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SYNTHESIS OF NEW SUGAR DERIVATIVES HAVING POTENTIAL ANTITUMOUR ACTIVITY

PART XV*. 2,3:4,5-DIANHYDRO-1,6-DIBROMO-1,6-DIDEOXY-D-IDITOL AND -GALACTITOL

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ABSTRACT

The synthesis of 2,3:4,5-dianhydro-1,6-dibromo-1,6-dideoxy-D-iditol and -galactitol and some of their derivatives, starting from 1,6-dibromo-1,6-dideoxy-3,4-*O*-isopropylidene-D-mannitol, is described. The galactitol derivative was formed via 3,5-di-*O*-acetyl-1,6-dibromo-1,6-dideoxy-D-mannitol, an unusual acyl-migration product of the corresponding 2,5-diacetate. The mechanism of this acyl migration is discussed.

INTRODUCTION

2,3:4,5-Dianhydro-1,6-dibromo-1,6-dideoxy-L-iditol[1] shows significant cytostatic properties, and in studying structure–activity relationships, the synthesis of its enantiomer was attempted.

RESULTS AND DISCUSSION

Acetylation of 1,6-dibromo-1,6-dideoxy-3,4-*O*-isopropylidene-D-mannitol[1] (**1**) yielded the 2,5-diacetate **1a**, the isopropylidene group of which was removed with acetic acid–conc. hydrochloric acid. Under such conditions, an *O*-acetyl migration from C-2 to C-3 (or C-5 to C-4) took place, leading to the unsymmetrical diester **3a**. The structure of compound **3a** was proved as follows. On treatment of **3a** with methanesulphonyl chloride, the ester **4** was obtained, the acetyl groups of which could be removed with hydrochloric acid containing methanol at room temperature. The syrupy, deacylated product **5** gave on mesylation the known[2] 1,6-dibromo-1,6-dideoxy-2,3,4,5-tetra-*O*-methanesulphonyl-D-mannitol (**6**). On removal of the acetyl groups from compound **4** under more drastic conditions, one mol. of methanesulphonic acid was split off simultaneously, yielding 2,5-anhydro-1,6-dibromo-1,6-dideoxy-4-*O*-methanesulphonyl-D-glucitol (**7**). The structure of this compound was proved by mesylation, leading to the di-*O*-mesyl derivative **8**, and by treatment with sodium methoxide, giving the dianhydride **9**. The presence of one epoxide ring in

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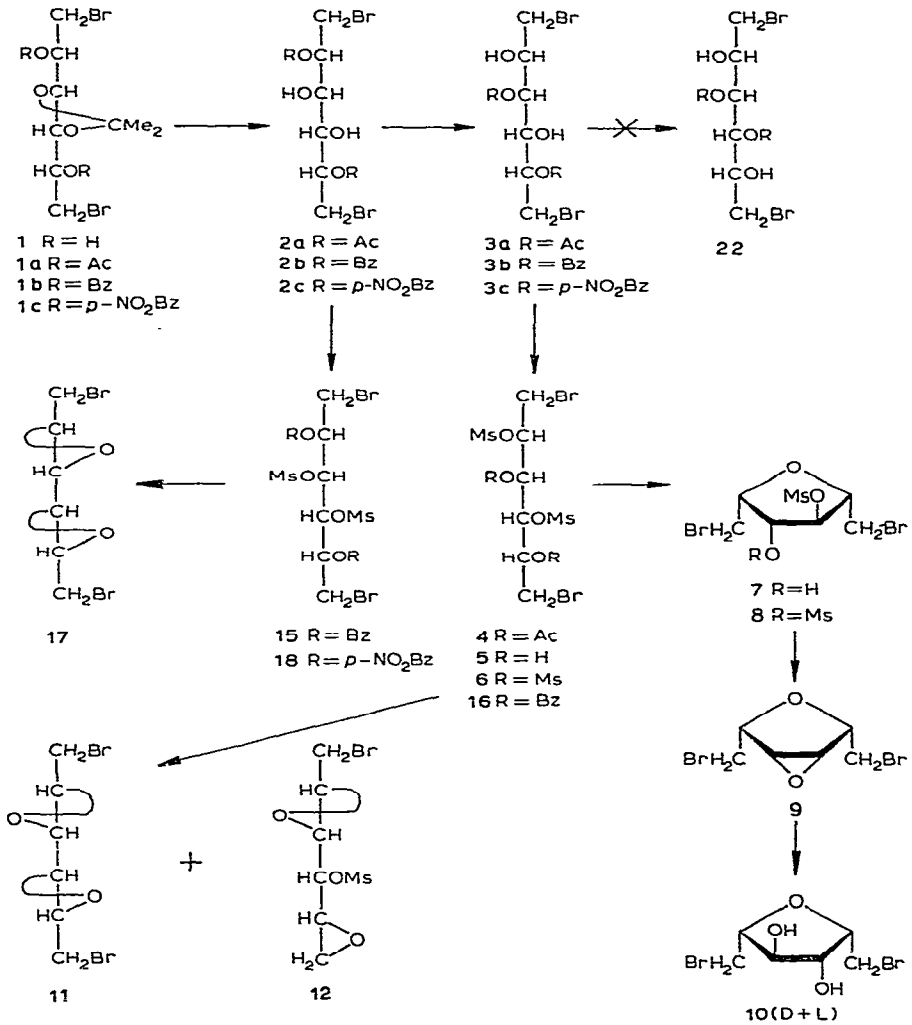
compound **9** was proved by its reaction with thiosulphate[3], which liberated 74% of hydroxide ion. The epoxide ring was hydrolysed by acid to yield the expected racemic mixture of 2,5-anhydro-1,6-dibromo-1,6-dideoxyglucitols (**10**), which consumed 1 mol. of periodate.

