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3,4-DI-*O*-ALKYLHEXITOL DERIVATIVES CONTAINING BIOLOGICAL ALKYLATING GROUPS AT C-1 AND C-6*

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ABSTRACT

For studying the structure–activity relationship of cytostatically active hexitol derivatives, 1,2 5,6-dianhydro-3,4-di-*O*-methyl-(**17**), -ethyl-, -allyl-, and -pentyl-D-mannitol, as well as 1,2 5,6-dianhydro-3,4-di-*O*-methyl-L-iditol, -galactitol, and -D-glucitol were synthesized In the synthesis of **17**, 2,5-di-*O*-acetyl-1,6-di-*O*-mesyl-3,4-di-*O*-methyl-D-mannitol was used as an intermediate that could be deacetylated to give 1,6-di-*O*-mesyl-3,4-di-*O*-methyl-D-mannitol, a compound that proved to be about ten times as active as 1,6-di-*O*-mesyl-D-mannitol ("Mannitol-Myleran"), a known cytostatic compound

INTRODUCTION

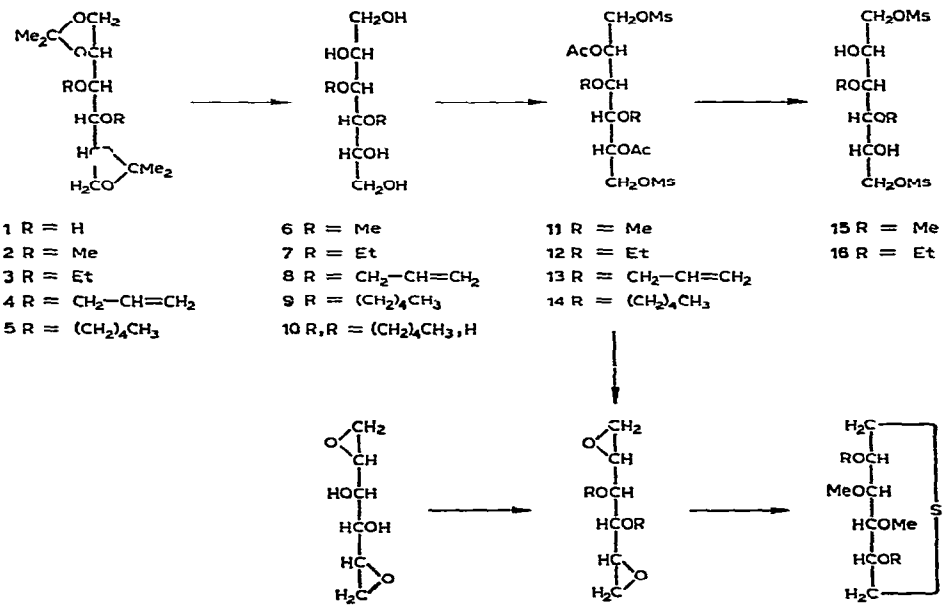
In order to study the structure–activity relationship of the ulcerostatically active 1,6-anhydro-2,5-di-*O*-methyl-3,4-di-*O*-(methylsulfonyl)-1(6)-thiohexitols[2], the synthesis of the corresponding isomers containing the methoxyl groups on C-3 and C-4 was undertaken Biological investigation of 3,4-di-*O*-methyl-1,6-di-*O*-(methylsulfonyl)-D-mannitol (**15**), an intermediate in the synthesis of the corresponding 1,6-anhydro-1(6)-thio-D-mannitol derivative **22**, revealed its significant cytostatic activity This was rather surprising, as, according to the literature[3,4], hexitol derivatives carrying biological alkylating groups on C-1 and C-6 are inactive if their hydroxyl groups on C-3 and C-4 are blocked by a base-resistant group As, in the compounds investigated[3,4], this group was an isopropylidene group, the lack of cytostatic activity is probably a consequence of the unfavorable steric arrangement, due to the presence of the rather inflexible dioxolane ring which would restrict the free motion of the molecule and determine the steric arrangement of the biological alkylating groups In our case, the presence of the 3,4-di-*O*-alkyl groups does not significantly hinder the free rotation of the atoms in the hexitol skeleton, consequently, it seemed probable that they might not change the biological activity of the original compounds Hence, it was decided to synthesize several 3,4-di-*O*-alkylated hexitol derivatives in

*Synthesis of New Sugar Derivatives Having Potential Anti-tumor Activity, Part XX For Part XIX, see ref 1

order to study the influence of different *O*-alkyl groups, as well as the configuration of the hexitol, on the cytostatic activity

