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3,4-DI-*O*-ALKYL-1,6-DIBROMO-1,6-DIDEOXYHEXITOLS*

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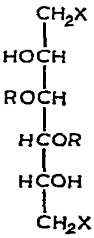
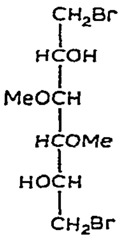
ABSTRACT

For studying the structure–activity relationship of cytostatically active hexitol derivatives, 1,6-dibromo-1,6-dideoxy-3,4-di *O*-methyl-D-mannitol (**4**), -L-iditol (**5**), -D-glucitol (**6**), and -galactitol (**8**), as well as -3,4-di-*O*-ethyl- (**27**), and -di-*O*-allyl-D-mannitol (**28**) were synthesized by treating the corresponding 1,2:5,6-dianhydrohexitol derivatives **9**, **16**, **20**, **24**, **25**, and **26**, respectively, with aqueous lithium bromide and neutralizing the liberated base with acetic acid. The reaction of diepoxides **9**, **16**, and **20** with hydrogen bromide yielded 2,5-anhydro-monobromo derivatives **12**, **17**, **21**, and **23**. The structures of **12** and **17** were proved by converting them with base into the 1,6:2,5-dianhydro compound. The biological activity of dibromides **5** and **8** proved to be comparable to that of DBD ®**, a well known cytostatic.

INTRODUCTION

The cytostatic activity of 1,6-dibromo-1,6-dideoxy-D-mannitol (**1**) was first published[2] in 1963, and several years later, the corresponding galactitol isomer **7** (DBD ®), which proved to be even more active, and which inhibited the growth of various transplanted tumors, was introduced into clinical practice[3]. Previously, we


1 X = Br, R = H
2 X = MsO, R = H
3 X = MsO, R = Me
4 X = Br, R = Me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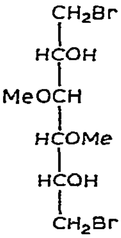
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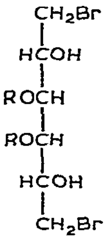
7 R = H
8 R = Me

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*Synthesis of New Sugar Derivatives Having Potential Antitumor Activity. XXI. For Part XX, see ref. 1.
**1,6-Dibromo-1,6-dideoxygalactitol, also known as dibromodulcitol.

had shown[1] that, in the case of 1,6-di-*O*-mesyl-D-mannitol (**2**), the cytostatic activity could be significantly increased by methylating the hydroxyl groups at C-3 and C-4 to give **3**. To investigate the validity of this structure–activity relationship in 1,6-dibromo-1,6-dideoxyhexitols of different configurations, the synthesis of the corresponding 3,4-di-*O*-methyl-D-mannitol (**4**), -L-iditol (**5**), -D-glucitol (**6**), and -galactitol (**8**) isomers was decided on.

DISCUSSION

It is known that, on treatment with hydrogen halides, hexitol derivatives containing one terminal, oxirane ring give the corresponding halohydrins having terminal halogen atoms[4]. A similar reaction was observed with 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-D-mannitol which, on treatment with hydrochloric or hydriodic acid, gave, besides the corresponding 1,6-dihalogeno-3,4-*O*-isopropylidene derivatives, the fully hydrolyzed 1,6-dideoxy-1,6-dihalogeno-D-mannitols[5]. The same procedure was used[6] for the synthesis of the 1,6-dibromo derivative **4**, obtained in a yield of 91 %.

Based on these facts, we treated 1,2:5,6-dianhydro-3,4-di-*O*-methyl-D-mannitol (**9**) with hydrogen bromide according to the literature[6], but obtained 2,5-anhydro-6-bromo-6-deoxy-3,4-di-*O*-methyl-D-glucitol* (**12**) instead of the desired 1,6-dibromo derivative **4**, which was formed only in traces. Due to the C_2 symmetry of the starting material **9**, the addition of hydrogen bromide on the 1,2- or 5,6-oxirane ring, and subsequent, intramolecular attack of the hydroxyl group so formed on the secondary carbon atom of the other protonated oxirane ring (**10** and **11**) leads to the same isomer (**12**).

