SYNTHESIS OF NEW SUGAR DERIVATIVES HAVING POTENTIAL ANTI-TUMOUR ACTIVITY

PART XVI*. DERIVATIVES OF D-MANNITOL WHICH ARE DIFFERENTLY SUBSTITUTED AT C-1 AND C-6

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ABSTRACT

The synthesis of 1-bromo-6-chloro-1,6-dideoxy-D-mannitol, 1-bromo-1,6-dideoxy-6-iodo-D-mannitol, 1-bromo-1-deoxy-6-*O*-methanesulphonyl-D-mannitol **19**, and some of their derivatives, via 5,6-anhydro-2,4-*O*-benzylidene-1-bromo-1-deoxy-D-mannitol **3**, is described. Treatment of epoxide **3** with methanesulphonic acid gave, in addition to compound **19**, 3,6-anhydro-2,4-*O*-benzylidene-1-bromo-1-deoxy-D-mannitol as the main product. The *R* configuration of the asymmetric benzylidene carbon atom in the benzylidene derivatives was established by n.m.r. spectroscopy.

INTRODUCTION

D-Mannitol derivatives that are symmetrically substituted at positions 1 and 6 are well known[1]. Some of them *e.g.*, 1,6-dibromo-1,6-dideoxy- or 1,6-di-*O*-methane sulphonyl-D-mannitol[2] display significant cytostatic activity. There are few derivatives of D-mannitol carrying different reactive substituents at C-1 and C-6, and we now report on the synthesis of D-mannitol derivatives having different halogen atoms or a methanesulphonyl group and a halogen atom at positions 1 and 6.

RESULTS AND DISCUSSION

3,5-Di-*O*-acetyl-2,4-*O*-benzylidene-1,6-dibromo-1,6-dideoxy-D-mannitol **2**, prepared from 3,5-di-*O*-acetyl-1,6-dibromo-1,6-dideoxy-D-mannitol[3] **1** gave, on treatment with sodium methoxide, 5,6-anhydro-2,4-*O*-benzylidene-1-bromo-1-deoxy-D-mannitol **3**. The presence of an epoxide ring in compound **3** was proved conclusively by i.r. and n.m.r. data (see Experimental).

Treatment of the epoxide **3** under mild conditions with an excess of sodium methoxide resulted in cleavage of the epoxide ring, yielding the methyl ether **5**; the bromine atom was not affected under these conditions. The epoxide ring in **3** was easily opened by hydrogen bromide to give the dibromo derivative **6**, which gave

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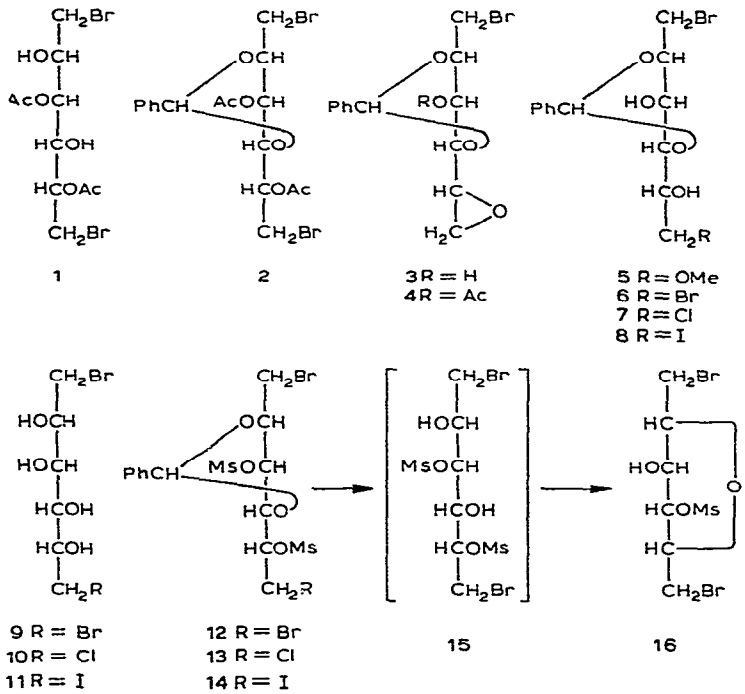
compound **2** after acetylation, and the known 1,6-dibromo-1,6-dideoxy-D-mannitol[7] **9** after hydrolysis. By the same route, the 1-bromo-6-chloro (**7**, **10**) and 1-bromo-6-iodo derivatives (**8**, **11**) were formed with hydrogen chloride and hydrogen iodide, respectively. These compounds constitute the first 1,6-dihalogeno derivatives of D-mannitol bearing different halogen atoms.

