Note

Potential antitumor agents. Some 1,6-disubstituted galactitol and mannitol derivatives*

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The 1,6-dibromo-1,6-dideoxy derivatives (**1** and **10**) of galactitol and of D-mannitol, respectively, are clinically useful antitumor agents[1-3]. Recently, the antitumor activity of the dichlorodideoxy, diiododideoxy, di-*O*-methylsulfonyl, and di-*O*-*p*-tolylsulfonyl analogs of **1** and **10** was reported[4]. The activity in these series of alkylating agents varied noticeably, and did not necessarily follow their tendency to form, in solution, the 1,2:5,6-dianhydro derivatives[5] previously shown to be active[6]. To complete the series of halo derivatives, we have studied the preparation of the 1,6-dideoxy-1,6-difluoro analogs of **1** and **10**. To further explore the biological effect of configurational change in the alditol chain, we have also synthesized 1,6-dibromo-1,6-dideoxy-L-mannitol (**35**), the L enantiomer of **10**.

1,6-Dideoxy-1,6-difluorogalactitol (**5**) was readily synthesized from 2,3:4,5-di-*O*-isopropylidene-1,6-di-*O*-(methylsulfonyl)galactitol (**7**), by direct displacement with tetraethylammonium fluoride, and subsequent deblocking. (The likelihood that the isopropylidene and other acetals of galactitol are attached in the 2,3:4,5 arrangement[7,8] rather than[9,10] 2,4:3,5 was recently confirmed by mass spectrometry[11,12].) The dichloro derivative (**4**) was also prepared from **7**, more conveniently than from galactitol and hot fuming hydrochloric acid in a sealed tube[4,9]. Use of 80% trifluoroacetic acid as an excellent deblocking reagent for these acetals was described in a preliminary communication[10]. The 1,6-diiodides (**2** and **11**) in both the galactitol and D-mannitol series could be obtained directly from the bromides (**1** and **10**, respectively) and sodium iodide, without the use of blocked intermediates, and without isolating the corresponding 1,2:5,6-diepoxides as intermediates[5].

Attempts to synthesize 1,6-dideoxy-1,6-difluoro-D-mannitol were unsuccessful, owing to the instability of the acetals of mannitol as intermediates in the necessary displacement reactions. Such instability was in striking contrast to the results in the corresponding galactitol series. When these studies were initiated, the acetalation of

