as described above for **2**, **8** (91%) had $[\alpha]_D^{20}$ + 66° (*c* 1). N.m.r. data ($CDCl_3$): ^{1}H, δ 1.29, 1.44 (2 s, 6 H, CMe_2), 3.35 (s, 3 H, OMe), 4.36 (t, 1 H, $J_{3,4}$ 3.9, $J_{4,5}$ 4.1 Hz, H-4), 4.60 (d, 1 H, $J_{2,3}$ 5.9 Hz, H-2), 4.76 (m, 2 H, H-3,6a), 4.86 (dd, 1 H, $J_{5,6b}$ 6.9, $J_{6a,6b}$ 9.0 Hz, H-6b), 4.97 (s, 1 H, H-1), 5.22 (m, 1 H, H-5); ^{13}C, δ 23.6, 25.2 [$(CH_3)_2C$], 54.6 (OCH_3), 69.8 (C-6), 77.2, 78.6, 78.8, 84.4 (C-2,3,4,5), 107.1 (C-1), 112.9 [$(CH_3)_2C$].

Anal. Calc. for $C_{10}H_{16}O_8S$: C, 40.54; H, 5.44. Found: C, 40.50; H, 5.48.

*Methyl 6-deoxy-2,3-*O*-isopropylidene-α-*D*-manno-heptodialdo-1,4-furanoside 7-(dimethyl dithioacetal)* (**10**). — Prepared from **8**, as described above for **4**, **10** (81%) had $[\alpha]_D^{20}$ + 63° (*c* 1). N.m.r. data ($CDCl_3$): ^{1}H, δ 1.33, 1.49 (2 s, 6 H, CMe_2), 1.93–2.26 (m, 8 H, SMe and H-6a,6b), 2.90 (d, 1 H, $J_{5,OH}$ 5.6 Hz, HO-5), 3.31 (s, 3 H, OMe), 3.77 (dd, 1 H, $J_{3,4}$ 3.7, $J_{4,5}$ 7.8 Hz, H-4), 4.02 (dd, 1 H, H-7), 4.23 (m, 1 H, H-5), 4.57 (d, 1 H, $J_{2,3}$ 5.9 Hz, H-2), 4.83 (dd, 1 H, H-3), 4.91 (s, 1 H, H-1); ^{13}C, δ 11.6, 12.9 [$(SCH_3)_2$], 24.6, 25.8 [$(CH_3)_2C$], 38.8 (C-6), 50.7 (C-7), 54.3 (OCH_3), 67.8, 79.8, 81.5, 84.6 (C-2,3,4,5), 106.7 (C-1), 112.5 [$(CH_3)_2C$].

Anal. Calc. for $C_{13}H_{24}O_5S_2$: C, 48.12; H, 7.46. Found: C, 48.20; H, 7.52.

*Methyl 6-deoxy-2,3-*O*-isopropylidene-α-*D*-manno-heptofuranoside* (**11**). — Prepared from **10**, as described above for **5**, **11** (88%) had $[\alpha]_D^{20}$ + 48° (*c* 1). N.m.r. data ($CDCl_3$): ^{1}H, δ 1.33, 1.48 (2 s, 6 H, CMe_2), 1.82–1.98 (m, 2 H, H-6a,6b), 2.75 (bs, 1 H, HO-7), 3.24 (bs, 1 H, HO-5), 3.31 (s, 3 H, OMe), 3.82 (dd, 1 H, $J_{3,4}$ 3.7, $J_{4,5}$ 7.8 Hz, H-4), 3.90 (bt, 2 H, H-7a,7b), 4.12 (m, 1 H, H-5), 4.57 (d, 1 H, $J_{2,3}$ 5.9 Hz, H-2), 4.84 (dd, 1 H, H-3), 4.91 (s, 1 H, H-1); ^{13}C, δ 24.5, 25.9 [$(CH_3)_2C$], 35.9 (C-6), 54.5 (OCH_3), 61.2 (C-7), 70.2, 79.8, 81.6, 84.6 (C-2,3,4,5), 106.9 (C-1), 112.5 [$(CH_3)_2C$].