As neither the anhydro compound **12**, nor its acetate **13** or *p*-nitrobenzoate **14**, could be crystallized, **12** was converted by treatment with potassium *tert*-butoxide into the corresponding, 1,6:2,5-dianhydro derivative (**15**), the structure of which was proved by n.m.r. spectroscopy.

A similar rearrangement-reaction of 1,2:5,6-diepoxy-hexane under acidic conditions, yielding a 2,5-disubstituted tetrahydrofuran derivative, was described almost simultaneously by Ross[7] and Wiggins and Wood[8] in 1950. The latter authors emphasized the different behavior of the corresponding 3,4-*O*-isopropylidene-D-mannitol derivative, which reacts with acids without formation of a 2,5-anhydro ring; this difference was explained by taking into account the different conformations of the diepoxides. In the hexane derivative, the two oxirane rings can approach each other quite readily by rotation of the carbon chain, whereas, in the 3,4-*O*-isopropylidene-hexitol derivative, the dioxolane ring forces them into a *trans* arrangement; consequently, formation of a 2,5-anhydro ring is only possible after cleavage of the iso-

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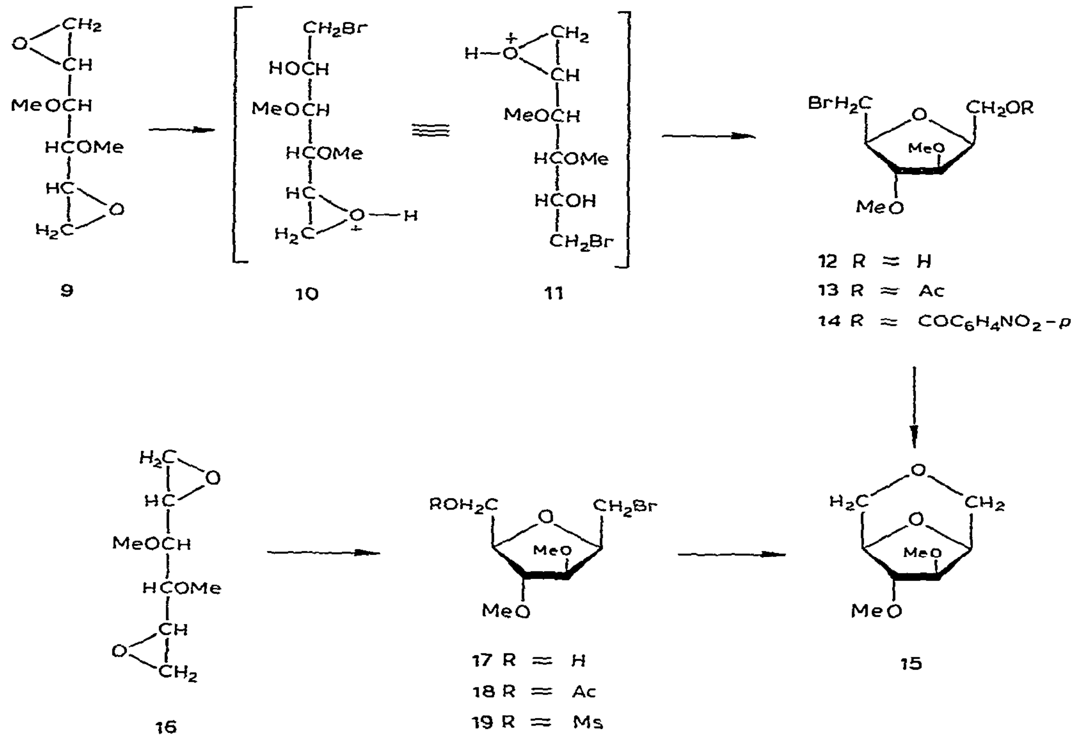
*Compound **12** could be named 2,5-anhydro-1-bromo-1-deoxy-3,4-di-*O*-methyl-L-gulitol, but its derivatives in which R $\neq$ H are D-glucitol isomers; therefore, to avoid confusion, the latter configuration is also used when R = H.



propylidene group. As the oxirane rings are much more sensitive than the dioxolane ring towards acids, addition of the nucleophile at C-1 and C-6 will predominate.