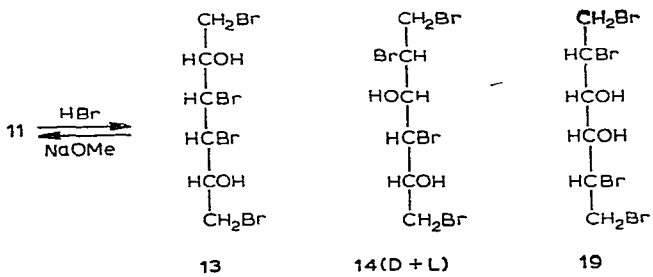


The di-*O*-mesyl derivative **4** gave, on treatment with sodium methoxide, two products having alkylating properties [reaction with 4-(*p*-nitrobenzyl)pyridine[4]], one of which was 2,3:4,5-dianhydro-1,6-dibromo-1,6-dideoxygalactitol (**11**). Compound **11** was optically inactive and had an i.r. spectrum similar to that of the corresponding L-iditol derivative[1] **17**-L; the n.m.r. spectra of **11** and **17**-L were identical. The reaction of **11** with sodium thiosulphate gave only 55% of the theoretical yield of hydroxide ion (*cf.* 74% reported for similar, nonterminal diepoxides[3]); the authentic L-iditol derivative **17**-L liberated 60% of hydroxide ion. These relatively low yields are

probably associated with the intermediates of the thiosulphate reaction which contain free hydroxyl groups, and from which hydrobromic acid is eliminated, thereby decreasing the hydroxide ion concentration.

The second product, which was obtained as a homogeneous syrup, appeared to contain two anhydro rings, one bromine atom, and one methanesulphonate group. Because of the unsymmetrical structure of compound **4**, on treatment with base HO-5 is able to attack C-4 or C-6 with displacement of the methanesulphonyloxy group or bromine atom, respectively. Likewise HO-3 can attack either C-2 or C-4. However, formation of the 2,3:5,6-diepoxide **12** is more likely, since HO-3 is *threo* to MsO-4, and *erythro* to MsO-2. Structure **12** was supported by the n.m.r. data. The signal for the proton adjacent to the mesyloxy group consists of two doublets (δ 4.32; J 5 and 3.5 Hz) as a result of two vicinal couplings. Since the signal for the H-1 protons is a singlet, $J_{1,2}$ is zero and hence the mesyloxy group must be located at C-4.

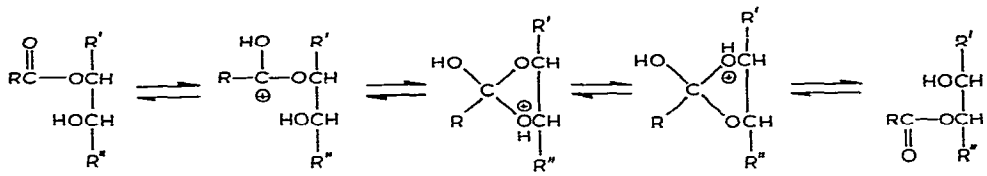
Opening of the epoxide ring in the galactitol compound **11** by conc. hydrobromic acid gave a mixture of two tetrabromo-hexitols in the ratio 1:4, neither of which consumed periodate. The cleavage reaction could lead to the tetrabromo derivatives **13**, **14**, and **19**, but it is very likely that the first epoxide cleavage will occur at C-3 or C-4, since the presence of bromine atoms at positions 1 and 6 makes an attack at C-2 or C-5 unfavoured. Thus, **19** is unlikely to be formed. The remaining epoxide ring will be flanked by bromine atoms, so that cleavage can yield the allitol derivative **13** or the racemic mixture of the tetrabromo-mannitols **14**. According to mass spectral data[5], the structure of the minor component is **13** and that of the major, **14**.