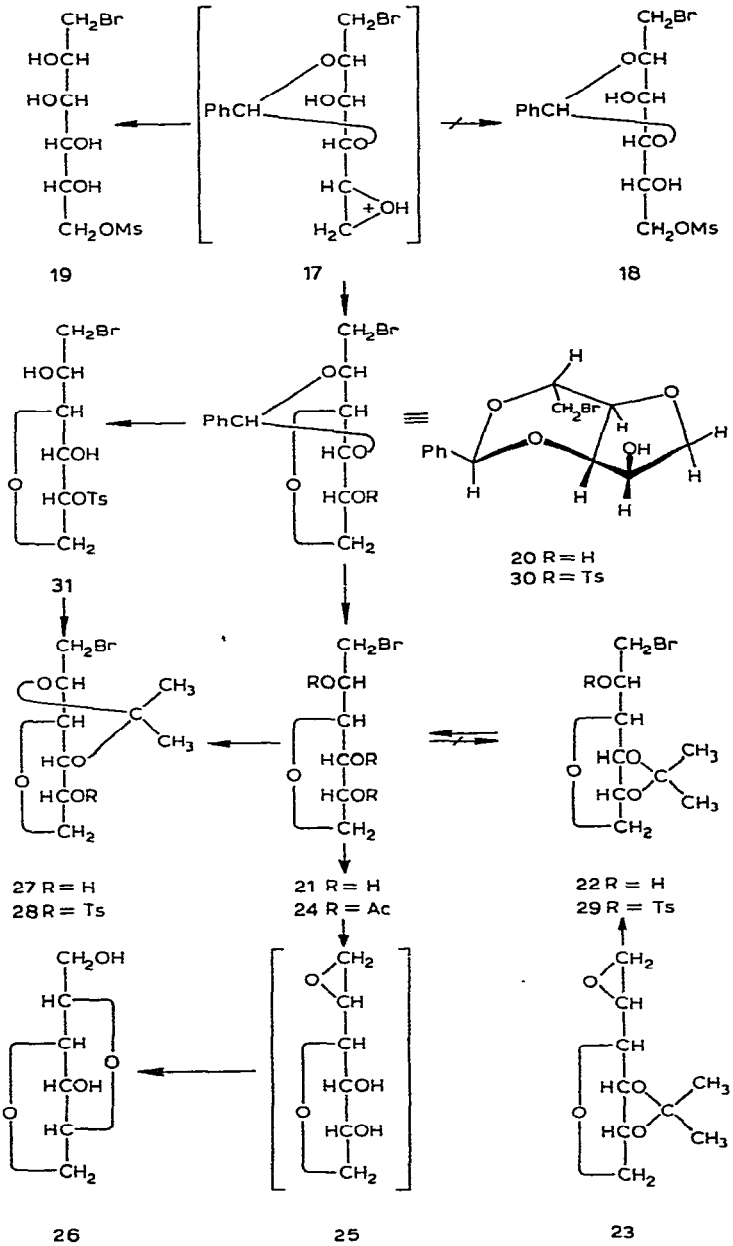
Mesylation of the benzylidene derivatives **6**, **7**, and **8** led to the corresponding dimesyl derivatives **12**, **13**, and **14**. Acid hydrolysis of the benzylidene group from **12** afforded the known[3] 2,5-anhydro-1,6-dibromo-1,6-dideoxy-4-*O*-mesyl-D-glucitol (**16**), presumably via the diol **15**.



In order to obtain 1-bromo-1-deoxy-6-*O*-methanesulphonyl-D-mannitol (**19**), the addition of methanesulphonic acid to epoxide **3** was investigated. Instead of the expected addition product **18**, the debenzylidenated ester **19** was obtained as a minor product, in addition to the anhydro compound **20**, the structure of which was elucidated as follows. The absence of a primary hydroxyl group was indicated by the i.r. data and by the failure to react with trityl chloride–pyridine. Consequently, the protonated form (**17**) of compound **3** must have reacted by attack of HO-3 at C-6. Removal of the benzylidene group from compound **20**, by hydrogenolysis or by acid hydrolysis, gave syrupy 3,6-anhydro-1-bromo-1-deoxy-D-mannitol (**21**). This compound (previously prepared[5] from the dianhydro-isopropylidene derivative **23** via **22**) was purified as the triacetate **24**. Treatment of **24** with sodium methoxide gave 1,4:2,5-dianhydro-L-gulitol (**26**), presumably[6] via the epoxide **25**.

