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Note

Convenient syntheses of L-*glycero*-D-*manno*-heptose and D-*glycero*-D-*manno*-heptose*

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L-*glycero*-D-*manno*-Heptose (**1**) and D-*glycero*-D-*manno*-heptose (**2**) are components of a number of bacterial polysaccharides[2], but only meagre amounts of these heptoses are available from natural sources. Interest in the synthesis of oligosaccharides containing either **1** or **2** for biological evaluation has revealed a pressing need for convenient syntheses of these heptoses. L-*glycero*-D-*manno*-Heptose (**1**) was synthesised[3] originally from L-galactose (itself obtained from D-galactose), using the nitromethane procedure to ascend the series, while a recent synthesis[4] of **1** involved an interchange of the reducing and non-reducing ends of D-*glycero*-D-*galacto*-heptose, obtained *via* the stereoselective addition of 2-lithio-1,3-dithiane to 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose. D-*glycero*-D-*manno*-Heptose (**2**) has been prepared from D-altrose, using either the cyanohydrin[5] or nitromethane[6] procedure to ascend the series, and by a total synthesis from D-glyceraldehyde and furan[7].

We have shown[8] that the OsO_4-catalysed bishydroxylation of benzyl (*E*)-5,6-dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hept-5-enofuranoside (**4**; prepared in six, high-yielding steps from D-mannose *via* **3**) produces a mixture (92%) of benzyl 2,3-*O*-isopropylidene-β-L-*glycero*-D-*manno*-heptofuranoside (**5**) and the α-D-*glycero*-L-*gulo* isomer **6** in the ratio 7:1. The heptofuranoside **5**, a derivative of L-*glycero*-D-*manno*-heptose (**1**), was readily separated from the contaminating isomer **6** by formation of the crystalline triacetate **7**. Zemplén deacetylation of **7** regenerated **5**, which was transformed into **1** following catalytic debenzylation and acid hydrolysis†. L-*glycero*-D-*manno*-Heptose (**1**) obtained in this way was sufficiently pure for most purposes, and it was characterised as the crystalline dibenzyl dithioacetal **8**[9]. Further purification could be achieved by formation of the α,β-hexa-acetate **9**, which, on Zemplén deacetylation, gave **1** {$[\alpha]_D$ +14° (*c* 2.5, water)} as a syrup††.

*Higher-carbon sugars, Part 5. For Part 4, see ref. 1.
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†Direct conversion of **5** into **1**, by acid hydrolysis, is also possible.
††Hudson and co-workers[9] found that crystallisation of the enantiomer of **1** (as the monohydrate), m.p. 77–78°, $[\alpha]_D$ −14° (equil.; *c* 1.15, water), required up to four months.

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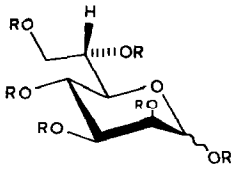

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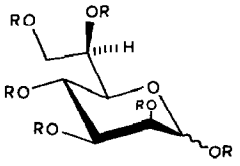
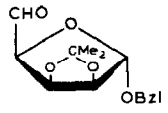
9 R = Ac



2 R = H
13 R = Ac, α-anomer



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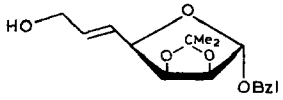

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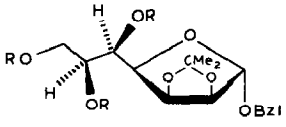

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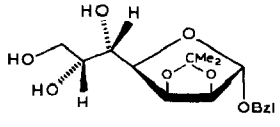
7 R = Ac



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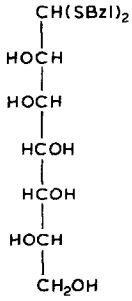

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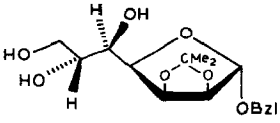

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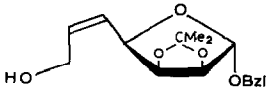

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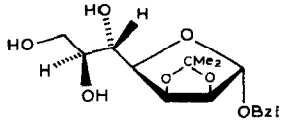

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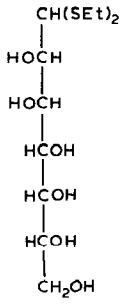

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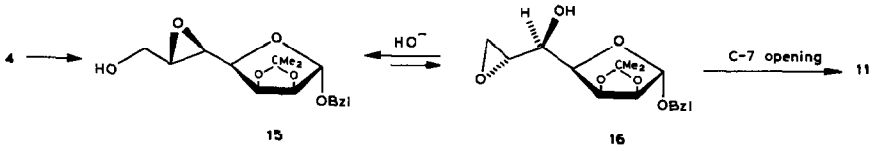
A useful practical feature of this route is that the triacetate **7** has a long shelf-life and is readily transformed into **1** as required.