Ten years later, Vargha and Kasztreiner[9] investigated the reaction of various 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-hexitols, and proved that, under acidic conditions, 2,5-anhydro derivatives are also formed. From the reaction of the D-glucitol derivative, they separated a crystalline 2,5-anhydrodi-*O*-benzylidene-L-iditol in a yield of 18%.

It is obvious that, in our case, the diepoxide **9** resembles the diepoxyhexane much more than it does the 3,4-*O*-isopropylidene-D-mannitol derivative, as the methoxyl groups at C-3 and C-4 do not significantly restrict the free rotation of the carbon chain; consequently, the two oxirane rings can approach each other sterically, and the very stable, energetically favored, 2,5-anhydro derivatives will be formed. Change of the solvent systems, the concentration, and the temperature had no effect on the ratio of **4** to **12**.

In an attempt to avoid formation of the anhydro ring, we applied the method introduced by Jarman and Ross[10] for unprotected 1,2:5,6-dianhydrohexitols, which avoids a strongly acidic medium by using a large excess of lithium bromide and titrating the liberated hydroxyl ions (in the presence of phenolphthalein as internal indicator) with acid* at 35–40°. The diepoxide **9** reacted very slowly under these conditions,

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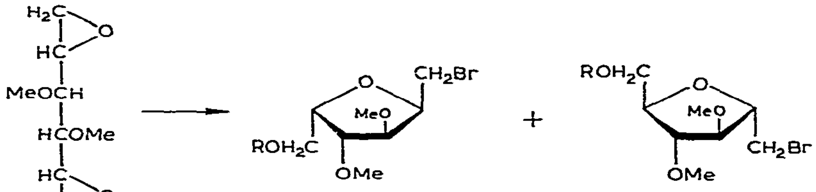
*The M hydrochloric acid used by the authors[10] was changed in our experiments to hydrobromic acid, in order to preclude formation of bromo-chloro derivatives and, according to t.l.c., the 2,5-anhydride **12** was again the main product, and the dibromide **4** was formed only as a minor component. Consequently to avoid even temporary protonation of the oxirane rings (which is the necessary step for anhydro-ring formation), the hydrobromic acid was replaced by acetic acid; this proved to be the solution to the problem, as, under these conditions, dibromide **4** was obtained in a yield of 74%, and only a trace of **12** was formed.

Treatment of the 1,2:5,6-dianhydro-L-iditol derivative **16** with aqueous hydrobromic acid gave, besides a trace of dibromide **8**, the expected 2,5-anhydro-1-bromo-1-deoxy-D-glucitol derivative **17**, which did not crystallize. As neither its acetate **18** nor its mesylate **19** was crystalline, **17** was converted by means of potassium *tert*-butoxide into the dianhydride **15**, which proved to be identical with that obtained from the corresponding D-mannitol diepoxide **9**.

The diepoxy-D-glucitol isomer **20** gave, under similar conditions, a mixture of 2,5-anhydro-1-bromo-1-deoxy-3,4-di-*O*-methyl-L-iditol (**21**) and the corresponding D-mannitol isomer (**23**) that could not be separated. G.l.c. investigation of the mixture of their acetates (**22** + **29**) showed that they were present in the ratio of 9:11.

It is interesting to compare the n.m.r. spectra of the 2,5-anhydro-6-bromo isomers **12**, **13**, and **14** with those of the 1-bromo derivatives **17**, **18**, and **19**. In the former isomers, the bromomethylene group is in *trans* relationship to the neighboring methoxyl group, and consequently, its free rotation is not hindered; due to this, the two methylene protons give a singlet-like signal. On the other hand, in the 1-bromo compounds, the aforementioned two groups are in *cis* arrangement, and the rotation of the bromomethylene group is therefore restricted. As a consequence, the two



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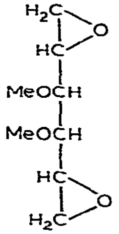
21 R = H
22 R = Ac