RESULTS AND DISCUSSION

3,4-Di-*O*-methyl-D-mannitol[5,6] (**6**) was prepared from 1,2 5,6-di-*O*-isopropylidene-D-mannitol[7] (**1**) by methylation with dimethyl sulfate–sodium hydroxide in dimethyl sulfoxide solution, affording, after distillation, pure **2** This was hydrolyzed according to the literature[5], to give **6** Partial mesylation of **6** and subsequent acetylation yielded the mixed ester **11**, the acetyl groups of which could be selectively removed with hydrochloric acid containing methanol at elevated temperature. On treatment with methanolic sodium methoxide, the 1,6-di-*O*-mesyl-3,4-di-*O*-methyl-D-mannitol (**15**) obtained, as well as its diacetate **11**, gave the corresponding 1,2 5,6-dianhydride (**17**) Essentially the same route was applied for the synthesis of the corresponding 3,4-di-*O*-ethyl (**3**→**7**→**12**→**18**), -di-*O*-allyl (**4**→**8**→**13**→**19**), and -di-*O*-pentyl derivatives (**5**→**9**→**14**→**20**), but, in the last two examples, alkylation of compound **1** was conducted with allyl and pentyl bromide, respectively, in the presence of sodium hydride Hydrolysis of the distilled di-*O*-pentyl compound **5** gave, besides the desired **9**, some of the mono-*O*-pentyl derivative **10** In contrast to those of the di-*O*-methyl derivative **11**, the acetyl groups of the corresponding mixed esters **12**, **13**, and **14** could not be selectively removed without decomposition of the material; only the



Scheme 1

di-*O*-ethyl derivative **12** gave a chromatographically homogeneous 1,6-dimesyl ester (**16**), which was, however, unstable at room temperature

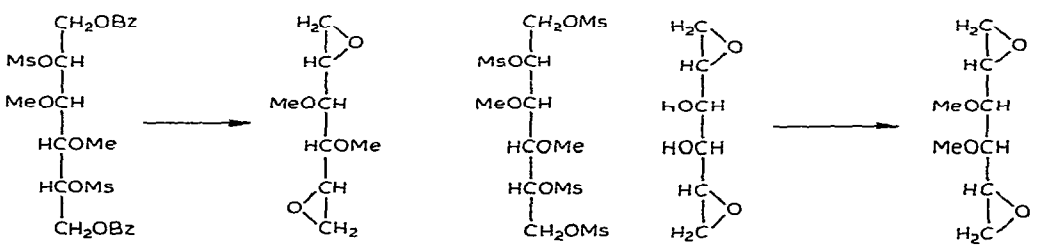
The presence of the oxirane rings in derivatives **17–20** was proved by an independent, synthetic route, namely, alkylation of the known 1,2 5,6-dianhydro-D-mannitol[8] (**21**) with the appropriate alkyl halide in the presence of silver oxide

Treatment of the di-*O*-methyl derivative **17** with sodium sulfide gave, besides some polymeric material, 1,6-anhydro-3,4-di-*O*-methyl-1(6)-thio-D-mannitol (**22**), which was separated as its diacetate **23** Deacetylation according to Zemplén gave crystalline **22**, which could not, however, be converted into **24** because, on mesylation, decomposition occurred

When 3,4-di-*O*-methyl-D-mannitol (**6**) was treated in pyridine at low temperature with benzoyl chloride (2 2 equiv) and then with mesyl chloride, the mixed ester **25** was obtained, on treatment with sodium methoxide, **25** gave, *via* inversion at C-2 and C-5, the 1,2 5,6-dianhydro-L-iditol derivative **26**

Complete mesylation of **6** yielded the 1,2,5,6-tetra-*O*-mesyl derivative **27** which, in contrast to 1,2,5,6-tetra-*O*-mesyl-D-mannitol[9], possessed only weak cytostatic activity This provides further, indirect evidence that the biologically active metabolite of the latter compound must be 2,3 4,5-dianhydro-1,6-di-*O*-mesyl-L-iditol[10], which can not be formed from **27** as the corresponding hydroxyl groups at C-3 and C-4 are blocked

As both of the d anhydro-3,4-di-*O*-methylhexitols **17** and **26** showed significant cytostatic activity, the corresponding galactitol derivative **29** was prepared by alkylation of the known, cytostatically active 1,2 5,6-dianhydrogalactitol[8 11] (**28**) Interestingly, on methylation, the toxicity and the activity of the original compound were decreased to the same extent, and consequently, the therapeutic index remained unchanged

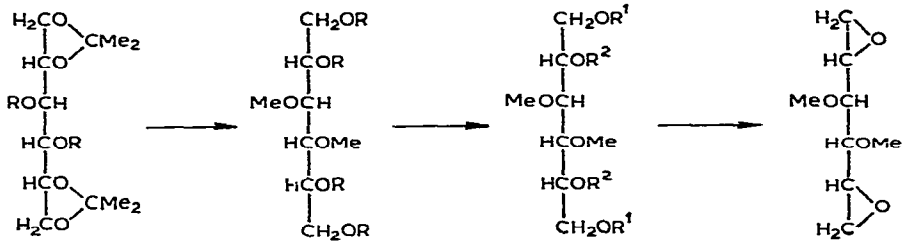


25 26 27 28 29

Scheme 2

For further comparison, 1,2 5,6-dianhydro-3,4-di-*O*-methyl-D-glucitol (**37**) was synthesized As the starting material, 1,2 5,6-di-*O*-isopropylidene-D-glucitol (**30**) was needed, and this had been obtained (in 7 7% yield) by Anderson *et al*[12] by treating D-glucitol with zinc chloride in acetone The same authors also described[12] its crystalline 3,4-di-*O*-benzoyl derivative **31**. We combined the procedures, and