An analogous approach can be used to synthesise D-*glycero*-D-*manno*-heptose (**2**), since the OsO_4-catalysed bishydroxylation of benzyl (*Z*)-5,6-dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hept-5-enofuranoside (**10**, also prepared from **3**) furnished a mixture (75%) of benzyl 2,3-*O*-isopropylidene-α-D-*glycero*-D-*manno*-hepto-

furanoside (**11**) and the β-L-*glycero*-L-*gulo* isomer **12** in the ratio 6:1[8]. In this case, acetylation of the mixture of **11** and **12** failed to yield a crystalline triacetate. However, purification of **11** at this stage turned out to be unnecessary, since acid hydrolysis of **11** and **12** together provided a mixture of products containing principally D-*glycero*-D-*manno*-heptose (**2**)*, which, on acetylation, afforded the crystalline α-hexa-acetate **13**[6] in 53% yield. Zemplén deacetylation of **13** then gave **2** {$[\alpha]_D$ +22° (*c* 1.8, methanol)} as a syrup, which was characterised as the crystalline diethyl dithioacetal **14**[5–7].

Whereas the foregoing syntheses of the heptoses **1** and **2** evolved *via* appropriate Wittig olefination of the common precursor **3**[8], both heptoses can also be elaborated from the (*E*)-allylic alcohol **4**. This approach to **2** entailed titanium-catalysed epoxidation[11] of **4** with di-isopropyl L-(+)-tartrate, which afforded a single, crystalline epoxide (88% yield) predicted to be benzyl 5,6-anhydro-2,3-*O*-isopropylidene-β-L-*glycero*-D-*manno*-heptofuranoside (**15**), on the assumption that the diastereofacial selectivity of the reagent would outweigh the influence of the chirality already existing in **4**. The identity of **15** was established by its conversion into **11** (identified by ^{1}H-n.m.r. spectroscopy), *via* preferential hydrolysis of the terminal epoxide **16** (the product of a Payne rearrangement[12] of **15** *in situ*) with sodium hydroxide in aqueous 1,4-dioxane. The configuration at C-6 is inverted in this sequence of reactions. Although **11** appeared to be the only triol produced from **15**, the hydrolysis was sluggish and gave, under the best conditions (see Experimental), a 63% yield of **11**. Acid hydrolysis of **11**, as before, yielded D-*glycero*-D-*manno*-heptose (**2**), which was again characterised as the diethyl dithioacetal **14**[5–7]. While it is aesthetically pleasing to be able to prepare both **1** and **2** from the (*E*)-allylic alcohol **4**, on the whole we prefer the alternative preparation of **2** from the (*Z*)-allylic alcohol **10**, especially for relatively large-scale work.



EXPERIMENTAL

General methods. — T.l.c. was performed on Kieselgel G, and detection was effected with 1% sulphuric acid. ^{1}H-N.m.r. spectra were recorded for solutions in deuteriochloroform (internal Me_4Si) with a Bruker Spectrospin (90 MHz) spectrometer. Optical rotations were measured with a Perkin–Elmer 141 automatic polarimeter, using 1-dm tubes. Melting points are uncorrected.

*A minor component of the mixture is L-*glycero*-L-*gulo*-heptose, which co-exists with small proportions of the 1,6- and 1,7-anhydrides[10].

*Benzyl 5,6,7-tri-O-acetyl-2,3-O-isopropylidene-β-*L-glycero-D-manno-*heptofuranoside* (**7**). — A solution of a 7:1-mixture of **5** and **6** (0.274 g, 0.805 mmol; prepared from **4** as previously described[8]) in anhydrous pyridine (3 mL) and acetic anhydride (1.5 mL) was kept overnight at room temperature and then poured, with stirring, into ice–water. The precipitate was filtered off, washed with water, and recrystallised from ethanol to give **7** (0.313 g, 83%), m.p. 126–127°, $[\alpha]_D$ +43° (*c* 1, chloroform) (Found: C, 59.5; H, 6.6. $C_{23}H_{30}O_{10}$ calc.: C, 59.2; H, 6.5%). ^{1}H-N.m.r. data: *inter alia*, δ 7.33 (m, 5 H, Ph), 5.07 (s, 1 H, H-1), 2.09 and 2.04 (2 s, ratio 1:2, 9 H, 3 OAc), and 1.43 and 1.27 (2 s, 6 H, CMe_2).