Treatment of the tetrabromo-hexitols **13** and **14** with sodium methoxide gave solely the galactitol diepoxide derivative **11**; no products having terminal epoxide groups were detected. This result can be explained by conformational analysis, since the hydroxyl groups will attack, preferentially, carbon atoms, carrying vicinal *erythro* bromine atoms.

The acetyl migration in compound **2a**, affording the unsymmetrical diester **3a**, can be explained as follows. The formation of cyclic, orthoester intermediates is well known in acyl migration in carbohydrates[6–16]. Based on this, in the proton-catalysed acyl migration **20** $\rightleftharpoons$ **21**, the equilibrium will be determined by the relative energies. In the protonated ortho-acid intermediates, the C-O link of the more positive O-atom will be split more easily. In compound **2**, O-2 and O-5 will carry the greater positive charge in the protonated, hypothetical ortho-acid intermediates, as they are more

strongly influenced by the electron-withdrawing effect of the bromine atoms. Accordingly, a double migration should occur, leading to the symmetrical diester **22**. Stopping of this rearrangement at the unsymmetrical stage can be explained by the probable conformation of the intermediate. Protonation of the acetyl carbonyl group of the rearranged product **23** would involve an attack of the sterically favoured carbonyl group of the other acetyl group, rather than that of HO-4 which is located in a sterically unfavoured *erythro* position. The eight-membered cyclic cation **24** so formed may be stable enough to prevent further migration of the acetyl groups. The seven-membered cyclic cation **25** has been suggested by Jerkeman[17] as an intermediate in certain acetyl migrations.



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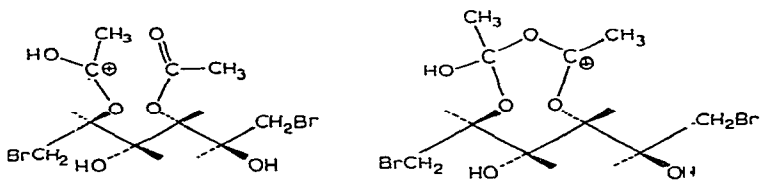

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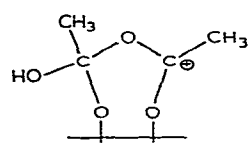

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It follows from the above mechanism that it should be possible to avoid the acyl migration by decreasing the positive charge on the carbonyl carbon atom. By using the benzoate group, the corresponding isopropylidene derivative **1b** was obtained, which, on acidic treatment, gave a mixture of the required dibenzoate **2b** and its rearranged isomer **3b**. In this series, the acyl migration was a much slower process than the cleavage of the isopropylidene group, so that, after complete hydrolysis of the protecting group (monitored by t.l.c.), the product mixture contained mainly compound **2b** and a small proportion of **3b**. Mesylation of this mixture led to a mixture of disulphonates **15** and **16**, the latter being the minor product. Treatment of this mixture with sodium methoxide gave, *inter alia*, 2,3:4,5-dianhydro-1,6-dibromo-1,6-dideoxy-D-iditol (**17**) and its galactitol isomer **11**.

When the acidic treatment of **1b** was continued after the removal of the isopropylidene group, the proportion of the rearranged product **3b** increased, due to

the slow acyl migration. This reaction was complete in 10 days, at which time mesylation and treatment with sodium methoxide gave only the galactitol diepoxide derivative **11**.

For further studies, the *p*-nitrobenzoic ester **1c** was synthesised, since its migration tendency should be further diminished. Removal of the isopropylidene group from **1c** led to the diester **2c**, and no migration product **3c** could be detected. Mesylation of **2c** gave **18**, which, on treatment with sodium methoxide, gave methyl *p*-nitrobenzoate and the expected D-iditol derivative **17**; no isomeric products were formed.

Biological investigation of the dibromo-diepoxides **17**-L, **17**, and **11** revealed identical LD_{50} values (1700 mg/kg, mouse, i.p.) for all three isomers. The L-iditol derivative **17**-L showed the strongest cytostatic activity against the Yoshida sarcoma (96% inhibition at a dose of 100 mg/kg/day × 5). The galactitol isomer **11** was somewhat less active (73% inhibition), and the D-iditol derivative **17** showed the lowest activity (47% inhibition) at the same dose.

