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Note

Nucleophilic displacement reactions in carbohydrates. Part XIII[1]. A synthesis of benzyl 5,6-acetylepimino-5,6-dideoxy-2,3-*O*-isopropylidene-β-L-gulofuranoside

J. S. Brimacombe*, F. Hunedy, and M. Stacey
Chemistry Department, The University, P. O. Box 363, Birmingham 15 (Great Britain)

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The adduct formed by iodine azide and 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-enose (**1**) has been shown[2] by X-ray crystallographic analysis to be 6-azido-5,6-dideoxy-5-iodo-1,2-*O*-isopropylidene-β-L-idofuranose (**2**). The addition can be said to exhibit [I-C(5)]-regiospecificity[3], or, in more familiar terms, an *anti*-Markovnikov addition has occurred. Since the addition of iodine azide to a number of terminal, unsaturated sugars was planned, it was desirable to establish a convenient chemical proof of structure of the adducts formed. It should be possible[4] to convert the adducts (*e.g.*, **2**) into 5,6-epimino derivatives (*e.g.*, **3**; R = H or Ac) by treatment with lithium aluminium hydride and *N*-acetylation. Provided that other terminal, unsaturated sugars exhibit the same regiospecificity towards iodine azide as **1**, identification of the derived epimino derivative will establish the stereochemistry of the adduct at C-5. No 5,6-epimino sugars were known at the instigation of this work, but syntheses of *N*-substituted derivatives having the D-*gluco*-[5], L-*altro*-[6], L-*ido*-[6,7], L-*talo*-[7], and L-*manno*-[7] configurations have been described recently. In view of projected studies on the addition of iodine azide to the unsaturated sugar **4**, we sought to prepare benzyl 5,6-acetylepimino-5,6-dideoxy-2,3-*O*-isopropylidene-β-L-gulofuranose (**11**). A synthesis of this epimine was achieved by procedures essentially similar to those already described[5,6].

Monomethanesulphonylation of the diol[8] **5** gave, principally, benzyl 2,3-*O*-isopropylidene-6-*O*-methanesulphonyl-α-D-mannofuranoside (**6**), whose structure was established by its conversion into 6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose (**7**) following desulphonyloxylation with lithium aluminium hydride, and hydrogenolysis of the glycosidic substituent. The identity of compound **7** was readily established by comparison of its physical and spectroscopic properties with those of the L enantiomer[9]. The sulphonic ester group of **6** was smoothly displaced with azide ion in *N*,*N*-dimethylformamide to give benzyl 6-azido-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranoside (**8**), which was esterified to give the 5-methanesulphonate (**9**).

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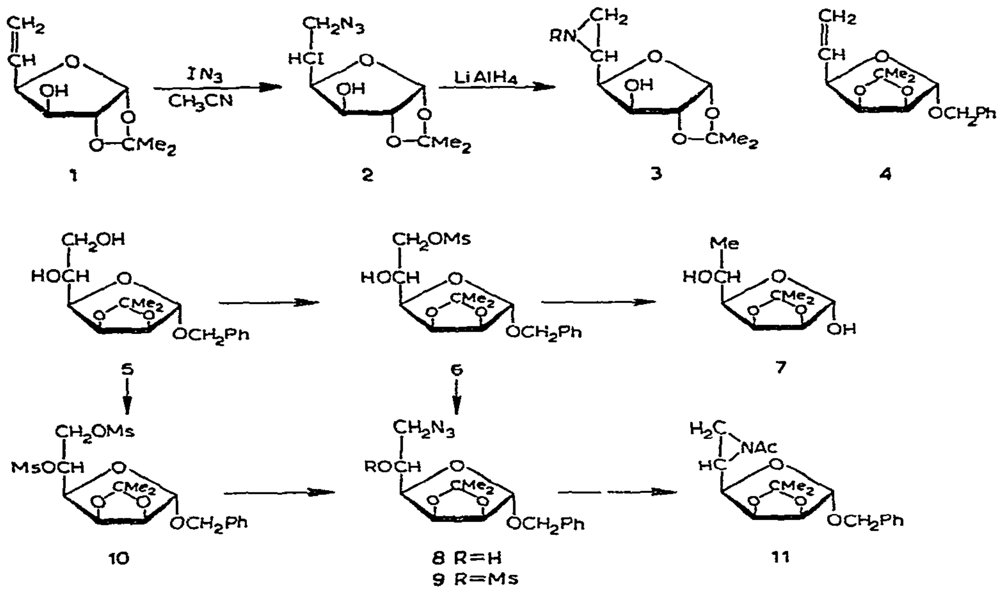
*To whom inquiries should be addressed at The Chemistry Department, The University, Dundee DD1 4HN, Scotland.