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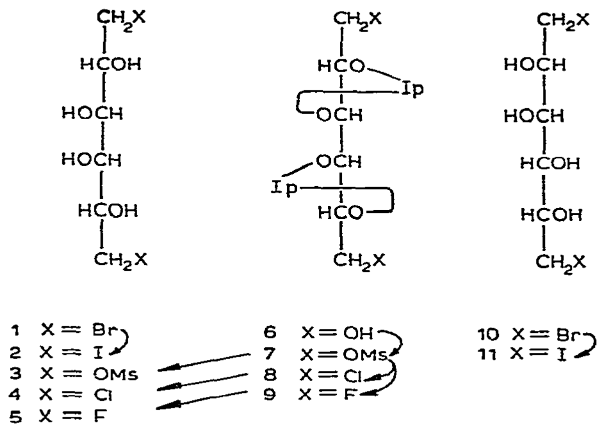
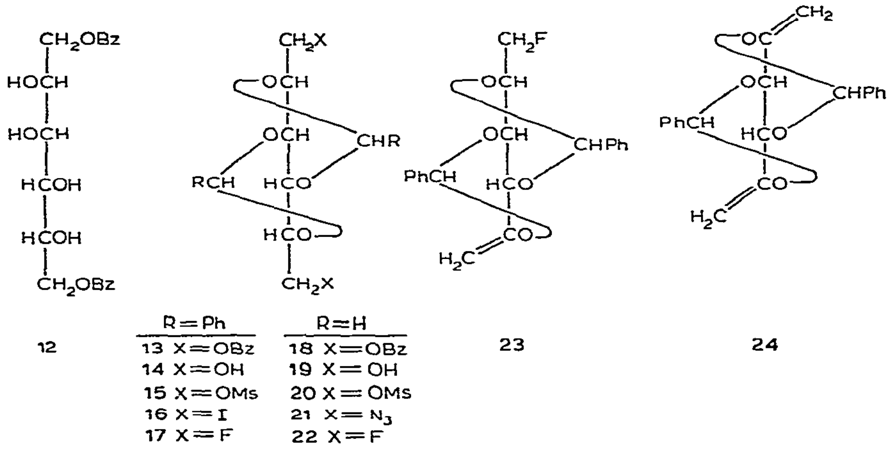
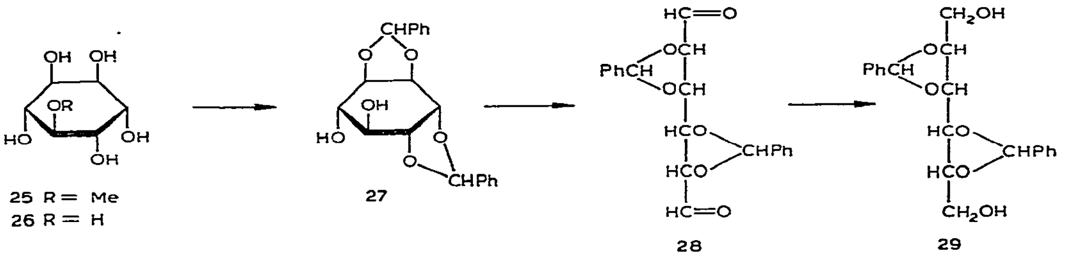


1,6-di-*O*-benzoyl-D-mannitol (**12**) was seen as a conventional approach for obtaining the intermediates suitably blocked at the non-terminal hydroxyl groups. The 2,3,4,5-di-*O*-benzylidene-D-mannitol[13] thus obtained was of previously undetermined structure. The 2,4:3,5 arrangement (**14**) seemed likely from the n.m.r. spectrum[14], and this assignment was recently confirmed by the mass spectrum[11]. Access to the 2,3:4,5-di-*O*-benzylidene-D-mannitol (**29**) of chemically proven structure was available from (+)-inositol (**26**), although this synthesis had been carried out only with (−)-inositol to give the L enantiomer[15] of **29**. When the series from (+)-inositol was carried through, direct comparison of the two isomers (**14** and **29**) clearly showed their non-identity.



A pure sample of the 2,3:4,5 isomer (**29**) as a reference standard could be obtained only with difficulty. This compound, as a crude product, showed an extraneous benzylidene singlet in the n.m.r. spectrum, and on purification it seemed to decompose with loss of benzaldehyde. Furthermore, purified samples could not be

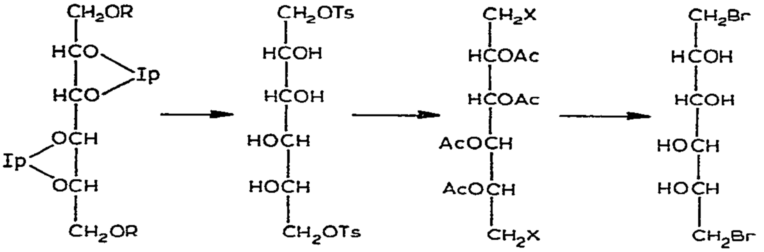


subjected to mesylation, tosylation, or even benzoylation without decomposition to water-soluble products. This indicated a degree of strain in the dioxolane rings of **29** that was unexpected, even though it was recognized that two unfavored αC-rings[7,16,17] (namely, having the adjacent ring-substituents *cis*) are joined in this molecule.