23 R = H
29 R = Ac



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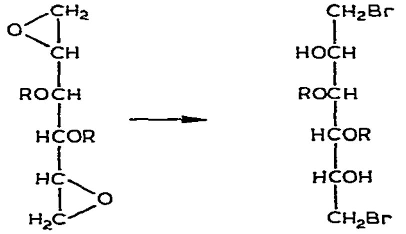

25 R = Et
26 R = $CH_2CH{=}CH_2$

27 R = Et
28 R = $CH_2CH{=}CH_2$

TABLE I

TUMOR-INHIBITORY ACTIVITY OF COMPOUNDS **4**, **5**, **8**, **27**, AND **28**

	Compound					
	4	**5**	**8**	**27**	**28**	DBD
	Inhibition (%)					
Yoshida s c sarcoma (p.o)[a]	100	100	35	30	0	94[b]
Rauscher leukemia (i p.)[c]	100[d]	52	15	0	0	—

[a] s c. = subcutaneous; p o. = *per os* [b] At a dose of 6 × 25 mg. [c] i p. = intraperitoneal [d] At a dose of 4 × 30 mg.

corresponding, diastereotopic protons appear as a very broad, complex multiplet, due to the geminal and vicinal couplings.

The diepoxides **16**, **20**, and **24** could readily be converted into the 1,6-dibromo-1,6-dideoxy-L-iditol (**5**), -D-glucitol (**6**), and -galactitol (**8**) derivatives, respectively, by treating them with aqueous lithium bromide as already described for the synthesis of the D-mannitol isomer **4**

For investigating the influence of the length of the alkyl chains at O-3 and O-4 on the biological activity, 1,6-dibromo-1,6-dideoxy-3,4-di-*O*-ethyl- (**27**) and -3,4-di-*O*-allyl-D-mannitol (**28**) were prepared, starting from the corresponding diepoxides **25** and **26**, respectively. In biological tests, the 3,4-di-*O*-alkyl-1,6-dibromo derivatives **4**, **5**, **8**, **27**, and **28** showed $\mathrm{LD}_{50}^{\mathrm{ip}}$ values (in mice) of >300 mg/kg. Their cytostatic activities *versus* subcutaneous (s.c.) Yoshida sarcoma and Rauscher leukemia in daily doses of 100 mg/kg for four days are listed in Table I.

Interestingly, whereas, for the series of the corresponding diepoxides, the activity decreased in the following order: galactitol (**24**) > D-glucitol (**20**) ≫ D-mannitol (**9**) > L-iditol (**16**), this was changed for the 1,6-dibromo analogs to L-iditol (**5**) > galactitol (**8**) ≫ D-mannitol (**4**). Most striking is the high activity of the compound having the L-*ido* configuration, proving that, in this instance, the corresponding diepoxide **16** may be excluded as being a biologically active metabolite.

EXPERIMENTAL

General methods. — Melting points are uncorrected. T.l.c. was effected on Kieselgel G with ethyl acetate–carbon tetrachloride, 2:1 (*A*), 1:1 (*B*), 1:2 (*C*), and 1:3 (*D*). For detection, 1:1 0.1M potassium permanganate–M sulfuric acid was used at 105°. Column chromatography was performed on Kieselgel 40 (63–200 μm). ^{1}H-N.m.r. spectra (60 MHz) were recorded at room temperature with a JEOL 60-HL spectrometer for solutions in chloroform-*d*, with tetramethylsilane as the internal standard. G.l.c. was conducted with an F-21 Perkin–Elmer gas chromatograph, using a glass column (2 m × 4 mm) packed with 1 % of XE-60 on Chromosorb W; temperatures: 100° start, heating rate 3°.min^{-1}; carrier gas: nitrogen at 45 mL.min^{-1}.

All evaporations were performed in a rotary evaporator under diminished pressure, after the organic solutions had been dried with sodium sulfate. Light petroleum refers to the fraction having b.p. 60–80°. Optical rotations were determined at $c = 1$.