isolated from the crude reaction-mixture, after the benzoylation, the dibenzoate **31** in a yield of 18% Zemplén saponification of **31** gave **30** in practically quantitative yield, methylation of **30** afforded the dimethyl ether **32**, and hydrolysis thereof with acid gave **33** as a homogeneous syrup* For further characterization, **33** was converted into its tetraacetate **34**, which could be purified by distillation Pure **33**, obtained by Zemplén deacetylation of pure **34**, was converted into the esters **35** or **36**, which, without further purification, were treated with sodium methoxide to give the desired diepoxide **37**



30 R = H
31 R = Bz
32 R = Me

33 R = H
34 R = Ac

35 R^1 = Ms, R^2 = Ac
36 R^1 = Ts, R^2 = H

37

Scheme 3

From biological investigation of the 3,4-di-*O*-alkylated epoxides, the following general conclusions concerning the structure–activity relationship could be drawn (*a*) The alkylated derivatives are generally less toxic than the parent compounds having free hydroxyl groups at C-3 and C-4 (*b*) The cytostatic activity decreases with elongation of the chain of the alkyl groups on O-3 and O-4 (*c*) The configuration of the hexitol has the following influence on the activity galactitol > D-glucitol ≫ D-mannitol > L-iditol, this is remarkable, as, for most biological-alkylating hexitol derivatives, those having the D-*manno* configuration are the most active

Comparison of the activity of the 3,4-di-*O*-methyl-D-mannitol diepoxide **17** with that of the corresponding 1,6-di-*O*-mesyl compound **15** provided another surprise For the non-alkylated derivatives, the corresponding epoxides are always the more toxic, but also the more active, compounds[13], whereas, for the 3,4-di-*O*-methyl derivatives, the toxicity was approximately the same for both types of compound (LD_{50} 100 mg/kg), but the activity against Yoshida s c. sarcoma at a dose of 4 × 100 mg/kg (p o) was only 17% for the epoxide **17**, but 99% for the di-*O*-mesyl derivative **15** Compared to 1,6-di-*O*-mesyl-D-mannitol ("Mannitol-Myleran"), compound **15** showed about ten times the activity

*Compound **33** had been synthesized for g l c investigation[14], but no data were given

EXPERIMENTAL

General methods — Melting points are uncorrected. T.l.c. was effected on Kieselgel G with ethyl acetate (*A*), with ethyl acetate–carbon tetrachloride 2:1 (*B*), 1:1 (*C*), 1:2 (*D*), 1:3 (*E*), and 1:5 (*F*), and with ethanol–ethyl acetate 1:1 (*G*), 1:2 (*H*), and 1:9 (*I*). 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*, or dimethyl sulfoxide-d_6, with tetramethylsilane as the internal standard.

All evaporations were performed in a rotary evaporator under diminished pressure, after the organic solutions had been dried with sodium sulfate. Boiling pressures are given in torr*. Light petroleum refers to the fraction having b.p. 60–80°. Optical rotations were determined in chloroform (*c* 1.00), if not stated otherwise.

*1,2:5,6-Di-O-isopropylidene-3,4-di-O-methyl-*D*-mannitol* (**2**) — To a stirred solution of compound[7] **1** (73 g) in dimethyl sulfoxide (350 mL) were simultaneously added a solution of sodium hydroxide (56 g) in water (56 mL) and dimethyl sulfate (66.5 mL) at such a rate that the temperature of the reaction mixture did not exceed 60°. Stirring was continued at this temperature for 30 min. After standing overnight at room temperature, the mixture was poured into water, and extracted with chloroform. The extract was dried, and evaporated, and the residue was distilled, to give pure **2** (73 g, 90%), b.p.$_{0.5}$ 106–110°, $[\alpha]_D^{20}$ +9.6°, R_F 0.70 (*C*), ^{1}H-n.m.r. data: δ 1.31 and 1.37 (2 CMe$_2$), and 3.46 (2 OMe).

Anal. Calc. for $C_{14}H_{26}O_6$: C, 57.91; H, 9.03. Found: C, 57.82; H, 8.91.

*3,4-Di-O-ethyl-1,2:5,6-di-O-isopropylidene-*D*-mannitol* (**3**) — A solution of **1** (20 g) in dimethyl sulfoxide (60 mL) was treated with a solution of sodium hydroxide (60 g) in water (60 mL) and diethyl sulfate (96 mL) as described for **2**, to give, after distillation, pure **3** (20.8 g, 85.8%), b.p.$_{0.4}$ 116–120°, $[\alpha]_D^{20}$ +13.5°, R_F 0.75 (*C*), ^{1}H-n.m.r. data: δ 1.17 (t) and 3.60 (m) (2 OEt), and 1.27 and 1.34 (2 CMe$_2$).