In contrast, the 2,4:3,5 isomer (**14**) was perfectly stable and could be converted into a crystalline bis(*p*-toluenesulfonate) or bis(methanesulfonate) (**15**). Any tendency toward instability expected from the "O-inside" conformation[7] as assigned[14] to **14** from the n.m.r. spectrum (from the downfield shift of the PhCH signal) appeared to be unimportant; although the terminal CH_2OH groups are in the less-favored, axial orientation, the phenyl groups are diequatorial in the "O-inside" conformation of **14**.

The 1,6-disulfonates (such as **15**) could be converted with sodium iodide in hot acetone or butanone into the 1,6-diiodide[13] (**16**) in nearly quantitative yield, but in dimethylformamide (DMF) at 100° elimination appeared as a minor side-reaction, according to chromatographic evidence. On treatment of **15** with tetraethylammonium fluoride in DMF at 100°, or in hot butanone or *p*-dioxane, elimination preponderated over displacement. Three products were obtained and separated by chromatography; these comprised a small proportion of the difluoride sought (**17**; 9% yield in one run), the 1-fluoro-5,6-olefin (**23**) as the main product, and the 1,2:5,6-diolefin (**24**). The diolefin was identical with a sample prepared from the diiodide (**16**) and silver fluoride in pyridine. (The di-*O*-methylene analog[18] of **24**, and apparently a chloro analog[19] of **23**, have been described[20].) Sharp infrared absorption at 6.02 μm, of strong intensity in **24** and of medium intensity in **23**, was diagnostic for the vinyl-ether type of unsaturation, and was absent from the spectrum of **17**. By the use of 2,4:3,5-di-*O*-methylene acetals in this series (**12**→**18** and so on) a 17% yield of difluoride (**22**) could be obtained from the bis(methanesulfonate) (**20**), and chromatographic purification was unnecessary because the by-products of (presumably) elimination were water-soluble. However, the commonly stable methylene acetals could not be removed, even with 80% trifluoroacetic acid. As in the benzylidene series, displacement by nucleophiles other than fluoride gave good yields from **20**, for example, to give the diazide **21**. To some extent, the elimination reaction must be attributed to the basicity of fluoride ion[21], especially in DMF, but the complete absence of elimination with the galactitol derivative (**7**) provides a strong contrast, also suggesting a generally increased steric strain in the 2,3,4,5-diacetals of mannitol, even in the more favorable (2,4:3,5) of the two possible arrangements.

1,6-Dibromo-1,6-dideoxy-L-mannitol (**35**) was synthesized from 2,3:4,5-di-*O*-isopropylidene-L-mannitol[22] (**30**), of known acetal ring-size owing to its preparation from 1,2:3,4-di-*O*-isopropylidene-(—)-inositol. Unlike the dibenzylidene analog (**29**), **30** was perfectly stable. Its bis(*p*-toluenesulfonate) (**31**), however, had to be stored at 0° and used within 1–2 days to avoid decomposition. After removal of the acetal groups, the 1,6-bis(*p*-toluenesulfonate) (**32**) and its 2,3,4,5-tetraacetate (**33**) showed no tendency to decompose, giving further evidence that the 2,3,4,5-diacetals of mannitol are subject to unfavorable non-bonded interactions. The bromide displacement was best performed with the tetra-*O*-acetyl bis(*p*-toluenesulfonate) (**33**) so that the product (**34**) could be purified from the water-soluble salts. Then, in a final step, deacetylation with methanolic hydrogen chloride afforded the dibromide (**35**), identical with the D enantiomer except for the optical rotation of equal magnitude but opposite sign.