*Benzyl 2,3-O-isopropylidene-β-*L-glycero-D-manno-*heptofuranoside* (**5**). — A solution of **7** (1.2 g, 2.6 mmol) in anhydrous methanol (40 mL) to which a small piece of sodium had been added was kept for 1 h at room temperature and then neutralised with Amberlite IR-120 (H^+) resin. The resin was filtered off and the filtrate was concentrated under reduced pressure. Chromatography of the residue on silica gel with ethyl acetate furnished **5** (0.85 g, 97%), $[\alpha]_D$ +75° (*c* 1, chloroform), as a syrup. ^{1}H-N.m.r. data: *inter alia*, δ 7.33 (m, 5 H, Ph), 5.08 (s, 1 H, H-1), 4.60 (ABq, 2 H, J_{AB} 12 Hz, PhCH_2), and 1.46 and 1.31 (2 s, 6 H, CMe_2). The ^{1}H-n.m.r. spectrum of **5** was indistinguishable from that of the principal product obtained on catalytic osmylation of **4**[8].

L-glycero-D-manno-*Heptose* (**1**). — A solution of **5** (0.85 g, 2.5 mmol) in anhydrous methanol (35 mL) containing 5% Pd/C (1 g) was shaken overnight at room temperature under a slight overpressure of hydrogen. Removal of the catalyst and the solvent gave the debenzylated compound (0.6 g, 96%) as a foam.

A solution of the debenzylated compound (0.6 g, 2.4 mmol) in M sulphuric acid (22 mL) was heated at 100° for 5 h, diluted, and then neutralised with Amberlite IR-45 (HO^-) resin. The resin was filtered off and washed thoroughly with water, and the filtrate and washings were combined and concentrated under reduced pressure to give **1** (0.47 g, ~93%) as a syrup that was sufficiently pure for most purposes. The dibenzyl dithioacetal **8**, prepared from **1** as described[9] for the D enantiomer, had m.p. 192–193° (from aqueous ethanol), $[\alpha]_D$ −29° (*c* 1.6, pyridine); lit. (D enantiomer)[9], m.p. 191° (corrected), $[\alpha]_D$ +30.3° (*c* 2.2, pyridine).

Further purification of **1** was accomplished as follows. A solution of **1** (0.35 g, 1.67 mmol) in acetic anhydride (7 mL) containing conc. sulphuric acid (4 drops) was kept overnight at room temperature and then poured into ice–water. The aqueous solution was extracted with chloroform, and the extract was processed in the usual way. Chromatography of the final residue on silica gel with ethyl acetate gave a mixture (0.605 g, 79%) of the α- and β-hexa-acetates **9** as a syrup. Zemplén deacetylation of **9** (0.593 g, 1.28 mmol), as previously described, afforded **1** (0.269 g), $[\alpha]_D$ +14° (*c* 2.5, water), as a syrup in essentially quantitative yield; lit.[4] $[\alpha]_D$ +14.1° (*c* 1.2, water).

*1,2,3,4,6,7-Hexa-O-acetyl-α-*D-glycero-D-manno-*heptopyranose* (**13**). — A solution of a 6:1-mixture of **11** and **12** (0.445 g, 1.31 mmol; prepared from **10** as previously described[8]) in M sulphuric acid (15 mL) was heated at 100° for 5 h,

diluted, and then neutralised with Amberlite IR-45 (HO^-) resin (16 g). The resin was filtered off and washed with water, and the filtrate and washings were combined and concentrated under reduced pressure to give a mixture of products (0.273 g, ~99%) containing principally **2**.

Acetylation of this mixture (0.733 g, ~3.5 mmol) in acetic anhydride (15.4 mL) containing conc. sulphuric acid (10 drops), as previously described[5], and chromatography of the residue on silica gel with ethyl acetate gave **13** (0.85 g, 53%), m.p. 139–140°, $[\alpha]_D$ +66° (*c* 2.1, chloroform); lit.[5] m.p. 138–139°, $[\alpha]_D$ +66.5° (*c* 2.5, chloroform). Initially, **13** was obtained as an unstable, crystalline modification having m.p. 107–108° (from ether–hexane), which slowly reverted to the higher-melting form. ^{1}H-N.m.r. data (360 MHz): δ 6.03 (d, 1 H, $J_{1,2}$ ~2 Hz, H-1), and 2.14, 2.13, 2.07, 2.05, 2.03, and 1.99 (6 s, 18 H, 6 OAc). In subsequent preparations, seeding with the higher-melting form avoided crystallisation of the other form.

