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Note

The reaction of 2,3:6,7-di-*O*-isopropylidene-5-*O*-methanesulphonyl-L-*glycero*-D-*manno*-heptofuranose with sodium methoxide: an aldehyde-group participation*†

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2,3-*O*-Isopropylidene-5-*O*-toluene-*p*-sulphonyl-L-rhamnofuranose (**1**) is transformed[3] into methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranoside (**3**) on treatment with sodium methoxide in methanol, inversion of the configuration having taken place at both C-4 and C-5. The corresponding benzyl glycoside **4** is formed in a similar reaction with sodium benzyl oxide in benzyl alcohol[4]. These base-catalysed reactions take place through the formation of the acyclic epoxide intermediate **2**, which then undergoes regiospecific ring-opening at C-4 with participation by the aldehyde group[5]. Analogous solvolyses occur with other hexofuranose[6] and -pyranose sulphonates[7], and related pentose[8] and heptose sulphonates[9], although other reactions sometimes intrude[10]. In the heptose series, the reaction of 2,3:6,7-di-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl-D-*glycero*-D-*gulo*-heptofuranose (**5**) with sodium methoxide in methanol provides access to D-*glycero*-L-*talo*-heptose by way of methyl 2,3:6,7-di-*O*-isopropylidene-β-D-*glycero*-L-*talo*-heptofuranoside[9] (**6**). Recent work on the synthesis of higher-carbon sugars, particularly the discovery that OsO_4-catalysed hydroxylation of the (*E*)-allylic alcohol **7** afforded principally benzyl 2,3-*O*-isopropylidene-β-L-*glycero*-D-*manno*-heptofuranoside[11] (**8**), indicated that this approach might be extended to the synthesis of discrete derivatives of other rare heptoses. We now describe the conversion of **8** into 2,3:6,7-di-*O*-isopropylidene-5-*O*-methanesulphonyl-β-L-*glycero*-D-*manno*-heptofuranose (**14**), which then reacted with sodium methoxide in a similar fashion to the L-rhamnofuranose sulphonate **1**.

Under exclusive kinetic control, acetonation[12] of **8** with 2-methoxypropene and a *trace* of toluene-*p*-sulphonic acid afforded benzyl 2,3:6,7-di-*O*-isopropyl-

*Dedicated to Dr. R. Stuart Tipson.
†Higher-carbon sugars, Part 9. For Part 8, see ref. 1. This paper is also regarded as Part 24 of Nucleophilic Displacement Reactions in Carbohydrates. For Part 23, see ref. 2.
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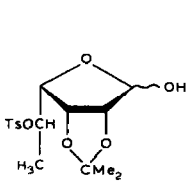
idene-β-L-*glycero*-D-*manno*-heptofuranoside (**9**) as the only product. However, as noted[12] for similar acetonations, the use of too much of the acid catalyst and prolonged reaction times promoted partial equilibration with the consequent formation of the more stable 2,3:5,6-diacetal **10**. The formation of both diacetals was helpful in establishing their structures. Thus, toluene-*p*-sulphonylation of a mixture of **9** and **10** gave exclusively the primary sulphonate **11**, which was separated from the relatively unreactive **9** by chromatography. The 7-deoxy compound **12** was isolated following reduction of **11** with lithium aluminium hydride in ether. This information established the 2,3:5,6-arrangement of the isopropylidene groups for **10**, and the expected[12] 2,3:6,7-arrangement for the kinetic product **9***.