*1,6-Dibromo-1,6-dideoxy-3,4-di-*O*-methyl-*D*-mannitol* (**4**). — To a stirred, aqueous solution of lithium bromide (43 mL; 90 g of LiBr per 100 mL) was added diepoxide[1] **9** (4.3 g), and the alkalinity developed was continuously neutralized with glacial acetic acid, in the presence of phenophthalein as the indicator. The temperature of the mixture was kept at 20° by gentle cooling. Two equivalents of acid were consumed during 2 h, while the dibromide formed was gradually precipitated. After being kept overnight at room temperature, the suspension was filtered and the solid was washed with water (7.2 g, 86.5%); after recrystallization from water (70 mL), it gave pure **4** (4.9 g, 59%), m.p. 126–127°, $[\alpha]_{\mathrm{D}}^{20}$ +56.7° (MeOH); R_F 0.55 (*B*).

Anal. Calc. for $C_8H_{16}Br_2O_4$: C, 28.59; H, 4.80; Br, 47.56. Found: C, 28.68; H, 4.59: Br, 47.31.

Recrystallization of crude **4** must be performed quickly, as, on heating in water, decomposition occurs, with liberation of hydrobromic acid.

*1,6-Dibromo-1,6-dideoxy-3,4-di-*O*-methyl-*L*-iditol* (**5**). — The diepoxide[1] **16** (1.7 g) was treated with the lithium bromide solution (31 mL) as described for compound **4**, and the crude dibromide precipitated was filtered off after 2 h, and washed with water. The dried material was dissolved in ether (250 mL) and light petroleum was added to incipient turbidity. The suspension was filtered through charcoal, and the filtrate was concentrated to 100 mL. The crystals deposited after adding light petroleum (50 mL), and cooling, were filtered off and washed with ether, to yield pure **5** (2.7 g, 77.5%), m.p. 107–109°, $[\alpha]_{\mathrm{D}}^{20}$ +40.2° (MeOH), +51.5° (water); R_F 0.55 (*B*).

Anal. Calc. for $C_8H_{16}Br_2O_4$: C, 28.59: H, 4.80; Br, 47.56. Found: C, 28.55; H, 4.91; Br, 47.62.

*1,6-Dibromo-1,6-dideoxy-3,4-di-*O*-methyl-*D*-glucitol* (**6**). — The diepoxide[1] **20** (1.7 g) was treated with the lithium bromide solution (34 mL) as described for compound **4**. The reaction was very fast, and two equivalents of acetic acid were consumed within 10 min, while a sticky material separated out. The mixture was diluted with water (15 mL) and extracted with ethyl acetate; the extract was washed with a small volume of water, dried, and concentrated to 15 mL. The crystals that separated after addition of light petroleum (15 mL) were filtered off, after cooling, and washed with ether, to give pure **6** (0.45 g, 13.4%), m.p. 151–154° (the molten material solidified at 225°, without further melting until 260°), $[\alpha]_{\mathrm{D}}^{20}$ +24.6° (MeOH); R_F 6.65 (*B*).

Anal. Calc. for $C_8H_{16}Br_2O_4$: C, 28.59; H, 4.80; Br, 47.56. Found: C, 28.42; H, 4.99; Br, 47.88.

*1,6-Dibromo-1,6-dideoxy-3,4-di-*O*-methylgalactitol* (**8**). — The diepoxide[1] **24**

(5.5 g) was treated with the lithium bromide solution (55 mL) as described for compound **4**. The reaction was complete in 5 min. The precipitated dibromide was filtered off, and washed successively with water, ethanol, and ether. The crude product (7.65 g, 72%) gave, on recrystallization from ethanol (200 mL), pure **8** (5.2 g, 49%), m.p. 157–158°; R_F 0.70 (*B*).

Anal. Calc. for $C_8H_{16}Br_2O_4$: C, 28.59; H, 4.80; Br, 47.56. Found: C, 28.62; H, 4.60; Br, 47.17.