30 R = H
31 R = Ts

32

33 X = OTs
34 X = Br

35

In a preliminary biological evaluation, the galactitols (**2**, **3**, **4**, and **5**) and the mannitols (**11** and **35**) were found inactive when tested against lymphoid leukemia L-1210 transplanted in mice*. The intermediates (**6–9**, **12–16**, **18–21**, **24–28**, and **30**) were also inactive against L-1210. So far, only 1,6-dideoxy-1,6-diiodogalactitol (**2**) and 1,6-dideoxy-1,6-diiodo-D-mannitol (**11**) have been tested against the more sensitive Walker carcinosarcoma 256 (intramuscular) in rats. Both were active, confirming the recent report[4]. Four daily doses were injected intraperitoneally, starting with the third day after implantation of the tumor, and the animals were sacrificed after seven days. A 50% reduction in tumor weight was achieved with 50 mg/kg doses of **2** and with 100 mg/kg doses of **11**; 90% reduction was achieved with 200 mg/kg of **2** and with 400 mg/kg of **11**. There were complete cures with **2** at 200 mg/kg (two mice cured out of six) and at 400 mg/kg doses (four mice out of six).

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*The compounds were screened under the auspices of the Cancer Chemotherapy National Service Center according to its protocols; see Ref. 23.

EXPERIMENTAL

General. — Melting points were determined on a Fisher–Johns hot-stage and are uncorrected. I.r. spectra were routinely determined in Nujol mull; acetates, benzoates, methanesulfonates, and *p*-toluenesulfonates showed the expected absorption bands. N.m.r. spectra were generally determined in chloroform-*d* solutions at 60 MHz with tetramethylsilane as internal reference, and with $CFCl_3$ as external reference for ^{19}F signals. Where specified, n.m.r. spectra in dimethyl sulfoxide-d_6 or in D_2O used external references. Optical rotations were determined on 1% solutions in 1-dm tubes with a Perkin–Elmer Model 141 automatic polarimeter. T.l.c. was performed on silica gel and the spots detected under u.v. light or with iodine vapor; all of the R_F values reported are for homogeneous samples. Evaporations were conducted on a spin evaporator under diminished pressure.

*2,3:4,5-Di-*O*-isopropylidene-1,6-di-*O*-(methylsulfonyl)galactitol* (**7**). — A solution of 5.12 g (19.4 mmol) of 2,3:4,5-di-*O*-isopropylidenegalactitol[24] (purified through the crystalline 1,6-dibenzoate, m.p. 186–186.5°, mis-named as the 2,4:3,5 diacetal in ref. 9) in 50 ml of pyridine was treated with 6.5 g (57.0 mmol) of methanesulfonyl chloride. The solution was warmed, kept for 28 h at room temperature, and then poured with stirring into 100 g of ice and water. The precipitated **7** (7.30 g, 89%) was collected and washed with water, m.p. 148–150°, and was used without recrystallization (lit.[25] m.p. 153–154°).

*1,6-Dichloro-1,6-dideoxy-2,4:3,5-di-*O*-isopropylidenegalactitol* (**8**). — A mixture of 4.00 g (9.57 mmol) of **7** with 8.00 g (73.1 mmol) of tetramethylammonium chloride and 5.30 g (125 mmol) of LiCl in 80 ml of DMF was stirred for 63 h at 105° (bath temp.). It was evaporated to 40–50 ml and poured into 250 ml of cold water. The precipitate was collected, washed with water, and dried, to yield 2.82 g (98%) of **8**, m.p. 115–116° (lit.[26] m.p. 114.5–115°).

*1,6-Dideoxy-1,6-difluoro-2,4:3,5-di-*O*-isopropylidenegalactitol* (**9**). — To a solution of 8.0 g (0.019 mol) of the disulfonate **7** in 80 ml of DMF was added 22 g (0.15 mol) of tetraethylammonium fluoride, which dissolved upon heating on the steam bath. After 15 h, the hot, amber solution was evaporated. The residual syrup was stirred with 30 ml of water, and the resultant precipitate was collected, affording 5.0 g (98%) of **9**, m.p. 79–81°. Recrystallization from ethanol–water yielded 3.2 g, m.p. 82–83°; R_F 0.25 (t.l.c., benzene); n.m.r. (^{19}F): ϕ +232.5 p.p.m., triplet of doublets ($J_{1-F,1-H'} = J_{1-F,1-H''} = 49$ Hz, $J_{1-F,2-H} = 24$ Hz).