Whereas **9** reacted sluggishly with toluene-*p*-sulphonyl chloride in pyridine, the corresponding reaction with methanesulphonyl chloride at 0° proceeded without difficulty to give benzyl 2,3:6,7-di-*O*-isopropylidene-5-*O*-methanesulphonyl-β-L-*glycero*-D-*manno*-heptofuranoside (**13**) in almost quantitative yield. The debenzylation of **13** proved to be somewhat capricious. In a preliminary experiment, debenzylation of **13** in methanol with 5% palladium on barium sulphate as the catalyst provided 2,3:6,7-di-*O*-isopropylidene-5-*O*-methanesulphonyl-β-L-*glycero*-D-*manno*-heptofuranose (**14**), whereas in other experiments with this catalyst or 5% palladium on charcoal, debenzylation was accompanied by cleavage of the 6,7-*O*-isopropylidene group to give 2,3-*O*-isopropylidene-5-*O*-methanesulphonyl-L-*glycero*-D-*manno*-heptofuranose (**15**). Acetonation of **15** in an acid-catalysed reaction with 2-methoxypropene restored the 6,7-*O*-isopropylidene group.

The mesylate **14** reacted with sodium methoxide in methanol during 3 days to give methyl 2,3:6,7-di-*O*-isopropylidene-β-L-*glycero*-L-*allo*-heptofuranoside (**16**) as the only substantial product. The gross structural features of **16** were evident from its ^{1}H-n.m.r. spectrum, which revealed that loss of the methanesulphonyloxy group from **14** was accompanied by the introduction of a methoxy group in the β-configuration at C-1 of the furanoid-ring form [δ 4.95 (s, 1 H, H-1) and 3.41 (s, 3 H, OMe)]. Acid hydrolysis of **16** and reduction of the resulting heptose furnished *meso-glycero-allo*-heptitol (**17**), which was readily identified from its characteristic ^{13}C-n.m.r. spectrum[13]. This evidence established that **16** is formed from **14** with inversion of the configuration at both C-4 and C-5, doubtless by way of aldehyde-group participation in ring-opening of the epoxide intermediate **18** at C-4.

A notable advantage of this approach to the synthesis of higher-carbon sugars is that, as **16**, the rare L-*glycero*-L-*allo*-heptose is delivered in a form predisposed towards further chemical manipulation.

*This expectation is based on the primary hydroxyl group of **8** being the favoured site for initial attack by the reagent[12].



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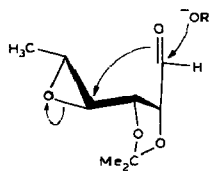

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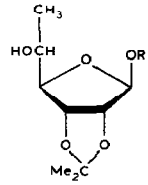

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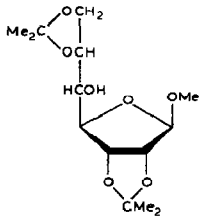
4 R = CH_2Ph



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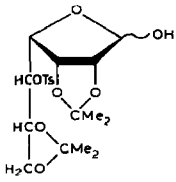

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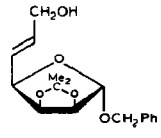

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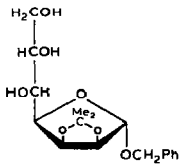

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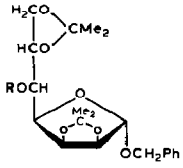
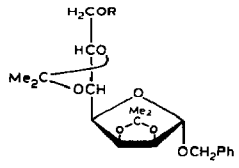
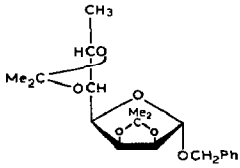


9 R = H
13 R = Ms



10 R = H
11 R = Ts



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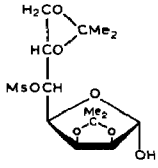

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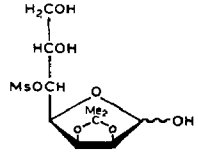

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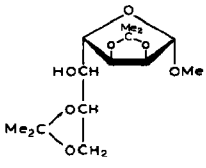

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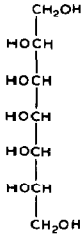

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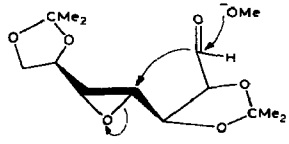

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EXPERIMENTAL

General methods. — T.l.c. was performed on Kieselgel G, and detection was effected with 1% sulphuric acid. Unless otherwise indicated, ^{1}H-n.m.r. spectra were recorded for solutions in chloroform-*d* (internal Me_4Si) either with a Bruker Spectrospin (90 MHz) spectrometer or by Edinburgh University n.m.r. Service (360 MHz). Optical rotations were measured with a Perkin–Elmer 141 automatic polarimeter, using 1-dm tubes. Melting points are uncorrected.