Anal. Calc. for $C_{16}H_{30}O_6$: C, 60.35; H, 9.50. Found: C, 60.24; H, 9.26.

*3,4-Di-O-allyl-1,2:5,6-di-O-isopropylidene-*D*-mannitol* (**4**) — Sodium hydride (55% suspension in oil, 20 g) was washed three times by decantation with light petroleum, then, dimethyl sulfoxide (80 mL) was added, and the mixture was stirred until foaming ceased. A solution of compound **1** (52.4 g) in dimethyl sulfoxide (160 mL) was now added, and, when the evolution of hydrogen had stopped, allyl bromide (40 mL) was added at such a rate as to keep the temperature below 50°. Thereafter, stirring was continued for 1 h at 50°, the mixture was then chilled, diluted three-fold with water, and extracted with chloroform (3 × 200 mL). The extracts were combined, washed with water until neutral, dried, and evaporated. The residue was purified by column chromatography, using solvent *F* for elution. The fractions having R_F 0.55 were combined, to give, after evaporation and distillation,

*1 Torr = 101 325/760 Pa

pure **4** (62 6 g, 91 5%), b p $_{0\,4}$ 125–130°, $[\alpha]_D^{20}$ +22° {lit [15] $[\alpha]_D^{20}$ +8 9°}; ^{1}H-n m r. data δ 1 31 and 1 35 (2 CMe_2); 300–370 Hz (CH_2=CH-)

Anal. Calc. for $C_{18}H_{30}O_6$. C, 63 13, H, 8 83 Found: C, 63 02, H, 8 98

*1,2 : 5,6-Di-O-isopropylidene-3,4-di-O-pentyl-*D*-mannitol* (**5**) — Compound **1** (26 5 g) was treated with pentyl bromide (31 mL) as described for compound **4** The crude product was purified by column chromatography with solvent *E* The fractions having R_F 0 75 were combined, to give, after evaporation and distillation, pure **5** (8 2 g, 20 4%), b p $_{0\,01}$ 118–121°, $[\alpha]_D^{20}$ +8 2°

Anal Calc for $C_{22}H_{42}O_6$ C, 65 63, H, 10 55 Found C, 65.49, H, 10 80.

*3,4-Di-O-methyl-*D*-mannitol* (**6**) — A solution of **2** (25 8 g) in acetic acid (200 mL) and water (100 mL) was heated on a steam bath for 30 min, and evaporated Two portions of water (and, subsequently, two of ethanol) were added to, and evaporated from, the residue, which solidified Recrystallization from ethanol gave pure **6** (14 1 g, 76%), m p 148–150°, $[\alpha]_D^{20}$ +37° (water) {lit [5] m p 144–146°, $[\alpha]_D^{20}$ +40 8° (water). lit [6] m p 145–148°, $[\alpha]_D^{20}$ +39° (water)}, R_F 0 55 (*G*), ^{1}H-n m r data δ 3 38 (2 OMe)

*3,4-Di-O-ethyl-*D*-mannitol* (**7**) — Compound **3** (20 g) was hydrolyzed similarly to **6**, yielding pure **7** (10 g, 67%), m p. 136–139°, $[\alpha]_D^{20}$ +42 7° (water), R_F 0 60 (*H*)

Anal Calc for $C_{10}H_{22}O_6$ C, 50 45, H, 9 31 Found C, 50 36, H, 9 45

*3,4-Di-O-allyl-*D*-mannitol* (**8**) — Compound **4** (7 g) was hydrolyzed as for **6**, yielding pure **8** (3 9 g, 74 4%), m p 111–113°, $[\alpha]_D^{20}$ +45° (water), {lit [16] m p 111–112°, $[\alpha]_D^{20}$ +42 3° (ethanol), +44 7° (water)}, R_F 0 65 (*I*)

*3,4-Di-O-pentyl-*D*-mannitol* (**9**) and *3-O-pentyl-*D*-mannitol* (**10**) — Compound **5** (7 5 g) was hydrolyzed similarly to **6**, but the crude product, obtained after evaporation, was separated by column chromatography with solvent *I* The fractions having R_F 0 75 gave, on evaporation, pure **10** as a semisolid residue (4 9 g, 81 5%) which could be recrystallized from ethyl acetate, m p 85–87°, $[\alpha]_D^{20}$ +37 6° (1 1 water–methanol)

Anal Calc for $C_{16}H_{34}O_6$ C, 59 59, H, 10 63 Found C, 59 91, H, 10 74

Evaporation of the fractions having R_F 0 30 gave (after treating the residue with chloroform) pure mono-*O*-pentyl derivative **10** (0 6 g, 12 8%), m p 78–80°, $[\alpha]_D^{20}$ +26 3° (water)