EXPERIMENTAL

Melting points are uncorrected. Thin-layer chromatography (t.l.c.) was carried out on Kieselgel G with carbon tetracloride–ethyl acetate, 1:1 (*A*), 3:1 (*B*), and 5:1 (*C*). The detection reagents were 0.1M potassium permanganate–M sulphuric acid (1:1) and 4-(*p*-nitrobenzyl)pyridine[4] (4-NBP). I.r. spectra were recorded with a U.R.10 instrument, and n.m.r. spectra (in $CDCl_3$ as solvent) with a JEOL J.N.M.-C-60 spectrometer. All evaporations were carried out in a rotary evaporator under diminished pressure after drying the solutions over sodium sulphate. Light petroleum had b.p. 60–80°. Optical rotations were determined on 1% solutions in chloroform, unless otherwise stated.

2,5-Di-O-acetyl-1,6-dibromo-1,6-dideoxy-3,4-O-isopropylidene-D-mannitol (**1a**). — A solution of compound[1] **1** (348 g) in pyridine (400 ml) was treated with acetic anhydride (300 ml). After 24 h at room temperature, the reaction mixture was poured into water. The precipitated oil solidified on treatment with fresh water. The crude product (423 g, 98%) was recrystallized from ethanol (700 ml)–water(350 ml) to yield compound **1a** (396 g, 91.5%); m.p. 49–50°; $[\alpha]_D^{20}$ +13.4°; R_F 0.8 (solvent *B*) (Found: C, 35.95; H, 4.53; Br. 37.11. $C_{13}H_{20}Br_2O_6$ calc.: C, 36.13; H, 4.67; Br, 36.99%).

3,5-Di-O-acetyl-1,6-dibromo-1,6-dideoxy-D-mannitol (**3a**). — The isopropylidene derivative **1a** (160 g) was dissolved in acetic acid (400 ml) by gentle heating, and the solution was cooled to room temperature and treated with conc. hydrochloric acid (100 ml). After 2 h, the mixture was poured on to ice (5 litres) and was neutralised with sodium carbonate (400 g). The partly precipitated diacetate was extracted with chloroform (3 litres), and the solution was washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated. The residue was re-evaporated with benzene to give a slurry that was diluted with benzene and filtered, and the product

(80 g, 55%) was washed. Addition of ether to the filtrate gave a second crop (36 g, 25%). Recrystallization from benzene or chloroform gave **3a** (102 g, 70%); m.p. 136–137°; $[\alpha]_D^{20}$ +6.37° (methanol); R_F 0.6 (solvent *A*) (Found: C, 30.75; H, 4.11; Br, 41.35. $C_{10}H_{16}Br_2O_6$ calc.: C, 30.63; H, 4.11; Br, 40.77%). The compound did not consume periodate.

*3,5-Di-*O*-acetyl-1,6-dibromo-1,6-dideoxy-2,4-di-*O*-methanesulphonyl-*D*-mannitol* (**4**). — A solution of crude **3a** (39.2 g) in pyridine (200 ml) was treated with mesyl chloride (20 ml) at 0°. The reaction mixture was left overnight at room temperature and then poured on to ice. The precipitate (48.7 g, 89%) was recrystallized from methanol (100 ml) to give **4** (44.2 g, 80.7%); m.p. 84–86°; $[\alpha]_D^{20}$ +21.3°; R_F 0.7 (solvent *A*) (Found: C, 26.25; H, 3.72; Br, 29.31, $C_{12}H_{20}Br_2O_{10}S_2$ calc.: C, 26.29; H, 3.69; Br, 29.16; S, 11.64%).

Deacetylation of compound **4**. — A solution of the diacetate **4** (5.5 g) in methanol (100 ml) containing 10% of hydrogen chloride was kept overnight at room temperature, then neutralised with sodium hydrogen carbonate, filtered, and evaporated. The residue was treated with water–chloroform, and the organic solution was washed with water, dried, and evaporated to give compound **5** as a colorless syrup; $[\alpha]_D^{20}$ −14°; R_F 0.35 (solvent *A*) (Found: Br, 31.75; S, 11.12. $C_8H_{16}Br_2O_8S_2$ calc.: Br, 34.43; S, 13.80%). The syrup did not consume periodate.