*Benzyl 2,3:6,7-di-O-isopropylidene-β-*L-glycero-D-manno-*heptofuranoside* (**9**). — To a stirred solution of compound[11] **8** (1.5 g, 4.41 mmol) in anhydrous dichloromethane (60 mL) at −23° was added 2-methoxypropene (0.6 mL, 6.27 mmol) and a *tiny* crystal of toluene-*p*-sulphonic acid monohydrate, and the solution was stirred for 30 min at −23°. More dichloromethane was then added, and the resulting solution was washed with saturated sodium hydrogencarbonate solution and water, dried ($MgSO_4$), and evaporated under diminished pressure. Chromatography of the residue on silica gel (elution with 10:1 dichloromethane–acetone) gave **9** (1.23 g, 73%), m.p. 92–93° (from ethyl acetate–hexane), $[\alpha]_D$ +60° (*c* 0.7, chloroform) (Found: C, 62.9; H, 7.1. $C_{20}H_{28}O_7$ calc.: C, 63.1; H, 7.4%). ^{1}H-N.m.r. data: *inter alia,* δ 7.33 (m, 5 H, Ph), 5.08 (s, 1 H, H-1), 4.56 (ABq, 2 H, J_{AB} 12 Hz, PhCH_2), and 1.47, 1.40, and 1.33 (3 s, 12 H, ratio 2:1:1, 2 CMe_2).

*Benzyl 2,3:5,6-di-O-isopropylidene-7-O-toluene-*p*-sulphonyl-β-*L-glycero-D-manno-*heptofuranoside* (**11**). — A typical experiment was conducted as follows, although the proportions of the diacetals **9** and **10** obtained in the first part of the experiment depended critically on the amount of catalyst used and the duration of the reaction.

To a stirred solution of compound[11] **8** (0.317 g, 0.93 mmol) in anhydrous dichloromethane (10 mL) at −23° was added 2-methoxypropene (0.13 mL, 1.36 mmol) and toluene-*p*-sulphonic acid monohydrate (3 mg), and the solution was stirred for 3 h at −23° and then processed as described in the preceding experiment. An approximately 1:1 mixture of benzyl 2,3:6,7- and 2,3:5,6-di-*O*-isopropylidene-β-L-*glycero*-D-*manno*-heptofuranoside (**9** and **10**, respectively) (0.35 g, 99%) was obtained after percolation of the final residue through silica gel with 10:1 dichloromethane–acetone.

To a cooled (0°) solution of the foregoing mixture of **9** and **10** (1.77 g, 4.65 mmol) in anhydrous pyridine (12 mL) was added a solution of toluene-*p*-sulphonyl chloride (1.33 g, ~7 mmol) in anhydrous pyridine (3 mL). After being stirred for 16 h at room temperature, the reaction mixture was processed conventionally. Chromatography of the residue on silica gel (elution with 50:1 dichloromethane–acetone) gave **11** (0.92 g, 37%), m.p. 105–106° (from ethyl acetate–hexane), $[\alpha]_D$ +12° (*c* 1, chloroform) (Found: C, 60.7; H, 6.2; S, 6.3. $C_{27}H_{34}O_9S$ calc.: C, 60.7; H, 6.4; S, 6.0%). ^{1}H-N.m.r. data: *inter alia,* δ 7.53 and 7.28 (2 m, 9 H, aromatic protons), 4.98 (s, 1 H, H-1), 4.46 (s, 2 H, PhCH_2), 2.33 (s, 3 H, MeAr), and 1.36, 1.30, and 1.24 (3 s, 12 H, ratio 1:2:1, 2 CMe_2). Subsequent elution with 10:1 dichloromethane–acetone gave **9** (0.85 g, 48%), m.p. and mixture m.p. 92–93°.