Subsequently, it was found that the primary sulphonic ester group of benzyl 2,3-*O*-isopropylidene-5,6-di-*O*-methanesulphonyl-α-D-mannofuranoside (**10**) could be selectively displaced with sodium azide in *N*,*N*-dimethylformamide, thereby affording a more direct route to **9**.

Treatment of **9** with lithium aluminium hydride at room temperature gave, after *N*-acetylation of the product, compound **11**. The n.m.r. spectrum of **11** supported the general structure assigned, but, more significantly, the i.r. spectrum exhibited a prominent absorption at *ca.* 1700 cm^{-1} characteristic[10] of the *N*-acetylepimino group, whereas absorptions attributable to a NH group were absent from the spectrum.

EXPERIMENTAL

Thin-layer chromatography (t.l.c.) and column chromatography on silica gel were conducted by using mixtures of toluene and acetone as the irrigant. Infrared spectra were recorded with a Perkin–Elmer Infracord spectrometer, and n.m.r. spectra were measured on *ca.* 10% solutions in deuteriochloroform with a Perkin–Elmer R-10 spectrometer. Light petroleum refers to the fraction having b.p. 40–60°.

Benzyl 2,3-O-isopropylidene-6-O-methanesulphonyl-α-D-mannofuranoside (**6**). — Methanesulphonyl chloride (1.15 ml) was added to a solution of the diol[8] **5** (3.1 g) in dry pyridine (50 ml), and the mixture was kept overnight at room temperature. Work up, in the usual way, gave the methanesulphonate **6** (3.5 g, 90%), m.p. 92–93° (from ether–light petroleum), $[\alpha]_D$ +69° (*c* 1, chloroform) (Found: C, 52.5; H, 5.8; S, 8.2. $C_{17}H_{24}O_8S$ calc.: C, 52.6; H, 6.2; S, 8.2%). N.m.r. data: τ *ca.* 2.70 (singlet, 5 aromatic protons), 4.92 (singlet, H-1), 5.45 (AB quartet, *J* 12 Hz, benzyl methylene protons), 6.96 (singlet, 3 protons, OMs), 8.54 and 8.68 (singlets, each 3 protons, CMe_2).

Benzyl 2,3-O-isopropylidene-5,6-di-O-methanesulphonyl-α-D-mannofuranoside (**10**). — A solution of the diol **5** (10 g) in dry pyridine (100 ml) was treated with methanesulphonyl chloride (15 ml) overnight at room temperature, whereupon the reaction mixture was worked up in the usual way to give the disulphonate **10** (14.6 g, 97%), m.p. 107–108° (from aqueous methanol), $[\alpha]_D$ +48° (*c* 1, chloroform) (Found: C, 45.9; H, 5.6; S, 13.8. $C_{18}H_{26}O_{10}S_2$ calc.: C, 45.9; H, 5.6; S, 13.85%). N.m.r. data: τ *ca.* 2.70 (singlet, 5 aromatic protons); 4.92 (singlet, H-1); 5.45 (AB quartet, *J* 12 Hz, benzyl methylene protons); 6.89, 6.95 (singlets, each 3 protons, OMs); 8.54 and 8.70 (singlets, each 3 protons, CMe_2).

6-Deoxy-2,3-O-isopropylidene-α-D-mannofuranose (**7**). — A solution of sulphonate **6** (1.7 g) in dry ether (50 ml) containing lithium aluminium hydride (1 g) was heated under gentle reflux for 18 h, whereafter ethyl acetate and water were added to decompose the excess of reagent. Solid material was filtered off, the solvents were removed, and the major component (1.1 g) of the product mixture was separated by chromatography on silica gel. A portion (0.51 g) of this component in methanol (25 ml) containing 10% palladised charcoal (0.3 g) was shaken overnight at room temperature with hydrogen at a pressure slightly greater than one atmosphere. Removal of the catalyst and solvent left a thick syrup which crystallised on standing. Recrystallisation from ether–light petroleum gave the acetal **7** (0.2 g), m.p. 90–91°, $[\alpha]_D$ −8° (*c* 1, water), whose i.r. spectrum was indistinguishable from that of the L enantiomer[9], m.p. 90°, $[\alpha]_D$ +6.4° (*c* 1, water).