Anal. Calc. for $C_{11}H_{20}O_6$: C, 53.22; H, 8.12. Found: C, 53.16; H, 8.14.

*Methyl 2,3,4,7-tetra-*O*-acetyl-6-deoxy-α-*D*-manno-heptopyranoside* (**12**). — A solution of **5** (0.65 g, 2.6 mmol) in 4:1 acetic acid–water (30 mL) was stirred at 60°, then concentrated, and toluene (3 × 20 mL) was evaporated from the residue. A solution of the residue in pyridine (3 mL) and acetic anhydride (3 mL) was kept for 12 h, then concentrated, and toluene (3 × 20 mL) was evaporated from the residue. Column chromatography (97:3 CH_2Cl_2–acetone) then gave **12** (0.78 g, 80%), $[\alpha]_D^{20}$ + 64° (*c* 1); lit.[11] $[\alpha]_D$ + 62° (*c* 0.4). N.m.r. data ($CDCl_3$): ^{1}H, δ 1.64–2.15 (m, 14 H, H-6a,6b and 4 OAc, 3.36 (s, 3 H, OMe), 3.86 (m, 1 H, H-5), 4.20 (m, 2 H, H-7a,7b), 4.65 (s, 1 H, H-1), 5.11 (t, 1 H, $J_{3,4}$ 10.0, $J_{4,5}$ 9.7 Hz, H-4), 5.24 (m, 1 H, H-2), 5.31 (dd, 1 H, $J_{2,3}$ 3.3 Hz, H-3); ^{13}C, δ 20.6, 20.7, 20.8 (CH_3COO), 30.2 (C-6), 54.9 (OCH_3), 60.1 (C-7), 66.2, 68.9, 69.4, 69.5 (C-2,3,4,5), 98.2 (C-1), 169.9 (CH_3COO).

*1,2,3,4,7-Penta-*O*-acetyl-6-deoxy-α-*D*-manno-heptopyranose* (α-**13**). — A solution of **12** (0.75 g, 2 mmol) in acetic anhydride (11 mL) and conc. H_2SO_4 (1.56 mL) was stirred for 1 h at 0° then for 1 h at 20°. Sodium acetate (2.8 g) was added, stirring was continued for 1 h, and the mixture was diluted with CH_2Cl_2 (50 mL), washed with water

(2 × 15 mL) and 0.9M $NaHCO_3$ (15 mL), dried ($MgSO_4$), and concentrated. Column chromatography (97:3 CH_2Cl_2–acetone) of the residue then yielded **13** (0.70 g, 86%), $[\alpha]_D^{20}$ +49° (*c* 1). N.m.r. data ($CDCl_3$): ^1H, δ 1.76–2.35 (m, 17 H, H-6a,6b and 5 OAc), 3.93 (m, 1 H, H-5), 4.18 (m, 2 H, H-7a,7b), 5.16 (t, 1 H, $J_{3,4}$ 10.0 Hz, $J_{4,5}$ 9.7 Hz, H-4), 5.25 (dd, 1 H, $J_{1,2}$ 1.9, $J_{2,3}$ 3 Hz, H-2), 5.32 (dd, 1 H, H-3), 6.02 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1); ^{13}C, δ 20.5, 20.6 (CH_3COO), 30.3 (C-6), 60.0 (C-7), 68.4, 68.7, 69.0 (C-2,3,4,5), 90.2 (C-1, $J_{C\text{-}1,H\text{-}1}$ 177 Hz), 168.0, 169.6, 169.8 (CH_3COO).

Anal. Calc. for $C_{17}H_{24}O_{11}$: C, 50.50; H, 5.98. Found: C, 50.45; H, 5.98.