*Benzyl 7-deoxy-2,3:5,6-di-*O*-isopropylidene-β-*L*-glycero-*D*-manno-heptofuranoside* (**12**). — A solution of **11** (0.2 g, 0.37 mmol) in anhydrous ether (10 mL) containing lithium aluminium hydride (60 mg, ~1.58 mmol) was boiled under reflux for 6 h, and the excess of the reagent was then decomposed with wet ethyl acetate. Inorganic material was filtered off and washed with ethyl acetate, and the filtrate and washings were combined, dried ($MgSO_4$), and concentrated under diminished pressure. Chromatography of the residue on silica gel (elution with 50:1 dichloromethane–acetone) gave **12** (0.134 g, 98%), b.p. ~125° (bath)/0.03 mmHg, $[\alpha]_D$ +55° (*c* 0.9, chloroform) (Found: C, 66.1; H, 7.9. $C_{20}H_{28}O_6$ calc.: C, 65.9; H, 7.7%). ^{1}H-N.m.r. data: *inter alia*, δ 7.30 (m, 5 H, Ph), 5.07 (s, 1 H, H-1), 4.55 (ABq, 2 H, J_{AB} 12 Hz, PhCH_2), 1.45, 1.36, and 1.32 (3 s, 12 H, ratio 2:1:1, 2 CMe_2), and 1.35 (d, 3 H, $J_{6,7}$ 6 Hz, Me-7).

*Benzyl 2,3:6,7-di-*O*-isopropylidene-5-*O*-methanesulphonyl-β-*L*-glycero-*D*-manno-heptofuranoside* (**13**). — Methanesulphonyl chloride (1.4 mL, ~18 mmol) was added gradually to a stirred and cooled (0°) solution of **9** (1.72 g, 4.52 mmol) in anhydrous pyridine (30 mL), and the reaction mixture was stirred for 3 h at 0° and then kept overnight at 0°. Conventional aqueous work-up and chromatography of the residue on silica gel (elution with 50:1 dichloromethane–acetone) gave **13** (1.85 g, 89%), m.p. 79–80° (from hexane), $[\alpha]_D$ +36° (*c* 1, chloroform) (Found: C, 55.0; H, 6.6; S, 6.8. $C_{21}H_{30}O_9S$ calc.: C, 55.0; H, 6.6; S, 7.0%). ^{1}H-N.m.r. data: *inter alia*, δ 7.36 (m, 5 H, Ph), 5.09 (s, 1 H, H-1), 4.58 (ABq, 2 H, J_{AB} 12 Hz, PhCH_2), 3.16 (s, 3 H, OMs), and 1.47, 1.38, and 1.31 (3 s, 12 H, ratio 2:1:1, 2 CMe_2).

*2,3:6,7-Di-*O*-isopropylidene-5-*O*-methanesulphonyl-β-*L*-glycero-*D*-manno-heptofuranose* (**14**). — (*a*) A solution of **13** (0.192 g, 0.42 mmol) in methanol (10 mL) containing 5% palladium on barium sulphate (0.3 g) was shaken overnight at room temperature under a slight overpressure of hydrogen. The catalyst was then filtered off and the filtrate was evaporated under diminished pressure. Chromatography of the residue on silica gel (elution with 10:1 ethyl acetate–methanol) furnished **14** (0.151 g, 98%), isolated as a syrup that crystallised with time. An analytical sample of **14** had m.p. 121–122° (from ethyl acetate–hexane), $[\alpha]_D$ −15° (*c* 0.5, chloroform) (Found: C, 45.9; H, 6.5; S, 8.4. $C_{14}H_{24}O_9S$ calc.: C, 45.6; H, 6.6; S, 8.7%). ^{1}H-N.m.r. data: *inter alia*, δ 5.36 (s, 1 H, H-1), 3.14 (s, 3 H, OMs), and 1.47, 1.45, 1.36, and 1.32 (4 s, 12 H, 2 CMe_2).