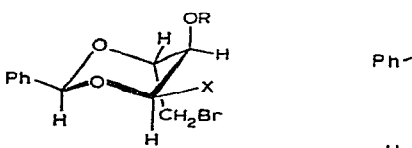
The different behaviour of the epoxides **3** and **25** towards sodium methoxide is noteworthy, but we cannot explain this difference by steric considerations.

The anhydride **21** was converted by acetone–sulphuric acid into 3,6-anhydro-1-bromo-1-deoxy-2,4-*O*-isopropylidene-D-mannitol (**27**) and not the known[5] 4,5-isomer **22**. The structure of **27** was proved by synthesis of its 5-toluene-*p*-sulphonate **28**, which was different from the isomeric 2-toluene-*p*-sulphonate[5] **29**. Tosylation of



the anhydride **20**, followed by debenzylidenation, gave 3,6-anhydro-1-bromo-1-deoxy-5-*O*-tosyl-D-mannitol (**31**) which was converted into **28** on isopropylidenation.

The *R* configuration of the benzylidene carbon atom in these acetals was assigned by n.m.r. spectroscopy. Thus, the H-3 signal for the monoacetate **4** had $J_{2,3}$ 2 Hz, characteristic for diequatorial protons. Assuming an equatorial phenyl group[8–11], this indicates that, of the theoretically probable structures **32** and **33**, the latter can be ruled out, since diaxial H-2 and H-3 protons should show a coupling constant of $J_{2,3}\sim 7$ Hz.



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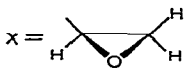

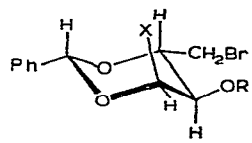

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In the biological tests, compounds **10**, **11**, and **19** showed $LD_{50}^{i.p.}$ values (mice) >1500 mg/kg.Their cytostatic activity, tested on subcutaneous Yoshida sarcoma and Walker 256 and Guerin carcinomas in daily doses of 100 mg/kg for 6 days, is listed in Table I.

TABLE I

TUMOUR INHIBITORY ACTIVITY OF COMPOUNDS **10**, **11**, AND **19**.

Compound	*Inhibition* (%)		
	Yoshida	*Walker*	*Guerin*
DBM[a]	92	90	63
10	42	37	—
11	99	96	58
19	96	97	65

[a]DBM, 1,6-dibromo-1,6-dideoxy-D-mannitol (Myelobromol®)

EXPERIMENTAL

Melting points are uncorrected. Thin-layer chromatography (t.l.c.) was carried out on Kieselgel G with ethyl acetate (*A*), carbon tetrachloride–ethyl acetate, 1:1 (*B*), 3:1 (*C*), and 5:1 (*D*). Detection was effected with 0.1M potassium permanganate–2M sulphuric acid (**1:1**), and 4-(*p*-nitrobenzyl)pyridine followed by 4M potassium hydroxide and heating at 105°. I.r. spectra were recorded with a U.R.10 instrument, and n.m.r. spectra (for solutions in $CDCl_3$) with a JEOL J.N.M.-C-60 spectrometer. All evaporations were carried out in a rotary evaporator under diminished pressure, after drying the organic solutions over sodium sulphate. The light petroleum had b.p. 60–80°.

Optical rotations were determined for 1% solutions in chloroform, unless otherwise stated.

3,5-Di-O-acetyl-2,4-O-benzylidene-1,6-dibromo-1,6-dideoxy-D-mannitol (**2**). — 3,5-Di-*O*-acetyl-1,6-dibromo-1,6-dideoxy-D-mannitol[3] (39.2 g) and zinc chloride (40 g) were stirred with benzaldehyde (200 ml) until dissolution occurred. After storage at room temperature for 48 h, the mixture was diluted with benzene (400 ml) and washed with water. The dried solution was evaporated, and benzaldehyde was removed at 120° (bath) 1 mmHg. The residue was dissolved in chloroform, washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated.