Acetylation of syrupy **5** (2.3 g) in pyridine (5 ml) with acetic anhydride (5 ml) gave a crude product which, on recrystallization from methanol, yielded the diacetate **4** (1.8 g, 65%), m.p. 84–86° alone and in admixture with the compound mentioned above.

Mesylation of **5** (2 g) in pyridine (15 ml) with mesyl chloride (2 ml) at 0° yielded, after 24 h at room temperature, 1.8 g of crude tetrasulphonate which, on recrystallization from ethyl acetate–ether, gave compound **6** (1.3 g, 48.6%), m.p. 105–107° alone and in admixture with authentic material[2].

*2,5-Anhydro-1,6-dibromo-1,6-dideoxy-4-*O*-methanesulphonyl-*D*-glucitol* (**7**). — A solution of **4** (22 g) in methanol (400 ml) and conc. hydrochloric acid (100 ml) was boiled for 7 h, and then neutralised with sodium hydrogen carbonate, filtered, and evaporated. A solution of the residue in chloroform was washed with water, dried, and evaporated. The syrupy residue was crystallized from ether–light petroleum, yielding compound **7** (10.8 g, 73.2%), m.p. 89–90°, $[\alpha]_D^{20}$ +23.37°, R_F 0.75 (solvent *A*) (Found: C, 23.01; H, 3.32; Br, 43.60; O, 21,52; S, 9.00. $C_7H_{12}Br_2O_5S$, calc.: C, 22.84; H, 3.28; Br, 43.43; O, 21.73; S, 8.71%). Derivative **7** was obtained by treating the syrupy compound **5** in a similar way.

*2,5-Anhydro-1,6-dibromo-1,6-dideoxy-3,4-di-*O*-methanesulphonyl-*D*-glucitol* (**8**). — The monomesyl derivative **7** (3.7 g) was dissolved in pyridine (20 ml) and treated with mesyl chloride (1.2 ml) at 0°. The reaction mixture was poured on to ice, after being kept overnight at room temperature, to yield crude compound **8** (4.5 g). Recrystallization from methanol–water (9:1, 100 ml) gave cotton-like crystals (3.9 g, 87.4%), m.p. 126–127°, $[\alpha]_D^{20}$ +32.9° (Found: C, 21.87; H, 2.98; Br, 35.95; S, 14.62. $C_8H_{14}Br_2O_7S_2$, calc.: C, 21.53; H, 3.16; Br, 35.82; S, 14.38%).

2,5:3,4-Dianhydro-1,6-dibromo-1,6-dideoxygalactitol **9**. — To a solution of the anhydro derivative **7** (36.8 g) in dry chloroform (450 ml), 2M methanolic sodium methoxide (51 ml) was added. After 15 min at room temperature, the slurry was washed with water, dried, and evaporated. The remaining mobile liquid was distilled to yield compound **9** (24.85 g, 91.2%), b.p. 73–75°/0.1 mmHg, R_F 0.8 (solvent *B*), $[\alpha]_D^{20}$ 0° (Found: C, 26.62; H, 2.99; Br, 58.53%. $C_6H_8Br_2O_2$ calc.: C, 26.50; H, 2.96; Br, 58.77%). N.m.r. data: δ 4.15 (2-proton triplet, J 7 Hz, H-2 and H-5), 3.95 (2-proton singlet, H-3 and H-4), 3.40 (4-proton doublet, J 7 Hz, H-1 and H-6).

To a solution of the dianhydro derivative **9** (0.2896 g) in 50% aqueous methanol (20 ml) at 55°, sodium thiosulphate pentahydrate (10 g) was added. The liberated alkali was continuously titrated with 0.1M hydrochloric acid, using phenolphthalein and keeping the solution just pink. The total acid consumption was 7.65 ml, corresponding to 74% of the theoretical alkalinity for a monoepoxide.

2,5-Anhydro-1,6-dibromo-1,6-dideoxy-DL-*glucitol* (**10**). — The monoepoxide **9** (2.8 g) was boiled in ethanol (25 ml) with M sulphuric acid (25 ml) for 8 h. The cooled solution was neutralised with sodium hydrogen carbonate and filtered, the salts were washed with ethanol, and the combined filtrate and washings were evaporated to a volume of 20 ml. After diluting with water (80 ml), the solution was extracted with ether. Evaporation of the washed and dried ether solution gave an oil which, on re-evaporation with chloroform, solidified. It was mixed with chloroform, filtered, and washed with chloroform. Racemic **10** (1.7 g, 58.5%) thus obtained could not be recrystallized; it had m.p. 77–79°, $[\alpha]_D^{20}$ 0° (ethanol), R_F 0.2 (solvent *B*) (Found: C, 25.02; H, 3.53; Br, 55.19. $C_6H_{10}Br_2O_3$ calc.: C, 24.85; H, 3.48; Br, 55.12%). The compound liberated no alkali on treatment with sodium thiosulphate, and consumed 1.08 mol. of periodate.