Benzyl 6-azido-6-deoxy-2,3-O-isopropylidene-α-D-mannofuranoside (**8**). — A solution of sulphonate **6** (2 g) in *N*,*N*-dimethylformamide (20 ml) containing sodium azide (2 g) was heated for 4 h at 70°, whereupon t.l.c. showed that all of the starting material had reacted. Water (30 ml) was added, and the solution was extracted with chloroform (2 × 50 ml), which was washed thoroughly with water and dried ($MgSO_4$). Removal of the solvent and distillation of the residue yielded the azide **8** (1.5 g, 87%), b.p. 140–150°/0.1 mm, $[\alpha]_D$ +67° (*c* 1.4, chloroform), ν_{max} 2100 cm^{-1} (N_3) (Found: C, 56.7; H, 6.6; N, 12.1. $C_{16}H_{21}N_3O_5$ calc.: C, 57.3; H, 6.3; H, 12.5%). N.m.r. data: τ *ca.* 2.70 (singlet, 5 aromatic protons), 4.93 (singlet, H-1), 5.40 (AB quartet, *J* 12 Hz, benzyl methylene protons), 8.55 and 8.69 (singlets, each 3 protons, CMe_2).

Benzyl 6-azido-6-deoxy-2,3-O-isopropylidene-5-O-methanesulphonyl-α-D-mannofuranoside (**9**). — (*a*) The azide **8** (0.1 g) in dry pyridine (5 ml) was treated with a slight excess of methanesulphonyl chloride for 3 h at room temperature, and the solution was then processed in the usual way. Compound **9** (0.12 g, 97%) had m.p. 73–74° (from ether–light petroleum), $[\alpha]_D$ +49.5° (*c* 1, chloroform), ν_{max} 2100 cm^{-1} (N_3) (Found: C, 49.05; H, 5.8; N, 9.7; S, 8.1. $C_{17}H_{23}N_3O_7S$ calc.: C, 49.4; H, 5.6; N, 10.2; S, 7.7%). N.m.r. data: τ *ca.* 2.70 (singlet, 5 aromatic protons), 4.94 (singlet, H-1), 5.45 (AB quartet, *J* 12 Hz, benzyl methylene protons), 6.95 (singlet, 3 protons, OMs), 8.56 and 8.72 (singlets, each 3 protons, CMe_2).

(*b*) A solution of the disulphonate **10** (3 g) in *N*,*N*-dimethylformamide (30 ml) containing sodium azide (0.48 g) was heated overnight at 85–90°, and the solution was processed essentially as described in the previous azide-exchange reaction.

Recrystallisation from ether–light petroleum gave compound **9** (2.6 g, 98%), m 73–74°, $[\alpha]_D$ +51° (*c* 1, chloroform), which could not be distinguished (i.r. and n.m spectroscopy, mixed m.p.) from the product obtained in (*a*).

*Benzyl 5,6-acetylepimino-5,6-dideoxy-2,3-O-isopropylidene-β-*L*-gulofuranos* (**11**). — A solution of **9** (2 g) in ether (50 ml) containing lithium aluminium hydri (*ca.* 1 g) was stirred for 16 h at room temperature, whereupon the excess of reage was decomposed by adding ethyl acetate and water. Removal of solids and the solver left a semi-crystalline material (1.2 g, ~85%) which failed to recrystallise sat factorily. A portion of crude epimine (0.14 g) was dissolved in dry methanol (6 m acetic anhydride (2 ml) was added, and the solution was left for 2 h at room temper ture. Removal of the solvents (aided by co-distillation with toluene) afforded a thi syrup which was chromatographed on silica gel to give the acetylepimine **11** (0.14 87%), m.p. 61–62° (from chloroform–light petroleum), ν_{max} 1710 cm^{-1} (NAc $[\alpha]_D$ +26 ±2° (*c* 0.6, chloroform) (Found: C, 65.2; H, 7.2; N, 3.6. $C_{18}H_{23}NO_5$ calc C, 64.85; H, 6.95; N, 4.2%). N.m.r. data: τ *ca.* 2.70 (singlet, 5 aromatic protons 4.85 (singlet, H-1), 5.43 (AB quartet, *J* 12 Hz, benzyl methylene protons), 7.7 (singlet, 3 protons, NAc), 8.52 and 8.70 (singlets, each 3 protons, CMe$_2$).

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