The evaporation was twice repeated with ethanol, and the residue was then crystallised from ethanol(100 ml)–light petroleum to give **2** (27.4 g, 57.4%), m.p. 98–100°, $[\alpha]_D^{20}$ *ca.* 0°, R_F 0.65 (solvent *D*). (Found: C, 42.55; H, 4.24; Br, 32.93. $C_{17}H_{20}Br_2O_6$ calc.: C, 42.52; H, 4.20; Br. 33.29%).

5,6-Anhydro-2,4-O-benzylidene-1-bromo-1-deoxy-D-mannitol (**3**). — A solution of compound **2** (48 g) in dry chloroform (500 ml) was treated with 2M methanol sodium methoxide (52 ml) below 10°. After standing for 10 min at room temperature, the reaction mixture was diluted with chloroform (1 litre) and washed with water. The dried solution was evaporated, and the crystalline residue was washed with ether to give **3** (28.4 g, 90%), m.p. 169–170°, $[\alpha]_D^{20}$ +42.5°, R_F 0.65 (solvent *B*). I.r. data: ν_{max}^{KBr} 3030 and 3010 cm^{-1} (epoxide CH coalesced with the band for aromatic CH at 3100–3000 cm^{-1}; n.m.r. data: δ 3.30 (1-proton multiplet, H-5), 2.9 (2-proton multiplet, H-6) (Found: C, 49.56; H, 4.85; Br, 25.41. $C_{13}H_{15}BrO_4$ calc.: C, 49.54; H, 4.74; Br, 25.36%).

On treatment with sodium thiosulphate[4], compound **3** liberated 95% of the alkali calculated for one epoxide ring.

2,4-O-Benzylidene-1-bromo-1-deoxy-3-O-methyl-D-mannitol (**5**). — A solution of the epoxide **3** (3.1 g) in dry chloroform (50 ml) and 2M methanolic sodium methoxide (10 ml) was kept at room temperature for one week. The mixture was then washed neutral with water, dried, and evaporated. After being washed with ether, the residue (2.1 g, 60.6%) was recrystallised from chloroform (25 ml) to give compound **5** (1,5 g, 43.2%), m.p. 145–147° $[\alpha]_D^{20}$ +51.6° (*p*-dioxane), R_F 0.25 (solvent *B*) (Found: C, 48.62; H, 5.75; Br. 22.78; CH_3O, 9.32. $C_{14}H_{19}BrO_5$ calc.: C, 48.43; H, 5.52; Br, 23.02; CH_3O, 8.95%).

3-O-Acetyl-5,6-anhydro-2,4-O-(R)-benzylidene-1-bromo-1-deoxy-D-mannitol (**4**). — A solution of the epoxide **3** (31.5 g) in pyridine (150 ml) and acetic acid (30 ml) was kept at room temp. for 5 h. T.l.c. then showed that reaction was not complete, but extention of the reaction time was accompanied by decomposition (brown colour). The reaction mixture was poured into water, and the crude product (27.5 g, 77%) recrystallised from benzene (50 ml) to yield compound **4** (22.3 g, 62.4%), m.p. 118–119°, $[\alpha]_D^{20}$ +9.05°, R_F 0.80 (solvent *B*) (Found: C, 50.50; H, 4.93; Br, 22.28, $C_{22}H_{24}BrO_8$ calc.: C, 50.44; H, 4.80; Br, 22.37%). N.m.r. data: δ 7.4 (5-proton, multiplet, aromatic), 5.80 (1-proton singlet, benzylidene CH), 5.15 (1-proton triplet, H-3, $J_{2,3} = J_{3,4} = 2$ Hz), 4.35 (1-proton triplet, H-2), 3.98 (1-proton quartet, H-4),

3,75 (2-proton doublet, H-1), 3.25 (1-proton multiplet, H-5), 2.80 (2-proton doublet, H-6), 2.15 (3-proton singlet, acetyl CH_3).