D-glycero-D-manno-*Heptose* (**2**). — Zemplén deacetylation of **13** (0.394 g, 0.85 mmol), as previously described, furnished **2** (0.178 g, 99%), $[\alpha]_D$ +22° (*c* 1.8, methanol); lit.[6] $[\alpha]_D$ +21° (*c* 3.6, methanol).

The diethyl dithioacetal **14**, prepared from **2** as previously reported[6], had m.p. 158–159° (from ethanol), $[\alpha]_D$ +30.5° (*c* 1.1, water); lit.[7] m.p. 158–159°, $[\alpha]_D$ +31.5° (*c* 1.1, water).

*Benzyl 5,6-anhydro-2,3-O-isopropylidene-β-*L-glycero-D-manno-*heptofuranoside* (**15**). — A 100-mL, one-neck, round-bottomed flask equipped with a Teflon-coated bar magnet was oven-dried, then fitted with a serum cap, and flushed with nitrogen. The flask was charged with anhydrous dichloromethane (25 mL; distilled from calcium hydride) and cooled to −23° (dry ice–carbon tetrachloride). Titanium(IV) isopropoxide (1.12 mL, 3.76 mmol) and di-isopropyl L-(+)-tartrate (1.11 g, 4.74 mmol) were then added in turn by syringe, and the mixture was stirred for 5 min prior to the addition of solutions of **4** (0.958 g, 3.13 mmol) in anhydrous dichloromethane (5 mL) and 3M *tert*-butyl hydroperoxide in toluene (3.15 mL, 9.45 mmol). The flask was stoppered, kept overnight in a freezer at −23°, and then placed in a cooling bath at −23°, and aqueous 10% tartaric acid (8 mL) was added to the stirred solution. The mixture, containing the solidified aqueous layer, was stirred at −23° for 30 min and then at room temperature for 1 h. After dilution with dichloromethane, the organic layer was separated, washed with a little water, dried (Na_2SO_4), and concentrated under reduced pressure. A solution of the residue in ether (24 mL) was cooled (0°) and stirred with M sodium hydroxide (9.6 mL) for 30 min. More ether was then added, and the ethereal layer was separated, washed with a little aqueous sodium chloride, dried (Na_2SO_4), and concentrated under reduced pressure*. Chromatography of the residue on silica gel with ethyl acetate gave **15** (0.886 g, 88%), m.p. 79–80° (from ether–hexane), $[\alpha]_D$ +43° (*c* 1, chloroform) (Found: C, 63.5; H, 7.2. $C_{17}H_{22}O_6$ calc.: C, 63.3; H, 6.9%). ^{1}H-N.m.r.

*For large-scale preparations of **15**, an alternative work-up[13] might be preferable.

data: *inter alia*, δ 7.31 (m, 5 H, Ph), 5.11 (s, 1 H, H-1), 4.55 (ABq, 2 H, J_{AB} 12 Hz, PhCH_2), and 1.44 and 1.29 (2 s, 6 H, CMe_2).

Benzyl 2,3-O-isopropylidene-α-D-glycero-D-manno-heptofuranoside (**11**). — A solution of **15** (0.3 g, 0.93 mmol) in 0.5M sodium hydroxide (5 mL) and 1,4-dioxane (1.5 mL) was heated in a sealed tube at ~70° for 40 h. After cooling, the dark-brown hydrolysate was extracted thoroughly with chloroform, and the extract was washed with dilute hydrochloric acid and water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on silica gel (elution with 1:2 dichloromethane–acetone) gave **11** (~0.199 g, ~63%) as a pale-yellow syrup. Further chromatography gave **11**, $[\alpha]_D$ +66° (*c* 2.1, chloroform), as a colourless syrup. ^{1}H-N.m.r. data: *inter alia*, δ 7.29 (m, 5 H, Ph), 5.11 (s, 1 H, H-1), 4.53 (ABq, 2 H, J_{AB} 12 Hz, PhCH_2), and 1.42 and 1.28 (2 s, 6 H, CMe_2). The ^{1}H-n.m.r. spectrum of **11** was indistinguishable from that of the principal product obtained on catalytic osmylation of **10**[8].

Acid hydrolysis of **11** and reaction of the resulting heptose **2** with acidified ethanethiol, as before, furnished the diethyl dithioacetal **14**, m.p. and mixture m.p. 158–159°.

ACKNOWLEDGMENTS

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