*2,5-Anhydro-6-bromo-6-deoxy-3,4-di-O-methyl-*D*-glucitol* (**12**). — A solution of diepoxide[1] **4** (17.4 g) in acetone (50 mL) was added dropwise to an ice-cold, stirred solution of conc. hydrobromic acid (20 mL) in water (20 mL). The mixture was stirred for 15 min at room temperature, and was then made neutral with solid sodium hydrogencarbonate. The precipitated salts were filtered off, and the filtrate was evaporated. Ethanol was added to, and evaporated from, the residue, which was then filtered with the aid of ethanol. The filtrate was evaporated, and the residue was purified by column chromatography using solvent *A* for elution. The fractions having R_F 0.55 were evaporated, to give pure **12** (20.2 g, 74%) as a syrup, $[\alpha]_D^{20}$ +15.6° ($CHCl_3$); ^{1}H-n.m.r. data: δ 4.28 (s, $BrCH_2$), 3.60 ($HOCH_2$), 3.38 and 3.32 (2 OMe).

Anal. Calc. for $C_8H_{15}BrO_4$: Br, 31.33. Found: Br, 31.61.

*1-O-Acetyl-2,5-anhydro-6-bromo-6-deoxy-3,4-di-O-methyl-*D*-glucitol* (**13**). — Crude **12**, obtained from 8.7 g of diepoxide **4**, was treated with pyridine (24 mL) and acetic anhydride (16 mL), to give, after the usual processing, and column chromatography with solvent *C*, pure **13** (11.7 g, 56%) as a syrup, $[\alpha]_D^{20}$ —8° ($CHCl_3$); R_F 0.65 (*C*); ^{1}H-n.m r. data: δ 4.1 (s, $BrCH_2$), 3.72 (m, $AcOCH_2$), 3.35 (s, 2 OMe), and 2.00 (acetyl-Me).

Anal. Calc. for $C_{10}H_{17}BrO_5$: C, 40.42; H, 5.77; Br, 26.89. Found: C, 40.68: H, 5.89; Br, 26.72.

*2,5-Anhydro-6-bromo-6-deoxy-3,4-di-O-methyl-1-O-(*p*-nitrobenzoyl)-*D*-glucitol* (**14**). — A solution of anhydride **12** (1.3 g) in pyridine (5 mL) was treated with *p*-nitrobenzoyl chloride (1 g). According to t.l.c., the reaction was complete within 15 min. After 1 h, the mixture was processed in the usual way, to give **14** as a yellow syrup (1.4 g, 70%), $[\alpha]_D^{20}$ —5° ($CHCl_3$); R_F 0.8 (*B*); ^{1}H-n.m.r. data: δ 8.25 (s, 4 H arom.) and 3.45 (2 OMe).

Anal. Calc. for $C_{15}H_{18}BrNO_7$: Br, 19.80; N, 3.17. Found: Br, 19.56; N, 3.02.

*1,6:2,5-Dianhydro-3,4-di-O-methyl-*D*-glucitol* (**15**). — A solution of **12** or **17** (5.1 g) in 0.5M 1-butanolic potassium 1-butoxide (45 mL) was boiled on a steam bath for 1 h. The cooled solution was made neutral with M hydrochloric acid, and was then evaporated. The residue was dissolved in chloroform, and the solution washed with water, dried, and evaporated, to give, after distillation, pure **15** (2.2 g, 63.3%); b.p.$_{0.4}$ 180°; $[\alpha]_D^{20}$ —22.5° ($CHCl_3$); R_F 0.55 (*B*); ^{1}H-n.m.r. data: δ 3.38 and 3.30 (2 OMe).

Anal. Calc. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.98; H, 7.87.

*2,5-Anhydro-1-bromo-1-deoxy-3,4-di-O-methyl-*D*-glucitol* (**17**). — A solution of diepoxide[1] **16** (3.4 g) in acetone (20 mL) was added to a cold, stirred solution of conc. hydrogen bromide (3 mL) in water (3 mL). The mixture was processed as described for compound **12**, to give a mixture which was separated by column chromatography using solvent *B* for elution. On evaporation, the fraction having R_F 0.75 gave pure dibromide **5** (0.25 g, 3.7%), identical with that already described.

Evaporation of the fractions having R_F 0.60 gave the anhydride **17** as a colorless syrup (3.5 g, 68.5%), $[\alpha]_D^{20}$ +76° ($CHCl_3$); ^1H-n.m.r. data: δ 4.05 (m, $BrCH_2$), 3.70 (s, $HOCH_2$), and 3.33 (2 OMe).

Anal. Calc. for $C_8H_{15}BrO_4$: Br, 31.33. Found: Br, 31.05.