2,4-O-Benzylidene-1,6-dibromo-1,6-dideoxy-D-mannitol (**6**). — The epoxide **3** (9.5 g) was dissolved in acetone (300 ml), and M hydrobromic acid (30 ml, 1 equiv.) was added at room temperature. Compound **6** crystallised immediately, and after 24 h the product (4 g, 33.6%), m.p. 145–148°, was collected and washed with methanol. The filtrate was neutralised with sodium hydrogen carbonate and evaporated. The residue was suspended in water, filtered off, and washed with water to yield a second crop (6 g, 50.4%), m.p. 150–151°. Recrystallization of the combined material from ethyl acetate (400 ml) gave, after diminishing the volume to 100 ml, compound **6** (8.3 g, 69.5%), m.p. 162–163°, $[\alpha]_D^{20}$ +49.8° (*p*-dioxane), R_F 0.65 (solvent *B*) (Found: C, 39.34; H, 4.24; Br, 40.29. $C_{13}H_{16}BrO_4$ calc.: C, 39.42; H, 4.07; Br, 40.35%).

Acetylation of compound **6** in pyridine–acetic anhydride gave the diacetate **2**, m.p. and m.m.p. 98–100°.

Hydrolysis of the benzylidene derivative **6** (0.4 g) with 0.1M methanolic hydrogen bromide (20 ml) at room temperature for 24 h gave 1,6-dibromo-1,6-dideoxy-D-mannitol[7] (**9**) (0.22 g, 71%), m.p. 177–178°.

2,4-O-Benzylidene-1-bromo-6-chloro-1,6-dideoxy-D-mannitol (**7**) *and 1-bromo-6-chloro-1,6-dideoxy-D-mannitol* (**10**). — A solution of the epoxide **3** (3.15 g) in acetone was treated with M hydrochloric acid (10 ml). After storage for 24 h at room temperature, the solution was neutralized with sodium hydrogen carbonate, filtered, evaporated, and re-evaporated with ethanol. The residue was extracted with hot ethyl acetate (30 ml), the filtered extract was evaporated, and the residue was recrystallized from ethyl acetate (25 ml), to give compound **7** (1.5 g, 42.6%), m.p. 162–164°, $[\alpha]_D^{20}$ +51.4° (*p*-dioxane), R_F 0.6 (solvent *B*) (Found: C, 44.62; H, 4.74; Br, 22.57; Cl, 10.10, $C_{13}H_{16}BrClO_4$ calc.: C, 44.40; H, 4.59; Br, 22.73; Cl, 10.08%).

The solid material remaining after the extraction with ethyl acetate was extracted with ethanol (20 ml), and the filtered extract was combined with the filtrate obtained from the recrystallization mentioned above. Evaporation gave a solid residue which was dissolved in methanol (10 ml) and treated with conc. hydrochloric acid (10 ml) on a steam bath for 30 min. The solution was filtered with charcoal and evaporated, and ethanol was twice re-evaporated from the residue which was then recrystallized from ethanol (10 ml) to give compound **10** (0.9 g, 34.2%), m.p. 172–174°. After two recrystallizations from ethanol, the product had m.p. 176–177°, $[\alpha]_D^{20}$ *ca.* 0° (water), R_F 0.75 (solvent *A*) (Found : C, 27.02; H, 4.75; Br, 29.94; Cl, 13.50, $C_6H_{12}BrClO_4$ calc.: C, 27.34; H, 4.59; Br, 30.32; Cl, 13.46%).

2,4-O-Benzylidene-1-bromo-1,6-dideoxy-6-iodo-D-mannitol (**8**) *and 1-bromo-1,6-dideoxy-6-iodo-D-mannitol* (**11**).— A solution of the epoxide **3** (6.3 g) in methanol (200 ml) was treated with freshly distilled, 58.5% hydriodic acid (3 ml) at room temperature. After 2.5 h, the slurry was filtered and washed with methanol, aqueous sodium hydrogen carbonate, and water. The crude product (5.1 g, 57.5%), m.p. 179–180°, was recrystallized from methanol (750 ml) to give **8** (3.2 g, 36.1%), m.p. 195–196°, $[\alpha]_D^{20}$ +41.85° (*N,N*-dimethylformamide), R_F 0.55 (Solvent *B*) (Found:

C, 35.36; H, 3.82; Br, 18.23; I, 29.34. $C_{13}H_{16}BrIO_4$ calc.: C, 35.23; H, 3.64; Br, 18.04; I, 28.64%).