2,3:4,5-Dianhydro-1,6-dibromo-1,6-dideoxygalactitol (**11**). — To a solution of the dimesyl derivative **4** (54.8 g) in dry chloroform (500 ml), 2M methanolic sodium methoxide (100 ml) was added at 0°. After 30 min, ice–water was added, and the separated organic layer was washed until neutral with cold water and then evaporated after drying. The mostly crystalline residue was boiled with methanol (50 ml), and the chilled solution was filtered. After being washed with ether, the product (13.6 g, 50%) was recrystallized from methanol (300 ml) to give diepoxide **11** (13 g, 47.7%), m.p. 131–132°, $[\alpha]_D^{20}$ 0°, R_F 0.65 (solvent *B*); ν_{max}^{KBr} 3020 (epoxide CH), 1210, 880–895 (epoxide), 465 cm^{-1} (C-Br). N.m.r. data: δ 3.40 (6-proton singlet, H-1,2,5,6), 3.05 (2-proton singlet, H-3,4) (Found: C, 26.74; H, 3.29; Br, 58.90. $C_6H_8Br_2O_2$, calc.: C, 26.50; H, 2.96; Br, 58.77%).

To a solution of the diepoxide **11** (0.2708 g) in 50% aqueous methanol (10 ml) at 55°, sodium thiosulphate pentahydrate (5 g) was added. The liberated alkali was titrated as described for compound **9**. The total acid consumption was 11.0 ml, corresponding to 55% of the theoretical alkalinity for a diepoxide.

2,3:5,6-Dianhydro-1-bromo-1-deoxy-4-O-*methanesulphonyl*-D-*glucitol* (**12**). — The methanolic mother liquor of compound **11** contained (t.l.c., solvent *B*) diepoxide **11** (R_F 0.65) and another compound (R_F 0.35) on development with 4-NBP. Separa-

tion of the two components on silicic acid (200 g, carbon tetrachloride) with solvent *B* gave the slower-moving compound **12** as a colourless syrup (5.8 g, 20.2%), $[\alpha]_D^{20}$ −1.5°. N.m.r. data: δ 4.32 (1-proton pair of doublets, J 5 and 3.5 Hz, H-4); 3.42 (2-proton singlet, H-1); 3.12 (3-proton singlet, mesyl); 3.50–3.0 (multiplet, H-2,3,5); 2.90 (2-proton doublet, $J_{5,6}$ 4 Hz, H-6). (Found: Br, 26.25; S, 10.76. $C_7H_{11}BrO_5S$ calc.: Br, 27.85; S, 11.15%). On treatment with sodium thiosulphate, compound **12** liberated 55% of the theoretical alkalinity.

Reaction of the diepoxide **11** *with conc. hydrobromic acid.* — A solution of **11** (5.4 g) in acetone (60 ml) was treated with conc. hydrobromic acid (30 ml) for 3 h at room temperature and then evaporated to a volume of 30 ml. The slurry was diluted with water (30 ml), filtered, and washed with water. The resulting mixture of compounds **13** and **14** (8.5 g, 98%), m.p. 110–115°, was dissolved in ethyl acetate and was fractionated on a column of silicic acid (800 g, carbon tetrachloride) with solvent *B*. Recrystallization of the residues (obtained by evaporation of the fractions) from ethyl acetate–ether gave the pure allitol derivative **13** (1.5 g, 17.3%), m.p. 127–128°, R_F 0.45 (solvent *B*) (Found: C, 16.98; H, 2.37; Br, 73.58%), and the racemic mannitol derivative **14** (6.1 g, 70.2%), m.p. 125–126°, R_F 0.35 (solvent *B*) (Found: C, 16.72; H, 2.39; Br, 73.42. $C_6H_{10}Br_4O_2$ calc.: C, 16.61; H, 2.32; Br, 73.68%). None of these compound consumed periodate, and both were optically inactive (acetone).

Treatment of the tetrabromo-hexitols with sodium methoxide. — (*a*) A solution of compound **13** (0.44 g) in methanol (5 ml) was treated with 2M methanolic sodium methoxide (1.2 ml) to yield, after work up as described for compound **11**, a crystalline compound (0.25 g, 91.8%) identical with the diepoxide **11**.