Anal. Calc. for $C_{12}H_{20}F_2O_4$: C, 54.1; H, 7.57; F, 14.3. Found: C, 54.1; H, 7.84. F. 14.2.

*1,6-Di-*O*-(methylsulfonyl)galactitol* (**3**). — A solution of 5.00 g (12.0 mmol) of **7** in 50 ml of 80% (*v/v*) trifluoroacetic acid–water was kept for 10 min at room temperature, diluted with 50 ml of abs. methanol, and chilled. The resultant crystals were collected and washed with methanol to yield 3.36 g (83%) of **3**, m.p. 140–141° (lit.[27] m.p. 148–150°).

Anal. Calc. for $C_8H_{18}O_{10}S_2$: C, 28.4; H, 5.36; S, 19.0. Found: C, 28.5; H, 5.30; S, 19.1.

1,6-Dichloro-1,6-dideoxygalactitol (**4**). — Similarly from **8**, the product **4** crystallized directly from the trifluoroacetic acid solution, without dilution, after 15 min. It was washed with water, ethanol, and ether, m.p. 181–182° dec. (96% yield) (lit.[9] m.p. 183–185° dec.).

1,6-Dideoxy-1,6-difluorogalactitol (**5**) was similarly obtained from **9** after 1 h, without dilution of the trifluoroacetic acid solution. It was washed with ether, m.p. 181–182° (86% yield); n.m.r. (^{19}F, in D_2O, external $CFCl_3$): ϕ +227.6 p.p.m., triplet of doublets ($J_{1-F,1-H'} = J_{1-F,2-H''} = 50$ Hz, $J_{1-F,2-H} = 18$ Hz).

Anal. Calc. for $C_6H_{12}F_2O_4$: C, 38.7; H, 6.49; F, 20.4. Found: C, 38.9; H, 6.36; F, 20.2.

*2,3:4,5-Di-O-benzylidene-*D*-mannitol* (**29**) was prepared as described for the L enantiomer.[15] (+)-Inositol (**26**) was obtained[28] from pinitol (**25**) and converted into 1,2:3,4-di-*O*-benzylidene-(+)-inositol (**27**), m.p. 166–166.5° (lit[15] m.p. 158–159.5° for the L enantiomer). Cleavage with lead tetraacetate and reduction of the dialdehyde (**28**) with $NaBH_4$ afforded crude **29** in 47% yield, m.p. 120–125°, exhibiting several signals for O–PhCH–O in the n.m.r. spectrum and 2 or 3 spots on t.l.c. in EtOAc. Recrystallization from ethanol–water afforded only partial purification and appeared to be accompanied by decomposition with formation of benzaldehyde (lit[15] for the L enantiomer, m.p. 120–127° crude, m.p. 137–141° after recrystallization). Fractional crystallization from benzene afforded a small, pure sample of **29**, m.p. 145–147°, $[\alpha]_D$ −43.5° (EtOH; lit[15] +50° for the L-enantiomer), R_F 0.4 in ethyl acetate. Characteristic spectral features also distinguished **29** from the isomer **14**; i.r. 13.0, 13.38, 13.80, 14.40 μm; n.m.r. (Me_2SO): δ 5.67 s (O–PhCH–O).

Anal. Calc. for $C_{20}H_{22}O_6$: C, 67.0; H, 6.20. Found: C, 67.1; H, 6.09.

*2,4:3,5-Di-O-benzylidene-*D*-mannitol* (**14**). — 1,6-Di-*O*-benzoyl-D-mannitol (**12**) was converted with benzaldehyde–zinc chloride into **13**, which was debenzoylated in 83% yield to give **14**, m.p. 213–214 (lit[13] m.p. 203–205°), $[\alpha]_D^{20}$ +69.2° (EtOH), $[\alpha]_D^{20}$ +75.9° (pyridine; lit. +76.7°), R_F 0.8 in EtOAc. There was no indication of instability, and it was clearly distinct from the isomer **29** in all physical properties measured; i.r. 12.92, 13.50, 14.32 μm; n.m.r. (Me_2SO): δ 5.89 s (O–PhCH–O).