1,2,3,4,7-Penta-O-acetyl-6-deoxy-α,β-D-manno-heptopyranose (**13**). — Pyridine (3 × 10 mL) was evaporated from **6** (194 mg, 1 mmol) which was then dissolved in pyridine (3 mL) and acetic anhydride (3 mL). After 16 h, the mixture was concentrated and toluene (3 × 20 mL) was evaporated from the residue. Column chromatography (97:3 CH_2Cl_2–acetone) then gave **13** (303 mg, 75%). ^{13}C-N.m.r. data ($CDCl_3$): δ 20.5, 20.6 (CH_3COO), 30.3 (C-6), 60.0 (C-7), 68.4, 68.7, 68.8, 69.0, 70.6, 71.7 (C-2,3,4,5), 90.2 (C-1α, $J_{C\text{-}1,H\text{-}1}$ 177 Hz), 90.4 (C-1β, $J_{C\text{-}1,H\text{-}1}$ 162 Hz), 168.0, 168.1, 169.6, 169.8, 170.0 (CH_3COO).

Anal. Calc. for $C_{17}H_{24}O_{11}$: C, 50.50; H, 5.98. Found: C, 50.57; H, 6.03.

Ethyl 2,3,4,7-tetra-O-acetyl-6-deoxy-1-thio-α,β-D-manno-heptopyranoside (**14**). — To a solution of **13** (808 mg, 2 mmol) in CH_2Cl_2 (20 mL) were added ethanethiol (163 μL, 1.1 equiv.) and $SnCl_4$ (70 μL, 0.3 equiv.). The mixture was stirred for 16 h, diluted with CH_2Cl_2 (50 mL), extracted with M KF (2 × 15 mL) and 0.9M $NaHCO_3$ (15 mL), dried ($MgSO_4$), and concentrated. Column chromatography (97:3 CH_2Cl_2–acetone) of the residue gave **14** (715 mg, 88%). ^{13}C-N.m.r. data ($CDCl_3$): δ 14.0 ($CH_3CH_2S\alpha$), 14.5 ($CH_3CH_2S\beta$), 19.9, 20.1, 20.2 (CH_3COO), 24.4 ($CH_3CH_2S\alpha$), 24.9 ($CH_3CH_2S\beta$), 29.6 (C-6α), 30.1 (C-6β), 59.5 (C-7), 66.5, 68.9, 69.1, 70.7 (C-2,3,4,5α), 68.4, 70.1, 71.3, 74.3 (C-2,3,4,5β), 81.1 (C-1α), 81.4 (C-1β), 169.0, 169.2, 170.0 (CH_3COO).

Anal. Calc. for $C_{17}H_{26}O_9S$: C, 50.24; H, 6.45. Found: C, 50.30; H, 6.53.

Ethyl 2,3,4,7-tetra-O-benzoyl-6-deoxy-1-thio-α,β-D-manno-heptopyranoside (**15**). — Sodium methoxide (40 mg) was added to a solution of **14** (406 mg, 1 mmol) in methanol. After 2 h, the mixture was neutralised with Dowex W50 (H^+) resin, filtered, and concentrated, and pyridine (2 × 5 mL) was evaporated from the residue. A solution of the residue in pyridine (10 mL) and benzoyl chloride (0.55 mL) was stirred for 16 h, then water (1 mL) was added, and the mixture was concentrated. A solution of the residue in CH_2Cl_2 (25 mL) was washed with 0.9M $NaHCO_3$ (2 × 5 mL), dried ($MgSO_4$), and concentrated. Column chromatography [1:1 light petroleum (b.p. 40–60°)–ether] of the residue yielded α-**15** (527 mg, 81%) and β-**15** (29 mg, 4%).

Compound α-**15** had $[\alpha]_D^{20}$ −63° (*c* 1). N.m.r. data: ^1H, δ 1.24 (t, 3 H, CH_3CH_2S), 2.16 (m, 2 H, H-6a,6b), 2.65 (m, 2 H, CH_3CH_2S), 4.50 (m, 2 H, H-7a,7b), 4.71 (m, 1 H, H-5), 5.53 (bs, 1 H, H-1), 5.80–5.83 (m, 3 H, H-2,3,4), 7.15–8.19 (m, 20 H, 4 Ph); ^{13}C, δ 14.2 (CH_3CH_2S), 25.1 (CH_3CH_2S), 30.4 (C-6), 60.4 (C-7), 67.3, 70.3, 70.4, 72.2 (C-2,3,4,5), 81.9 (C-1, $J_{C\text{-}1,H\text{-}1}$ 167 Hz), 128.0–133.2 (Ph), 165.0, 165.1, 165.5, 166.0 (PhCOO).