To the filtrate of the reaction mixture, more hydriodic acid (7 ml) was added, and the mixture was kept at room temperature overnight. The dark solution was neutralized with sodium hydrogen carbonate, filtered, and concentrated to 10 ml. After dilution with water (50 ml) and cooling, the precipitated crystals were filtered off and washed with water and with ether. The crude product **11** (1.4 g, 20.7%) was recrystallized from ethanol (15 ml), to give **11** (1.15 g, 17%), m.p. 165–166°, $[\alpha]_D^{20}$ +7.4° (*p*-dioxane), R_F 0.10 (solvent *B*) (Found: C, 20.35; H, 3.56; Br, 22.44; I, 35.82. $C_6H_{12}BrIO_4$ calc.: C, 20.30; H, 3.41; Br, 22.51; I, 35.75%).

Compound **11** was also obtained by hydrolysing (1 h) the benzylidene derivative **8** (5.1 g) in boiling methanol (100 ml) containing 5M hydrochloric acid (0.2 ml). The mixture was evaporated, and the residue, was suspended in ether, filtered off, and washed with ether. The crude product (2.9 g, 70.5%), m.p. 155°, was recrystallized from ethanol to yield **11** (2.4 g, 58.3%), m.p. 165–166° alone or in admixture with the compound described above.

2,4-O-Benzylidene-1,6-dibromo-1,6-dideoxy-3,5-di-O-methanesulphonyl-D-mannitol (**12**). — A solution of the dibromo derivative **6** (7.2 g) in pyridine (100 ml) was treated with methanesulphonyl chloride (5 ml) at room temperature overnight and then poured on to ice. The precipitate (11 g) was recrystallized from acetone (50 ml) by adding water (25 ml) to the decolourized solution to give **12** (7.4 g, 73.5%), m.p. 175–176°, $[\alpha]_D^{20}$ −8.4° (Found: C, 32.77; H, 3.71; Br. 29.48; S, 11.51. $C_{15}H_{20}Br_2O_8S_2$ calc.: C, 32.62; H, 3.65; Br. 28.94; S, 11.61%).

2,5-Anhydro-1,6-dibromo-1,6-dideoxy-4-O-mesyl-D-glucitol[3] (**16**). — A solution of compound **12** (0.3 g) in methanol (8 ml) and conc. hydrochloric acid (2 ml) was heated on a steam bath for 12 h. The solution was neutralized with sodium hydrogen carbonate, filtered, and evaporated. The residue was treated with chloroform–water, and the organic solution was washed with water, dried, and evaporated. The residue was crystallised from benzene–light petroleum to give compound **16** (0.12 g, 60%), m.p. 89–90° alone and in admixture with authentic material[3].

2,4-O-Benzylidene-1-bromo-6-chloro-1,6-dideoxy-3,5-di-O-methanesulphonyl-D-mannitol (**13**). — The bromo-chloro derivative **7** (7.2 g) was mesylated, as described for compound **6**, to give compound **13** (7.4 g, 71%), m.p. 176–177° (from acetone–water), $[\alpha]_D^{20}$ −7.1° (Found: C, 35.72; H, 4.18; Br, 15.33; Cl, 7.10; S, 12.55. $C_{15}H_{20}BrClO_8S_2$ calc.: C, 35.48; H, 3.97; Br, 15.74; Cl, 6.98; S, 12.62%).

2,4-O-Benzylidene-1-bromo-1,6-dideoxy-6-iodo-3,5-di-O-methanesulphonyl-D-mannitol (**14**). — The bromo-iodo derivative **8** (0.95 g) was mesylated as described above to give compound **14** (0.8 g, 62.4%), m.p. 147–149° (from acetone–light petroleum), $[\alpha]_D^{20}$ +26.4° (Found: C, 30.32; H, 3.79; Br, 13.74; I, 20.85; S, 10.29. $C_{15}H_{20}BrIO_8S_2$ calc.: C, 30,06; H, 3.36; Br, 13.33; I, 21.18; S, 10.70%).