*2,4:3,5-Di-O-benzylidene-1,6-di-O-(methylsulfonyl)-*D*-mannitol* (**15**) was obtained in 71% yield by the procedure used for **7**, m.p. 133–134° (lit.[25] m.p. 134–135°, misnamed as the 2,3:4,5-isomer).

Reaction of **15** *with tetraethylammonium fluoride*. — The procedure used for **9**, after 3 h of heating, afforded a precipitate (66% wt. recovery) consisting of three components by t.l.c. in benzene (R_F 0.2, 0.5, 0.7); there were three kinds of O–PhCH–O signals in the n.m.r. spectrum, observed as singlets at δ 6.30, 6.12 (close doublet, unresolved), and 5.92, in integrated peak-ratios of 23:70:7, respectively. Resolution of a 100-mg sample on one preparative t.l.c. plate afforded 24 mg of the fast-moving component, R_F 0.7, m.p. 96–97° after recrystallization from methanol–water, as the *diene* **24**, identical in i.r. and n.m.r. with that from **16**.

The middle band, R_F 0.5, was the major product (40 mg), m.p. 158–161° after recrystallization from ethanol, identified as the *1-fluoro-5,6-olefin* **23**; i.r. 6.02 μm (weak, C=C of enol ether); n.m.r.: δ 7.7–7.3 m (C_6H_5), 6.12 s and 6.10 s (O–PhCH–O, two kinds), 5.2–4.3 m (=CH_2, –CH–O, CH_2F).

Anal. Calc. for $C_{20}H_{19}FO_4$: C, 70.2; H, 5.60; F, 5.50. Found: C, 69.3; H, 5.72; F, 5.78.

The slow-moving band, R_F 0.2, afforded 10 mg of solid presumed to be *2,4:3,5-di-*O*-benzylidene-1,6-dideoxy-1,6-difluoro-*D*-mannitol* **17** from its fluorine analysis and absence of an i.r. band near 6.0 μm.

Anal. Calc. for $C_{20}H_{20}F_2O_4$: F, 10.5. Found: 10.3.

*2,4:3,5-Di-*O*-benzylidene-1,6-dideoxy-*D-threo-*hex-1,5-dienitol* (**24**). — A solution of 3.06 g (6.64 mmol) of 2,4:3,5-di-*O*-benzylidene-1,6-dideoxy-1,6-diiodo-D-mannitol[13] (**16**) in 18 ml of anhydrous pyridine was treated with 4.80 g (20.8 mmol) of silver fluoride and stirred for 17 h at room temperature. About 100 ml of dichloromethane was added to the dark-brown mixture. The solids were separated on a filter, and triturated with three 20-ml portions of dichloromethane. The combined filtrates were washed with cold 2M hydrochloric acid to remove pyridine, and then with 5% sodium hydrogen carbonate and with water, and were dried and evaporated (bath not above 35°). Final traces of pyridine were removed by evaporating toluene from the residue. Recrystallization from ethanol–water afforded 0.92 g (54%) of **24**, m.p. 98–98.5°, R_F 0.7 in benzene; i.r. 6.02 μm (strong, C=C of enol ether); n.m.r.: δ 7.7–7.3 m (C_6H_5), 6.30 s (O–PhCH–O), 5.00 d (=CH_2, J 0.5 Hz), 4.83 s (–CH–O).

Anal. Calc. for $C_{20}H_{18}O_4$: C, 74.5; H, 5.63. Found: C, 74.3; H, 5.54.

*1,6-Di-*O*-(methylsulfonyl)-2,4:3,5-di-*O*-methylene-*D*-mannitol* (**20**). — By the procedure used for **7**, 2,4:3,5-di-*O*-methylene-D-mannitol[29,30] afforded **20** in 69% yield; recrystallized from ethanol, it had m.p. 146–147°.