Acetylation of **17** (1.2 g) with acetic anhydride–pyridine gave, after the usual processing, **18** (1 g, 66.6%) as a syrup, $[\alpha]_D^{20}$ +96° ($CHCl_3$); R_F 0.65 (*C*); ^1H-n.m.r. data: δ 4.12 (m, $BrCH_2$), 4.10 (s, $AcOCH_2$), 3.40 and 3.35 (2 OMe), and 2.05 (2 acetyl-Me).

Anal. Calc. for $C_{10}H_{17}BrO_5$: Br, 26.89. Found: Br, 26.60.

Mesylation of **17** (1.2 g) with mesyl chloride–pyridine gave, after the usual processing, and purification by column chromatography (*C*), pure **19** (0.75 g, 45%) as a syrup, $[\alpha]_D^{20}$ +77.8°; R_F 0.45 (*C*).

Anal. Calc. for $C_9H_{17}BrO_6S$: Br, 23.98; S, 9.62. Found: Br, 23.63; S, 9.95.

*2,5-Anhydro-1-bromo-1-deoxy-3,4-di-*O*-methyl-*L*-iditol* (**21**) *and -*D*-mannitol* (**23**). — A solution of diepoxide[1] **20** (5.7 g) in methanol (30 mL) was added to a cooled and stirred solution of 6M methanolic hydrogen bromide (20 mL). After 1 h at room temperature, the solution was made neutral with solid sodium hydrogencarbonate, and filtered. The filtrate was evaporated, and the residue purified by column chromatography (*A*); on evaporation, the fractions having R_F 0.50 gave the isomeric mixture (**21** + **23**) as a syrup (6 g, 71.8%), $[\alpha]_D^{20}$ +89° ($CHCl_3$).

Anal. Calc. for $C_8H_{15}BrO_4$: Br, 31.3. Found: Br, 31.0.

Acetylation of the aforementioned mixture (**21** + **23**; 5.1 g) with acetic anhydride (15 mL) and pyridine (20 mL) gave, after the usual processing and distillation, a syrup (5.6 g, 94%) which, according to g.l.c., contained two isomers (**22** + **29**) in the ratio of 9:11; b.p.$_{0.1}$ 100–105°; $[\alpha]_D^{20}$ +60° ($CHCl_3$); R_F 0.85 (*A*); ^1H-n.m.r. data; δ 3.40 and 3.35 (3 + 1 OMe) and 2.00 (4 acetyl-Me).

Anal. Calc. for $C_{10}H_{17}BrO_5$: Br, 26.89. Found: Br, 26.32.

*1,6-Dibromo-1,6-dideoxy-3,4-di-*O*-ethyl-*D*-mannitol* (**27**). — A solution of diepoxide[1] **25** (4.3 g) in 2-propanol (5 mL) was added to a stirred, aqueous solution of lithium bromide (43 mL; 95 g of LiBr/100 mL), and the mixture was treated as described for compound **4**. After consumption of 1.5 mL of acetic acid, the turbid solution was diluted with water (20 mL), and extracted with ethyl acetate (400 mL); the extract was dried, and evaporated, and the residue was filtered with the aid of water, to give pure **27** (3.55 g, 46%), m.p. 99–101°, $[\alpha]_D^{20}$ +51° (MeOH); R_F 0.55 (*D*)

Anal. Calc. for $C_{10}H_{20}Br_2O_4$: C, 32.99; H, 5.54; Br, 43.90. Found: C, 32.81; H, 5.42; Br, 43.96.

*3,4-Di-*O*-allyl-1,6-dibromo-1,6-dideoxy-*D*-mannitol* (**28**). — The diepoxide[1] **26**

(3.4 g) was treated with lithium bromide as described for compound **27**, to give pure **28** (3.5 g, 60%), m.p. 72–75°, $[\alpha]_D^{20}$ +43.4° (MeOH); R_F 0.50 (*D*).

Anal. Calc. for $C_{12}H_{20}Br_2O_4$: C, 37.13; H, 5.19; Br, 41.18. Found: C, 37.02; H, 5.36; Br, 41.11.

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