(*b*) A solution of **13** (0.74 g, 1.61 mmol) in methanol (25 mL) containing 5% palladium on barium sulphate (1.4 g) was shaken overnight at room temperature under a slight overpressure of hydrogen. Work-up, as described in (*a*), and chromatography of the residue on silica gel (elution with 10:1 ethyl acetate–methanol) gave 2,3-*O*-isopropylidene-5-*O*-methanesulphonyl-L-*glycero*-D-*manno*-heptofuranose (**15**) (0.43 g, 81%), isolated as a syrup that was suitable for use in the next experiment. ^{1}H-N.m.r. data (CD_3OD): *inter alia*, δ 5.28 (s, 1 H, H-1), 3.19 (s, 3 H, OMs), and 1.43 and 1.31 (2 s, 6 H, CMe_2). Debenzylation of **13** in methanol with 5% palladium on charcoal also gave **15** in comparable yield.

2-Methoxypropene (0.2 mL, 2.1 mmol) was added to a cooled (0°) and stirred solution of **15** (0.41 g, 1.25 mmol) in anhydrous dichloromethane (20 mL) containing a tiny crystal of toluene-*p*-sulphonic acid monohydrate, and the reaction mixture was then stirred for 30 min at 0°. Work-up as described previously and chromatography of the residue on silica gel (elution with 10:1 ethyl acetate–methanol) furnished **14** (0.45 g, 98%), isolated as a syrup that crystallised with time. This compound, whose ^{1}H-n.m.r. spectrum was indistinguishable from that of **14** prepared previously, was used in the next experiment without further purification.

*Methyl 2,3:6,7-di-*O*-isopropylidene-β-*L*-glycero-*L*-allo-heptofuranoside* (**16**). — A solution of **14** (0.43 g, 1.17 mmol) in M sodium methoxide in methanol (34 mL) was kept for 3 days at room temperature, methanol (30 mL) was then added, and the base was neutralised (solid CO_2). Inorganic material was filtered off, the filtrate was evaporated under diminished pressure, and the residue was extracted with chloroform. The extract was washed with a little water, dried ($MgSO_4$), and evaporated under diminished pressure. Chromatography of the residue on silica gel (elution with 9:1 dichloromethane–acetone) gave **16** (0.241 g, 68%), b.p. 95–100° (bath)/0.03 mmHg. The distillate crystallised with time, and the crystalline material had m.p. 39–41° (without recrystallisation), $[\alpha]_D$ +53° (*c* 1.3, chloroform) (Found: C, 55.1; H, 8.0. $C_{14}H_{24}O_7$ calc.: C, 55.25; H, 7.95%). ^{1}H-N.m.r. data: *inter alia*, δ 4.95 (s, 1 H, H-1), 3.41 (s, 3 H, OMe), and 1.46, 1.40, 1.33, and 1.30 (4 s, 12 H, 2 CMe_2).

Hydrolysis of **16** (0.125 g, 0.41 mmol) with M sulphuric acid (5 mL) for 5 h at 100° followed by reduction of the resulting heptose in water (5 mL) with sodium borohydride (0.1 g, ~2.6 mmol), using the procedure previously described[11], gave *meso-glycero-allo*-heptitol (**17**) (0.075 g, 86%) having a ^{13}C-n.m.r. (90 MHz) spectrum identical to that reported in the literature[13].

ACKNOWLEDGMENTS

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