1-Bromo-1-deoxy-6-O-methanesulphonyl-D-mannitol (**19**) *and 3,6-anhydro-2,4-O-benzylidene-1-bromo-1-deoxy-D-mannitol* (**20**). — A slurry of the epoxide **3** (3.15 g) in dry chloroform (100 ml) was treated at 0° with methanesulphonic acid (0.7 ml). The

clear solution obtained was kept at room temperature for three days. The precipitated crystals were filtered off and washed with chloroform. Recrystallization of the product (0.75 g, 23.2%), m.p. 114–115°, from ethyl acetate (40 ml) gave compound **19** (0.45 g, 13.9%), m.p. 124–125°, $[\alpha]_D^{20}$ +2.14° (water), R_F 0.50 (solvent *A*) (Found: C, 26.16; H, 4.81; Br, 24.61, S, 9.63. $C_7H_{15}BrO_7S$ calc.: C, 26.02; H, 4.64; Br, 24.73; S, 9.92%).

The filtrate of the original reaction mixture was washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated. The residue was dissolved in ethyl acetate and chromatographed on a column of silicic acid (carbona tetrachloride) with solvent *C*. The fractions containing the component of R_F 0.6 (solvent *B*) were evaporated, and the solid residue was recrystallized from carbon tetrachloride (10 ml) to give compound **20** (1.4 g, 44.4%), m.p. 105–106°, $[\alpha]_D^{20}$ −26.6°; i.r. data: ν_{max}^{KBr} 3420 cm^{-1} (OH), with no intense band in the range 1020–1030 cm^{-1} characteristic of primary OH; n.m.r. data: δ 3.55 (2-proton doublet, H-1); all other protons gave complex peaks at higher δ values, and no peak appeared below 3.55 (except that for the OH signal at 2.3), thereby excluding the presence of an epoxide ring (Found C, 49.83; H, 4.85; Br, 25.78 O, 20.07.; $C_{13}H_{15}BrO_4$, calc.: C, 49.54; H, 4.76; Br, 25.36. O, 20.31).

3,6-Anhydro-1-bromo-1-deoxy-D-*mannitol* (**21**). — (*a*) A solution of the anhydro derivative **20** (7.7 g) in methanol (100 ml) containing conc. hydrochloric acid (10 ml) was boiled for 30 min. The solution was evaporated, and water was twice evaporated from the residue to remove the benzaldehyde. The residue was dissolved in ethanol, neutralized with sodium hydrogen carbonate, filtered with charcoal, and evaporated to a syrup, which was freed from traces of solvents at 40°/0.1 Torr. Compound **21** remained as a colourless syrup (4.8 g, 87%), $[\alpha]_D^{20}$ +1.4° (ethanol), R_F 0.25 (solvent *A*) (Found: C, 32.03; H, 5.11; Br, 34.78. $C_6H_{11}BrO_4$ calc.: C, 31.73; H, 4.88; Br, 35.20%) The syrup consumed 1.1 mol. of periodate.

(*b*) The benzylidene derivative **20** (3.15 g) was hydrogenolysed in methanol (200 ml) in the presence of acetic acid (1 ml) and palladised carbon (1 g) for 5 h; the theoretical amount of hydrogen was consumed. The filtered solution was evaporated, and methanol was twice distilled from the residue. Traces of the solvents were removed as described above to yield compound **21** as a colourless syrup (2.2 g, 97%) showing no optical activity but the same R_F (0.25, solvent *A*) as the syrup described in (*a*).

Neither of the syrups gave a trityl derivative when treated with pyridine–trityl chloride for 30 days at room temperature, and both gave the same derivatives **26**, **27**, and **28**.

2,4,5-Tri-O-*acetyl-3,5-anhydro-1-bromo-1-deoxy*-D-*mannitol* (**24**). — The syrupy compound **21** (2 g), with pyridine (10 ml) and acetic anhydride (5 ml) in the usual manner, gave the triacetate **24** as a colourless syrup (1.6 g, 51.5%), b.p. 135–137°/0.03 mmHg, $[\alpha]_D^{20}$ −17.2°, R_F 0.90 (solvent *A*) (Found: C, 40.87; H, 4.93; Br, 22.31. $C_{12}H_{17}BrO_7$ calc.: C, 40.81; H, 4.85; Br, 22.63%).

1,4:2,5-Dianhydro-L-*gulitol* (**26**). — The triacetate **24** (1.5 g) was treated with 2M sodium methoxide (2.2 ml) in methanol (10 ml). After 2 days at room tem-

perature, the mixture was neutralized by carbon dioxide and evaporated, and the residue was dissolved in ethanol, treated with ethyl acetate, filtered, and evaporated. The residue was recrystallized from ethyl acetate (10 ml) to yield compound **26** (0.4 g, 64.5%), m.p. and mixed m.p.[6] 117–118° $[\alpha]_D^{20}$ +93.5° (water). The optical rotation, and the i.r. and n.m.r. spectra were identical with those of the authentic sample[6].