Anal. Calc. for $C_{10}H_{18}O_{10}S_2$: C, 33.1; H, 5.01; S, 17.7. Found: C, 33.4; H, 5.08; S, 17.4.

*1,6-Dideoxy-1,6-difluoro-2,4:3,5-di-*O*-methylene-*D*-mannitol* (**22**). — A solution of 3.13 g (8.65 mmol) of **20** in 50 ml of dry DMF was treated with 9.91 g (66.5 mmol) of tetraethylammonium fluoride, heated at 100° overnight, and evaporated. The residual syrup was treated with ice–water in portions to give a precipitate (0.314 g, 17%), m.p. 85–90°, R_F 0.3 and 0.6 on t.l.c. in benzene. Recrystallization from water–methanol gave a 6.5% yield of **22**, m.p. 104–105°, R_F 0.3; n.m.r. (^{19}F): ϕ +230.5 p.p.m., triplet of doublets ($J_{1-F,1-H'} = J_{1-F,1-H''} = 48$ Hz, $J_{1-F,2-H} = 28$ Hz).

Anal. Calc. for $C_{18}H_{12}F_2O_4$: C, 45.7; H, 5.76; F, 18.1; mol wt, 210. Found: C, 45.6; H, 5.86; F, 17.3; mol.wt. (osmometer), 204.

*1,6-Diazido-1,6-dideoxy-2,4:3,5-di-*O*-methylene-*D*-mannitol* (**21**). — A solution of 0.362 g (1.00 mmol) of the disulfonate **20** in 10 ml of dry DMF was treated with 0.50 g (7.7 mmol) of sodium azide, heated for 15 min at 150° (bath temp), and evaporated. Addition of ice–water to the residue afforded a precipitate (0.180 g, 90%), m.p. 107–108°, which was recrystallized from abs. ethanol to yield 0.103 g (49%) of **21**, m.p. 111–111.5°, R_F 0.3 in benzene.

Anal. Calc. for $C_8H_{12}N_6O_4$: C, 37.5; H, 4.72; N, 32.8. Found: C, 37.6; H, 4.77; N, 33.0.

Hydrogenation over 5% Pd–charcoal and acidification afforded *1,6-diamino-1,6-dideoxy-2,4:3,5-di-*O*-methylene-*D*-mannitol dihydrochloride*, m.p. 220–225° dec. (lit[18,31] m.p. 220–224°).

*1,6-Dideoxy-1,6-diodo-*D*-mannitol* (**11**). — A mixture of 10.0 g (32.0 mmol) of 1,6-dibromo-1,6-dideoxy-D-mannitol (**10**) and 29.3 g (0.20 mol) of NaI in 120 ml of dry tetrahydrofuran was heated for 8 h at 65–75° under N_2. The pale color of iodine was discharged by adding a few crystals of $Na_2S_2O_3$ dissolved in 2 ml of water. The tetrahydrofuran was evaporated off, and 250 ml of water was added to the mixture to dissolve the salts. The white solid was collected, washed with water, and dried *in vacuo* to yield 9.73 g (75%) of **11**, m.p. 164–165.5° (lit[5,32] m.p. 165° dec., 165–167° dec.).

1,6-Dideoxy-1,6-diiodogalactitol (**2**) was obtained from 1,6-dideoxy-1,6-dibromogalactitol (**1**) in 64% yield by the same procedure, m.p. 175–177° dec. (lit.[5] m.p. 181° dec.).