Anal Calc for $C_{11}H_{24}O_6$ C, 52 37, H, 9 59 Found. C, 52 20, H, 9 54

*2,5-Di-O-acetyl-3,4-di-O-methyl-1,6-di-O-(methylsulfonyl)-*D*-mannitol* (**11**) — To a stirred solution of **2** (105 g) in dry pyridine (1 5 L) was added mesyl chloride (85 mL) during 1 h at −10° The mixture was kept for 30 min at 0°, and then for 30 min at room temperature Thereafter, it was chilled to −10°, and acetic anhydride (150 mL) was added at such a rate that the temperature did not exceed 0°. The mixture was kept overnight at 0°, poured into water, and extracted with chloroform The extract gave, after the usual processing, and evaporation, a solid residue which was recrystallized from ethyl acetate–light petroleum to afford crude **11** (161 g, 71 5%), m p 99–101° This was pure enough for further reactions, recrystallization

from ethanol (3 vol) provided pure **11**, m p 101–103°, $[\alpha]_D^{20}$ +18 7°, R_F 0 50 (*B*), ^{1}H-n m r data δ 2 12 (2 acetyl-Me), 3 05 (2 mesyl-Me), and 3 48 (2 OMe)

Anal Calc for $C_{14}H_{26}O_{12}S_2$ C, 37 33, H, 5 82, S, 14 24 Found C, 37 45, H, 5 95, S, 14 43

*2,5-Di-*O*-acetyl-3,4-di-*O*-ethyl-1,6-di-*O*-(methylsulfonyl)-*D*-mannitol* (**12**) — Compound **7** (26 g) was treated as described for **11**, to give, after recrystallization from ethanol (100 mL), pure **12** (42 6 g, 82%), m p 85–87°, $[\alpha]_D^{20}$ +24 6°, R_F 0 55 (*C*), ^{1}H-n m r data δ 1 18 (t) and 3 62 (m) (2 OEt), 2 10 (2 acetyl-Me), and 3 05 (2 mesyl-Me)

Anal Calc for $C_{16}H_{30}O_{12}S_2$ C, 40 15, H, 6 32, S, 13 40 Found C, 40 48, H, 6 30, S, 13 12

*2,5-Di-*O*-acetyl-3,4-di-*O*-allyl-1,6-di-*O*-(methylsulfonyl)-*D*-mannitol* (**13**) — Compound **8** (5 2 g) was treated as described for **11**, to give, after evaporation, a syrupy mixture which was separated by column chromatography, using solvent *C* The fractions having R_F 0 35 gave, on evaporation, **13** as a colorless syrup (6 2 g, 65%), $[\alpha]_D^{20}$ +23°, ^{1}H-n m r data δ 2 10 (2 acetyl-Me), 3 03 (2 mesyl-Me), and 305–370 Hz (CH_2=CH-)

Anal Calc for $C_{18}H_{30}O_{12}S_2$ S, 12 76 Found S, 12 38

Evaporation of the fraction having R_F 0 45 gave 1,2,5-tri-*O*-acetyl-3,4-di-*O*-allyl-6-*O*-(methylsulfonyl)-D-mannitol as a syrup, $[\alpha]_D^{20}$ +30°, ^{1}H-n m r data δ 2 04, 2 07 and 2 11 (3 acetyl-Me), 3 03 (mesyl-Me), and 305–370 Hz (CH_2=CH-)

*3,4-Di-*O*-methyl-1,6-di-*O*-(methylsulfonyl)-*D*-mannitol* (**15**) — A suspension of crude **11** (45 g) in 7 5M methanolic hydrogen chloride was refluxed on a steam bath Boiling was continued for 10 min after complete dissolution, and the solution was then evaporated The solid residue was filtered with the aid of ethanol (yield 25 g, 68%) to give, after recrystallization from ethanol (150 mL), pure **15** (22 g, 60%), m p 112–114°, $[\alpha]_D^{20}$ +35° (methanol), R_F 0 35 (*A*), ^{1}H-n m r data δ 3 12 (2 mesyl-Me) and 3 41 (2 OMe)

Anal Calc for $C_{10}H_{22}O_{10}S_2$ C, 32 78, H, 6 05, S, 17 50 Found C, 32 81, H, 6 08, S, 17 65

*3,5-Di-*O*-ethyl-1,6-di-*O*-(methylsulfonyl)-*D*-mannitol* (**16**) — Compound **12** (9 6 g) was deacetylated as described for **11**, to give, after evaporation, a syrup that could not be crystallized and which decomposed on standing overnight at room temperature, $[\alpha]_D^{20}$ +40° (methanol), R_F 0 60 (*A*)

Anal Calc for $C_{12}H_{26}O_{10}S_2$ S, 16 26 Found S, 15 88

*1,2 5,6-Dianhydro-3,4-di-*O*-methyl-*D*-mannitol* (**17**) — *Method a* A stirred solution of compound **11** (45 g), or its deacetylated derivative **15** (36 6 g), in dry chloroform (150 mL) was treated at 10° with 4 3M methanolic sodium methoxide (45 mL) After 1 h, the mixture was washed with water, dried, and evaporated The residue gave, on distillation, pure **17** (11 6 g, 66 8%) which solidified on cooling b $p_{1.5}$ 95–97°, m p 17–19°, $[\alpha]_D^{20}$ −10°, R_F 0 45 (*D*), ^{1}H-n m r data δ 2 80 (d, J 4 Hz, H-1,6) and 3 47 (2 OMe)