*3,6-Anhydro-1-bromo-1-deoxy-2,4-*O*-isopropylidene-*D*-mannitol* (**27**). — The anhydro compound **21** (2.0 g) was dissolved in acetone (150 ml) and treated with conc. sulphuric acid (0.5 ml). After storage for 24 h at room temperature, the solution was neutralized with sodium carbonate, filtered, and evaporated. The residue was extracted with ether, and the extract was filtered with charcoal and evaporated. Recrystallization of the residue from ether–light petroleum afforded compound **27** (1.75 g, 74.5%), m.p. 94–96°, $]\alpha[_D^{20}$ −4.4°, R_F 0.80 (solvent *A*) (Found: C, 40.46; H, 5.88; Br, 29.53. $C_9H_{15}BrO_4$ calc.: C, 40.47; H, 5.62; Br, 29.92%).

The isopropylidene derivative **27** (0.9 g) was dissolved in dry chloroform (10 ml) and treated with 2M methanolic sodium methoxide for 1 h at room temperature. The solution was then neutralized with carbon dioxide, washed dried, and evaporated. Recrystallization of the residue gave unchanged **27** (0.4 g).

*3,6-Anhydro-1-bromo-1-deoxy-2,4-*O*-isopropylidene-5-*O*-toluene-p-sulphonyl-*D*-mannitol* (**28**). — (*a*) The isopropylidene derivative **27** (0.6 g) was dissolved in pyridine (3.5 ml) and treated with toluene-*p*-sulphonyl chloride (0.6 g). The reaction mixture was kept at room temperature for one week, and then worked up in the usual manner to give compound **28** (0.55 g, 58%), m.p. 68–69° (from ether–light petroleum), $[\alpha]_D^{20}$ +14.1° (ethanol), R_F 0.80 (solvent *B*) (Found: C, 45.57; H, 4.93; Br, 18.88; S, 7.65. $C_{16}H_{21}BrO_6S$ calc.: C, 45.61; H, 5.02; Br, 18.97; S, 7.55%).

(*b*) The tosyl derivative **31** (0.3 g) was dissolved in acetone (20 ml) and treated with 1 drop of conc. sulphuric acid. After 5 h at room temperature, the solution was neutralized with sodium carbonate, filtered, and evaporated. The residue was recrystallized from ether–light petroleum to yield compound **28** (0.24 g, 72.7%), m.p. 68–69° alone and in admixture with the material described in (*a*).

*3,6-Anhydro-2,4-*O*-benzylidene-1-bromo-1-deoxy-5-*O*-toluene-p-sulphonyl-*D*-mannitol* (**30**). — The anhydro derivative **20** (3.15 g) was treated with pyridine (20 ml) and toluene-*p*-sulphonyl chloride (3 g), in the usual manner, to yield compound **30** (2.7 g, 73%), m.p. 85–86° (from methanol), R_F 0.90 (solvent *B*), $[\alpha]_D^{20}$ +27.8° (Found: C, 50.93; H, 4.75; Br, 16.91; S, 6.91. $C_{20}H_{21}BrO_6S$ calc.: C, 51.18; H, 4.51; Br, 17.03; S, 6.83%).

*3,6-Anhydro-1-bromo-1-deoxy-5-*O*-toluenesulphonyl-*D*-mannitol* (**31**). — The benzylidene derivative **30** (2.35 g) was hydrogenolysed in methanol (300 ml) in the presence of palladised carbon (3 g) and 1 drop of M sulphuric acid. After the theoretical amount of hydrogen had been consumed (7 h), the reaction mixture was filtered, neutralized with sodium hydrogen carbonate, and evaporated. The residue was recrystallized from methanol–water (1:1, 15 ml) to yield compound **31** (1.5 g, 78.9%),

m.p. 94–96°, $[\alpha]_D^{20}$ +17.7° R_F 0.45 (solvent *B*) (Found: C, 40.82; H, 4.67; Br, 20.64; S, 8.37. $C_{13}H_{17}BrO_6S$ calc.: C, 40.95; H, 4.50; Br, 20.96; S, 8.41%).

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