*2,3:4,5-Di-*O*-isopropylidene-1,6-di-*O*-*p*-tolylsulfonyl-*L*-mannitol* (**31**). — To a stirred, ice-cooled solution of 20.0 g (76.7 mmol) of 2,3:4,5-di-*O*-isopropylidene-L-mannitol[22] (**30**) in 80 ml of dry pyridine was added dropwise a solution of 109 g (573 mmol) of *p*-toluenesulfonyl chloride in 100 ml of dry pyridine. The solution was kept overnight at room temperature, treated with 5 drops of water, and stirred for 10 min to hydrolyze excess tosyl chloride, and poured into 200 g of ice and water. The mixture was stirred for 30 min, and the resultant white solid was collected on a filter and dried in air to yield 40.0 g (98%) of **31**, m.p. 85–86°. Recrystallization from 150 ml of 9:1 petroleum ether (b.p. 30–60°)–benzene afforded 35.0 g of **31**, m.p. 87–89°, R_F 0.7 in 4:1 benzene–ether. The compound was stored at 0° and was used within 1–2 days. It decomposed with darkening to a tar on storage for several days at room temperature.

Anal. Calc. for $C_{26}H_{34}O_{10}S_2$: C, 54.7; H, 6.01; S, 11.2. Found: C, 54.4; H, 5.86; S, 11.0.

*1,6-Di-*O*-*p*-tolylsulfonyl-*L*-mannitol* (**32**). — A solution of 40.0 g of **31** in 350 ml of 80% trifluoroacetic acid was kept for 20 h at room temperature, and evaporated. The solid residue was triturated with 500 ml of water and with 200 ml of petroleum ether, filtering each time, and was recrystallized from 300 ml of 1:1 ethanol–water to yield 31.0 g (88%) of **32**, m.p. 120–122°.

Anal. Calc. for $C_{20}H_{26}O_{10}S_2$: C, 49.0; H, 5.34; S, 13.0. Found: C, 49.0; H, 5.24; S, 12.7.

*2,3,4,5-Tetra-*O*-acetyl-1,6-di-*O*-*p*-tolylsulfonyl-*L*-mannitol* (**33**). — A solution of 310 mg of **32** in 25 ml of pyridine was treated with 1.0 ml of acetic anhydride, kept for 15 h at ice temperature, poured into 100 g of ice and water, and stirred for 30 min. Chloroform extraction afforded a syrup that crystallized upon trituration with cold petroleum ether. Recrystallization from 15 ml of methanol afforded 255 mg (62%) of **33**, m.p. 116–118°; after two recrystallizations, m.p. 119–120° (lit[13] m.p. 119–120° for the D enantiomer).

Anal. Calc. for $C_{28}H_{34}O_{14}S_2$: C, 51.0; H, 5.17; S, 9.74. Found: C, 51.0; H, 5.23; S, 9.72.

*2,3,4,5-Tetra-O-acetyl-1,6-dibromo-1,6-dideoxy-*L*-mannitol* (**34**). — A mixture of 10.0 g of **33** and 15.0 g of LiBr in 400 ml of dry acetone was heated in a steel bomb for 4 h at 100°. The orange solution was evaporated and the residue was triturated with 300 ml of water to yield 4.50 g (62%) of **34**, m.p. 115–117°. Recrystallization from 50 ml of methanol–water (1:1) afforded 4.15 g, m.p. 118–119 (lit[33] m.p. 125–126° for the D enantiomer).

*1,6-Dibromo-1,6-dideoxy-*L*-mannitol* (**35**). — A solution of 400 mg of **34** in 100 ml of anhydrous 5% methanolic hydrogen chloride was refluxed for 3 h, evaporated, and the solid residue recrystallized from 30 ml of 3:1 1,2-dichloroethane–methanol to give 255 mg (83%) of **35**, m.p. 179–180° dec, $[\alpha]_D^{20}$ $-13.2°$ (ethanol). The i.r. spectrum was identical with that of a sample of the D enantiomer (**10**), m.p. 179–180° dec (lit.[5,33] m.p. 173–175°, m.p. 177–178° dec), $[\alpha]_D^{20}$ $+12.0°$ (ethanol).

Anal. Calc. for $C_6H_{12}Br_2O_4$: C, 23.4; H, 3.90; Br, 51.8. Found: C, 23.4; H, 3.83; Br, 51.5.

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