Anal. Calc. for $C_{37}H_{34}O_9S$: C, 67.88; H, 5.23. Found: C, 67.71; H, 5.19.

Compound *β*-**15** had $[\alpha]_D^{20}$ −162° (*c* 1). N.m.r. data ($CDCl_3$): ^1H, *δ* 1.23 (t, 3 H, CH_3CH_2S), 2.23 (m, 2 H, H-6a,6b), 2.78 (m, 2 H, CH_3CH_2S), 3.97 (m, 1 H, H-5), 4.48–4.67 (m, 2 H, H-7a,7b), 5.05 (d, 1 H, $J_{1,2}$ 1.0 Hz, H-1), 5.63 (dd, 1 H, $J_{2,3}$ 3.1, $J_{3,4}$ 10.0 Hz, H-3), 5.73 (dd, 1 H, $J_{4,5}$ 9.0 Hz, H-4), 5.99 (dd, 1 H, H-2), 7.16–8.19 (m, 20 H, 4 Ph); ^{13}C, *δ* 14.8 (CH_3CH_2S), 25.6 (CH_3CH_2S), 31.1 (C-6), 60.7 (C-7), 69.9, 71.4, 72.6, 75.5 (C-2,3,4,5), 82.6 (C-1, $J_{C\text{-}1,H\text{-}1}$ 149 Hz), 128.2–133.4 (Ph), 165.5 (PhCOO).

Anal. Calc. for $C_{37}H_{34}O_9S$: C, 67.88; H, 5.23. Found: C, 67.91; H, 5.28.

*Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,7-tetra-*O*-acetyl-6-deoxy-α-*D*-manno-heptopyranosyl)-β-*D*-galactopyranoside* (**16**). — To a solution of **14** (102 mg, 0.25 mmol) and methyl 2,3,6-tri-*O*-benzyl-*β*-D-galactopyranoside[19] (97 mg, 0.21 mmol) in 1:1 1,2-dichloroethane–ether (3 mL) were added powdered molecular sieves (4 Å, 100 mg), and the mixture was stirred for 15 min at 0°. A solution of *N*-iodosuccinimide (56 mg, 0.25 mmol) and triflic acid (2.1 μL, 0.03 mmol) in 1:1 1,2-dichloroethane–ether (3 mL) was added, and the mixture was stirred for 5 min, then filtered, diluted with CH_2Cl_2 (30 mL), washed with M $Na_2S_2O_3$ (5 mL) and 0.9M $NaHCO_3$ (5 mL), dried ($MgSO_4$), and concentrated. Column chromatography (94:6 CH_2Cl_2–acetone) of the residue gave **16** (110 mg, 65%), $[\alpha]_D^{20}$ −13° (*c* 1). N.m.r. data ($CDCl_3$): ^1H, *δ* 1.50–1.72 (m, 2 H, H-6'a,6'b), 1.97–2.11 (4 s, 12 H, 4 AcO), 3.40 (dd, 1 H, H-3), 3.48–3.77 (m, 7 H, OMe and H-2,5,6a,6b), 3.90 (m, 1 H, H-5'), 4.12–4.28 (m, $J_{1,2}$ 7.4 Hz, H-1,4,7'a,7'b), 4.40–4.92 (m, 6 H, CH_2Ph), 4.94 (bs, 1 H, H-1'), 5.13 (t, 1 H, $J_{3',4'}$ 9.8, $J_{4',5'}$ 9.7 Hz, H-4'), 5.29 (m, 1 H, H-2'), 5.38 (dd, 1 H, $J_{2',3'}$ 3.3 Hz, H-3'), 7.24–7.35 (m, 15 H, 3 Ph); ^{13}C, *δ* 20.5, 20.7 (CH_3COO), 29.6 (C-6'), 56.8 (OCH_3), 60.4 (C-7'), 67.1 (C-6), 67.2, 68.9, 69.1, 69.9, 72.2, 74.5, 79.1, 79.4 (C-2,3,4,5 and C-2',3',4',5'), 72.8, 72.9, 74.7 (CH_2Ph), 98.2 (C-1', $J_{C\text{-}1',H\text{-}1'}$ 170 Hz), 104.8 (C-1, $J_{C\text{-}1,H\text{-}1}$ 158 Hz), 127.2–128.1 (Ph), 137.6, 138.1, 138.4 (Ph), 169.5, 169.6, 169.8, 170.5 (CH_3COO).