(*b*) Compound **14** gave, on similar treatment, 0.22 g (81%) of the diepoxide **11**.

*2,5-Di-*O*-benzoyl-1,6-dibromo-1,6-dideoxy-3,4-*O*-isopropylidene-*D*-mannitol* (**1b**). — A solution of compound **1** (34.8 g) in pyridine (200 ml) was treated at 10° with benzoyl chloride (30 ml). The reaction mixture was kept at room temperature overnight and then poured on to ice. The precipitate (56 g, m.p. 100–105°) was recrystallized from ethanol (120 ml) to give compound **1b** (46.0 g, 82.8%), m.p. 112–113°, $[\alpha]_D^{20}$ +3.9°, R_F 0.75 (solvent *C*) (Found: C, 49.46; H, 4.51; Br, 28.91. $C_{23}H_{24}Br_2O_6$ calc.: C, 49.66; H, 4.35; Br, 28.73%).

Removal of the isopropylidene group from **1b**. — To a vigorously stirred solution of **1b** (27.8 g) in acetic acid (100 ml), conc. hydrochloric acid (25 ml) was added. The slurry became clear after 5–6 h at room temperature. The mixture was worked up at different times by pouring on to ice. The precipitated oil was extracted with chloroform, the organic layer was washed with 5% aqueous sodium hydrogen carbonate and water, and evaporated to give an amorphous mixture (24–25 g, 93.5–97.2%) of isomers **2b** and **3b** (Found: Br, 29.82. $C_{20}H_{20}Br_2O_6$, calc.: Br, 30.96%). The ratio of the isomers depended on the time of the acidic treatment, and was accompanied by a change in optical rotation, as follows:

Time (h)	*6*	*8*	*48*	*240*
$[\alpha]_D^{20}$ (degrees)	+43.5	+34.6	+24.4	+13.6

On t.l.c., these mixtures gave only a single spot (R_F 0.4, solvent *C*), and no separation could be achieved by column chromatography on silicic acid.

A solution of the mixture of compounds **2b** and **3b** (24 g) in pyridine (130 ml) was treated with mesyl chloride (10 ml) at 0°. The solution was kept at room temperature overnight and then poured on to ice. The precipitated oil was extracted with chloroform, and the extract was washed (0.5M sulphuric acid, 5% sodium hydrogen carbonate), dried, and evaporated to a solid foam (28.2 g, 84%), containing the isomers **15** and **16** in a ratio equivalent to that of the starting mixture. The optical rotation of the mixtures varied between 35.7° and 28.3°. On t.l.c., these mixtures gave one spot having the same R_F value (0.40, solvent *B*) as the starting material, but giving a violet colour with 4-NBP (Found: C, 39.80; H, 3.36; Br, 23.91; S, 9.62. $C_{22}H_{24}Br_2O_{10}S_2$ calc.: C, 39.30; H, 3.60; Br, 23.77; S, 9.54%).

2,3:4,5-Dianhydro-1,6-dibromo-1,6-dideoxy-D-*iditol* (**17**). — The solid foam (67 g) obtained by mesylation of the dibenzoates **2b**+**3b** ($[\alpha]_D^{20}$ +43.5°) was dissolved in dry chloroform (600 ml) and treated with 2M methanolic sodium methoxide (105 ml). Analysis by t.l.c. (solvent *A*) then revealed five components (which reacted with 4-NBP) having R_F values 0.85 (weak), 0.80 (strong), 0.65 (medium), 0.40 (strong), and 0.25 (medium). The reaction mixture was kept at room temperature, and, after 20 min, it was washed until neutral with water, dried, and evaporated. The main bulk of the remaining methyl benzoate was removed at 0.5 Torr. The remaining orange syrup was crystallized from carbon tetrachloride (10 ml) to give crude compound **17** (4.7 g, 17.3%), m.p. 95–100°, which, from its optical rotation (+51°, acetone), was contaminated with 12% of the optically inactive galactitol isomer **11**. This mixture was recrystallized from carbon tetrachloride (50 ml) by slow cooling to 30°, and decanting off the solution from the cotton-like crystals. The latter were filtered off and washed with cold carbon tetrachloride (5 ml), giving the diepoxide **17** (2.8 g, 10.3%), m.p. 109–110°, $[\alpha]_D^{20}$ +58.4° (acetone); R_F 0.80 (solvent *A*), 0.65 (solvent *B*); the L-isomer[1] had m.p. 108–109°, $[\alpha]_D^{20}$ −56.1° (acetone). I.r. data: ν_{max}^{KBr} 3040; 3015 (epoxide CH), 1225, 910–880 (epoxide), 470 cm^{-1} (C-Br). N.m.r. data: δ 3.40 (6-proton singlet, H-1,2,5,6); 3.05 (2-proton singlet, H-3,4) (Found: C, 26.66; H, 2.98; Br, 58.73. $C_6H_8Br_2O_2$ calc.: C, 26.50; H, 2.97; Br, 58.77%).