Anal. Calc for $C_8H_{14}O_4$ C, 55 16, H, 8 10 Found C, 55 12, H, 8 35

Method b To a solution of diepoxide[8] **21** (4 7 g) in *N,N*-dimethylformamide (20 mL) were added freshly prepared silver oxide (20 g) and methyl iodide (10 mL), the temperature of the mixture being kept below 40° by gentle cooling When the exothermic reaction was over, the temperature was kept at 40° for 2 h The suspension was cooled, and the salts were filtered off and washed with acetone The filtrates were combined, and evaporated, and the residue, mixed with ethyl acetate, was passed through a short column The fractions having R_F 0 85 (*A*) were evaporated, and light petroleum was added to, and evaporated from, the solid residue, which was recrystallized from light petroleum (10 mL) at −50° Pure **17** was filtered off, and dried at +5° (4 g, 75 5%); it was identical with that described in *a*

1,2 5,6-Dianhydro-3,4-di-O-*ethyl*-D-*mannitol* (**18**) — *Method a* Compound **12** (23 9 g) was treated with sodium methoxide as described for **17**, to give, after distillation, pure **18** (5 3 g, 52 5%), b p $_{0\ 1}$ 67–70°, $[\alpha]_D^{20}$ −6 2°, R_F 0 60 (*E*): ^{1}H-n m r data δ 1 1 (t) and 3 62 (m) (2 OEt), and 2 74 (d, *J* 4 Hz, H-1,6)

Anal Calc for $C_{10}H_{18}O_4$ C, 59 38, H, 8 97 Found C, 59 26, H, 9 08

Method b A solution of compound **21** (4 g) in *N,N*-dimethylformamide (40 mL) was treated with silver oxide (20 g) and ethyl iodide (6 mL) as described for compound **17**, to give, after distillation, **18** (4 3 g, 78%), it was identical with that described in *a*

3,4-Di-O-*allyl-1,2 5,6-dianhydro*-D-*mannitol* (**19**) — *Method a* Compound **13** (8 6 g) was treated with sodium methoxide as described for **17** The residue obtained after evaporation of the chloroform solution was separated by column chromatography with solvent *C* The fractions having R_F 0 80 were combined, and evaporated, and the residue was distilled, to give pure **19** (1 6 g, 41 4%), b p $_{0\ 3}$ 112–115°, $[\alpha]_D^{20}$ 0°, ^{1}H-n m r data δ 2 68 (d, *J* 4 Hz, H-1,6), and 290–370 Hz (CH_2=CH-)

Anal Calc for $C_{12}H_{18}O_4$ C, 63 69, H, 8 02 Found C, 63 52; H, 8 22

Method b Diepoxide **21** (4 g) was treated with allyl bromide (6 mL) as described for compound **18**, to give, after distillation, **19** (3 7 g, 62%), identical with that described in *a*

1,2 5,6-Dianhydro-3,4-di-O-*pentyl*-D-*mannitol* (**20**) — To a stirred solution of **9** (9 6 g) in pyridine (100 mL) was added a solution of mesyl chloride (5 mL) in pyridine (50 mL) during 1 h at −10° The mixture was kept for 1 h at 0°, and then acetic anhydride (10 mL) was added The mixture was kept overnight at room temperature, and processed as described for **11**, to give crude **14** (16 8 g) This was dissolved in dry chloroform (40 mL), and treated with sodium methoxide as described for **17**, but the residue from the evaporated solution was purified by column chromatography with solvent *E*. Evaporation of the fractions having R_F 0 75 gave pure **20** (2 4 g, 28%), $[\alpha]_D^{20}$ +9 5°, ^{1}H-n m r data δ 2 60 (d, *J* 4 Hz, H-1,6)

Anal Calc for $C_{16}H_{30}O_4$ C, 67 00, H, 10 56 Found C, 66 92, H, 10 32

2,5-Di-O-*acetyl-1,6-anhydro-3,4-di*-O-*methyl-1(6)-thio*-D-*mannitol* (**22**) — Sodium sulfide nonahydrate (9 g) was added to a solution of diepoxide **17** (6 g) in ethanol (60 mL) and water (25 mL) The mixture was stirred for 1 h at room temperature, and was then evaporated (without neutralization) Two portions of

ethanol and, subsequently, chloroform were added to, and evaporated from, the residue, which was then dissolved in pyridine (50 mL) and treated with acetic anhydride (70 mL) The mixture was kept overnight at room temperature, and then evaporated The residue was dissolved in pyridine (10 mL), to give, after the usual processing, a syrup which was purified by column chromatography with solvent *C* Evaporation of the fractions having R_F 0 75 gave pure **22** as a colorless syrup (4 6 g, 45 7%), $[\alpha]_D^{20}$ +20°, ^{1}H-n m r data δ 2 05 (2 acetyl-Me) and 3 50 (2 OMe)