Anal. Calc. for $C_{43}H_{52}O_{15}$: C, 63.85; H, 6.48. Found: C, 63.87; H, 6.45.

*Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,7-tetra-*O*-benzoyl-6-deoxy-α-*D*-manno-heptopyranosyl-β-*D*-galactopyranoside* (**17**). — Prepared as described above for **16**, but with **15** as the glycosylating agent, **17** (85%) had $[\alpha]_D^{20}$ −29° (*c* 1). N.m.r. data ($CDCl_3$): ^1H, *δ* 1.85 (m, 2 H, H-6'a,6'b), 4.30 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 5.23 (d, 1 H, $J_{1',2'}$ 1.8 Hz, H-1'), 5.75 (dd, 1 H, $J_{2',3'}$ 3.1 Hz, H-2'), 5.81 (t, 1 H, $J_{3',4'}$ 10.0, $J_{4',5'}$ 9.8 Hz, H-4'), 5.95 (dd, 1 H, H-3'); ^{13}C, *δ* 30.1 (C-6'), 57.0 (OCH_3), 61.2 (C-7'), 67.3 (C-6), 67.9, 69.9, 70.9, 72.6, 74.8, 79.3, 79.7 (C-2,3,4,5 and C-2',3',4',5'), 73.2, 73.3, 74.8 (CH_2Ph), 98.5 (C-1', $J_{C\text{-}1',H\text{-}1'}$ 173 Hz), 105.1 (C-1, $J_{C\text{-}1,H\text{-}1}$ 156 Hz), 127.3–133.3 (Ph), 137.6, 138.2, 138.5 (Ph), 165.2, 165.5, 165.6, 166.2 (PhCOO).

Anal. Calc. for $C_{63}H_{60}O_{15}$: C, 71.58; H, 5.72. Found: C, 71.58; H, 5.71.

*Methyl 4-*O*-(6-deoxy-α-*D*-manno-heptopyranosyl)-β-*D*-galactopyranoside* (**18**). — To a solution of compound **17** (106 mg, 0.1 mmol) in MeOH (5 mL) was added sodium methoxide (20 mg). After 18 h, the mixture was neutralised with Dowex W50 (H^+) resin, filtered, and concentrated. The residue was eluted with MeOH from a column (2 × 50 cm) of Sephadex LH-20. The appropriate fractions were collected and concentrated. A solution of the residual oil in 10:5:2 2-propanol–water–acetic acid (10 mL) was hydrogenated in the presence of 10% Pd/C for 24 h, then filtered, and

concentrated. Elution of the residue from a column (2 × 60 cm) of Sephadex LH-20 with 1:1 water–MeOH gave **18** (30 mg, 81%), $[\alpha]_D^{20}$ −43° (*c* 1, water). N.m.r. data (D_2O): ^1H, δ 1.62–1.07 (m, 2 H, H-6′a,6′b), 4.28 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 4.73 (d, 1 H, $J_{1',2'}$ 1.8 Hz, H-1′); ^{13}C, δ 34.0 (C-6′), 57.8 (OCH_3), 59.0 (C-7′), 60.9 (C-6), 70.6, 70.7, 70.8, 71.5, 72.7, 75.5, 77.8 (C-2,3,4,5 and C-2′,3′,4′,5′), 102.0 (C-1′), 10.4 (C-1).

Anal. Calc. for $C_{14}H_{26}O_{11}$: C, 45.40; H, 7.08. Found: C, 45.44; H, 7.10.

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