When the solid foam, obtained by mesylation of the mixed dibenzoates **2b**+**3b** ($[\alpha]_D^{20}$ +13.4°), was treated as above, the crude galactitol derivative **11** (12%, m.p. 124–126°) was obtained. Recrystallization from methanol gave compound **11**, m.p. 130–131° alone and in admixture with the diepoxide prepared from the dimesyl derivative **4**.

*1,6-Dibromo-1,6-dideoxy-3,4-*O*-isopropylidene-2,5-di-*O*-(p-nitrobenzoyl)*-D-*mannitol* (**1c**). — To a solution of **1** (34.8 g) in pyridine (200 ml), *p*-nitrobenzoyl chloride (41 g) was added, with stirring, below 10°. The reaction mixture was kept overnight at room temperature and then poured on to ice. The precipitate (63 g) was recrystallized from ethanol (1 litre) to yield yellow plates of **1c** (56 g, 86.5%), m.p. 116–118°, $[\alpha]_D^{20}$ −3.19°, R_F 0.65 (solvent *C*) (Found: C, 42.91; H, 3.47; Br, 24.90; N, 4.36. $C_{23}H_{22}Br_2N_2O_{10}$ calc.: C, 42.74; H, 3.43; Br, 24.73; N, 4.34%).

1,6-Dibromo-1,6-dideoxy-2,5-di-O-(p-*nitrobenzoyl*)-D-*mannitol* (**2c**). — Compound **1c** (30 g) was dissolved with gentle heating in acetic acid (150 ml), the solution was quickly cooled to 20°, and conc. hydrochloric acid was added with vigorous stirring. The resulting slurry was stirred for 24 h, then cooled, and filtered, and the product was washed with 50% aqueous acetic acid (50 ml) to yield a microcrystalline, yellow powder (27.7 g, 98.5%). This product, on boiling with benzene (300 ml), cooling, and filtering, gave **2c** (25.0 g, 89.0%), m.p. 147–148°, $[\alpha]_D^{20}$ +71.0°, R_F 0.15 (solvent *C*) (Found: C, 39.71; H, 3.38; Br, 26.45; N, 4.75. $C_{20}H_{18}Br_2N_2O_{10}$ calc.: C, 39.62; H, 2.99; Br, 26.37; N, 4.62%).

1,6-Dibromo-1,6-dideoxy-3,4-di-O-*methanesulphonyl-2,5-di*-O-(p-*nitrobenzoyl*)-D-*mannitol* (**18**). — A solution of compound **2c** (6.1 g) in pyridine (50 ml) was treated with mesyl chloride (2 ml). The reaction mixture was kept overnight at room temperature and then poured on to ice. The precipitate (7.0 g, 92%) was treated three times with cold methanol (20 ml), giving crude **18** (5.2 g, 68.5%), m.p. 90–100°, $[\alpha]_D^{20}$ +50.2°; attempts at recrystallization failed (Found: C, 34.64; H, 3.05; Br, 20.83; N, 3.72; S, 8.56. $C_{22}H_{22}Br_2N_2O_{14}S_2$ calc.: C, 34.65; H, 2.91; Br, 20.96; N, 3.67; S, 8.41%).

A solution of the crude ester **18** (3.8 g) in dry chloroform (50 ml) was treated with 2M methanolic sodium methoxide (6 ml). The reaction mixture showed three spots on t.l.c. (R_F 0.65, 0.25, and 0.15, solvent *B*) with 4-NBP. After 15 min at room temperature, the slurry was washed with water, dried, and evaporated. Recrystallization from ether (10 ml) gave methyl *p*-nitrobenzoate (0.6 g). The filtrate was evaporated, and the residue put on a column of silicic acid (carbon tetrachloride). Elution with solvent *B* yielded a fraction containing, in addition to the component of R_F 0.65, methyl *p*-nitrobenzoate. The latter component was not detected by 4-NBP. The residue, obtained by evaporating this fraction, was recrystallized from carbon tetrachloride (5 ml) to yield the diepoxide **17** (0.17 g, 12.6%), m.p. 108–110° alone and in admixture with compound **17** obtained from the dibenzoate **2b**.

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