Anal Calc for $C_{12}H_{20}O_6S$ S, 10 96. Found S, 10 64

1,6-Anhydro-3,4-di-O-*methyl-1(6)-thio*-D-*mannitol* (**23**) — A solution of the diacetate **22** (3 g) in dry chloroform (10 mL) and methanol (10 mL) was treated with 4M methanolic sodium methoxide (0 1 mL), and kept overnight at room temperature Sodium ions were removed with a cation-exchange resin, and the solution was evaporated On recrystallization from acetone–light petroleum, the residue gave pure **23** (1 9 g, 95%), m p 94–96°, $[\alpha]_D^{20}$ −28 5°, R_F 0 55 (*A*), ^{1}H-n m r data δ 3 50 (2 OMe)

Anal Calc for $C_8H_{16}O_4S$ C, 46 13, H, 7 74, S, 15 40 Found C, 46 33, H, 7 65, S, 15 34

1,6-Di-O-*benzoyl-3,4-di*-O-*methyl-2,5-di*-O-(*methylsulfonyl*)-D-*mannitol* (**25**) — To a stirred solution of compound **6** (21 g) in pyridine (300 mL) was added benzoyl chloride (25 5 mL) during 1 h at −10° The mixture was kept for 1 h at room temperature, and then chilled to −10°, and mesyl chloride (25 mL) was added at this temperature The mixture was kept overnight at room temperature, to give, after the usual processing, and crystallization from ethanol, pure **25** (24 6 g, 42 8%), m p 140–142°, $[\alpha]_D^{20}$ +21 4°, R_F 0 40 (*D*), ^{1}H-n m r data δ 3 07 (2 mesyl-Me) and 3 62 (2 O-Me)

Anal Calc for $C_{24}H_{30}O_{12}S_2$ C, 50 16, H, 5 26, S, 11 16 Found C, 50 25, H, 5 37, S, 11 21

1,2 5,6-Dianhydro-3,4-di-O-*methyl*-L-*iditol* (**26**) — Compound **25** (15 4 g) was treated with sodium methoxide as described for **17**, to give, after distillation, pure **26** (3 8 g, 82%), which solidified on cooling, b p $_{0\,1}$ 70–72°, m p 40–42°, $[\alpha]_D^{20}$ −9°, R_F 0 45 (*D*), ^{1}H-n m r data δ 2 92 (H-1,6) and 3 42 (2 OMe)

Anal Calc for $C_8H_{14}O_4$ C, 55 16, H, 8 10 Found C, 54 88, H, 7 83

3,4-Di-O-*methyl-1,2,5,6-tetra*-O-(*methylsulfonyl*)-D-*mannitol* (**27**) — A solution of compound **6** (4 2 g) in pyridine (60 mL) was treated with mesyl chloride (8 mL) to give, after the usual processing, and crystallization from ethyl acetate, pure **27** (8 22 g, 78 7%), m p 126–128°, $[\alpha]_D^{20}$ +28 4°, R_F 0 80 (*A*), ^{1}H-n m r data δ 3 12 and 3 20 (4 mesyl-Me), and 3 63 (2 OMe)

Anal Calc for $C_{12}H_{26}O_{14}S_4$ C, 27 58, H, 5 02, S, 24 54 Found C, 27 49, H, 5 25, S, 24 36

1,2 5,6-Dianhydro-3,4-di-O-*methylgalactitol* (**29**) — Dianhydrogalactitol[8,11] (**28**, 4.1 g) was methylated as described for **17** After column chromatography with solvent *C*, the fractions having R_F 0 80 were evaporated, and the solid residue was

recrystallized from light petroleum (25 mL), to give pure **29** (3 5 g, 71 5%), m p. 45–46°, ^{1}H-n.m r. data· δ 3.15 (H-1,6) and 3 60 (2 OMe)

Anal Calc for $C_8H_{14}O_4$ C, 55.16, H, 8 10 Found. C, 55.08, H, 8 25

1,2 5,6-Di-O-*isopropylidene*-D-*glucitol* (**30**). — A suspension of the dibenzoate **31** (76 g) in dry methanol (380 mL) containing 4M methanolic sodium methoxide (0 2 mL) was refluxed for 1 h The solution was cooled, and made neutral with carbon dioxide, to give, after evaporation, and crystallization from dibutyl ether, pure **30** (34 75 g, 81 8%) Evaporation of the mother liquor gave, after removal of the methyl benzoate by distillation, and recrystallization of the solid residue from dibutyl ether, a second crop of **30** (6 2 g, 11 5%), m p 93–94°, $[\alpha]_D^{20}$ 0° (pyridine) {lit [12] m p 95–95 5°, $[\alpha]_D^{20}$ —0 25° (*c* 10, pyridine)}, R_F 0 65 (*A*), ^{1}H-n m r data δ 1 25, 1 28, and 1 33 (1, 1, and 2 CMe_2), and 3 42 and 3 45 (2 OMe)

3,4-Di-O-*benzoyl-1,2 5,6-di*-O-*isopropylidene*-D-*glucitol* (**31**) — D-Glucitol (364 g) was added to a stirred solution of zinc chloride (740 g) in acetone (3 5 L) The clear solution obtained after 30 min was kept for 2 h at room temperature and then poured into a vigorously stirred, ice-cooled solution of potassium carbonate (880 g) in water (880 mL) The precipitate was filtered off, and washed with acetone (500 mL), and then separately with chloroform (1 5 L) The acetonic filtrate was evaporated, the resicue was dissolved in the chloroform solution, and the solution was washed with water, dried, and evaporated The residue was dissolved in pyridine (1 5 L), and benzoyl chloride (400 mL) was added dropwise while the temperature of the mixture was kept below +10° The mixture was kept overnight at room temperature, then, it was cooled to 5°, water (100 mL) was added slowly, and the mixture was poured into water, to give, after extraction with chloroform, and the usual processing, a syrupy residue which was treated with methanol and chilled to —5°. The crystals that separated were filtered off and washed with methanol, to give pure **31** (169 g, 18%), m p 135–136°, $[\alpha]_D^{20}$ +54 5° {lit [12] m p 134–135°, $[\alpha]_D^{20}$ +53 7° (*c* 10)}, R_F 0 60 (*F*)

1,2 5,6-Di-O-*isopropylidene-3,4-di*-O-*methyl*-D-*glucitol* (**32**) — The D-glucitol derivative **30** (40 g) was methylated with dimethyl sulfate as described for the D-mannitol isomer **2**, to give, after distillation, pure **32** (42 g, 92 5%), b p $_{0\ 4}$ 106–108°, $[\alpha]_D^{20}$ —10 8°, R_F 0 75 (*C*)

Anal Calc for $C_{14}H_{26}O_6$ C, 57 91, H, 9 03 Found C, 57 99, H, 9 21

3,4-Di-O-*methyl*-D-*glucitol* (**33**) — To a solution of tetraacetate **34** (38 g) in dry methanol (100 mL) was added 4M methanolic sodium methoxide (0 1 mL) After two days at room temperature, the mixture was freed of sodium ions by means of a cation-exchange resin The solution was evaporated, to give pure **33** as a colorless syrup (20 5 g, 97 5%), $[\alpha]_D^{20}$ +22 2°, +15 3° (water), R_F 0 55 (*G*), ^{1}H-n m r data δ 3 46 and 3 54 (2 OMe).

Anal Calc for $C_8H_{18}O_6$. CH_3O, 29 4 Found CH_3O, 29.1

1,2 5,6-Tetra-O-*acetyl-3,4-di*-O-*methyl*-D-*glucitol* (**34**) — The di-*O*-isopropylidene derivative **32** (42 g) was hydrolyzed as described for **6**, and chloroform (2 × 200 mL) was added to, and evaporated from, the residue obtained by evapora-

tion The residue was dissolved in pyridine (200 mL) and treated with acetic anhydride (150 mL), to give, after the usual processing, and distillation, pure **34** (46 5 g, 91%), b p $_{0\,4}$ 165–170°, $[\alpha]_D^{20}$ +5 3°, R_F 0 55 (*C*)

Anal. Calc. for $C_{16}H_{26}O_{10}$ C, 50 79, H, 6 93, Found C, 50 69; H, 6 86

1,2 5,6-Dianhydro-3,4-di-O-*methyl*-D-*glucitol* (**37**) — *Method a* To a stirred solution of **33** (20 g) in pyridine (100 mL) was added a solution of *p*-toluenesulfonyl chloride (40 g) in pyridine (100 mL) during 30 min at 0° The mixture was then kept for 30 min at room temperature, and then chilled to 0°, and water (10 mL) was added After the usual processing, the chloroform solution, containing the 1,6-di-*O*-tosyl derivative **36**, was concentrated to 500 mL, then, methanol (50 mL) and 4 3M methanolic sodium methoxide (50 mL) were added at 0° After 30 min, the mixture was washed with water, dried, and evaporated, and the residue was distilled to give pure **37** (5 g, 30%), which solidified on cooling, b p $_{0\,1}$ 63–65°, m p 23–24°, $[\alpha]_D^{20}$ −7 6°, R_F 0 45 (*D*), ^{1}H-n m r data δ 2 62 (d, *J* 4 Hz, H-1,6), and 3 35 and 3 45 (2 OMe)

Anal Calc for $C_8H_{14}O_4$ C, 55 16, H, 8 10 Found C, 55 02, H, 8 30

Method b To a stirred solution of **33** (20 g) in pyridine (200 mL) was added a solution of methanesulfonyl chloride (17 mL) in pyridine (100 mL) during 1 h at −10° The temperature was then raised to 0°, and after 30 min, acetic anhydride (30 mL) was added The mixture was kept overnight at room temperature, and then processed in the usual way The chloroform solution, containing the mixed ester **35**, was treated with methanolic sodium methoxide as described in method *a*, to give pure **37** (6 g, 36 2%), identical with that described in *a*

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