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Note

Synthesis of 1,3,6-tri-*O*-*p*-tolylsulfonyl-D-mannitol

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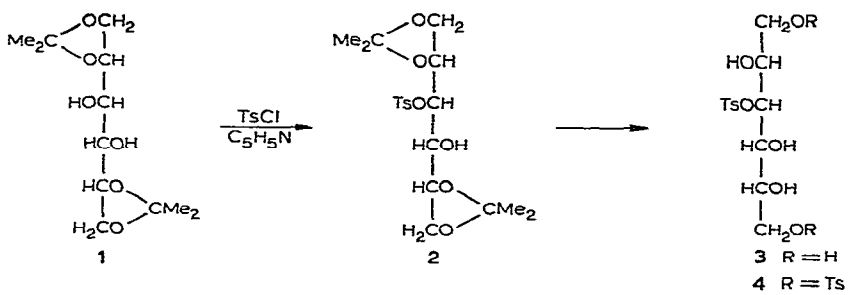
Many papers dealing with the synthesis of alditol derivatives having potential cytotoxic activity have been published. All of these products have substituents at the α and ω carbon atoms, and some are substituted in other positions. The most common substituent is the methylsulfonyl group[1], although compounds having halogen atoms or anhydro rings at the terminal carbon atoms have also been reported[2].

To open up the way to the syntheses of α,γ,ω-substituted derivatives of alditols, which might also show cytotoxic activity, the synthesis of 1,3,6-tri-*O*-*p*-tolylsulfonyl-D-mannitol (**4**) was undertaken.

As alditols react with two moles of methanesulfonyl or *p*-toluenesulfonyl chloride, under controlled conditions[3], to give the α,ω-disulfonates in yields of 20–25%, the synthesis of compound **4** by selective *p*-toluenesulfonylation of 3-*O*-*p*-toluenesulfonyl-D-mannitol (**3**) was attempted.



Some modifications were introduced into the procedure for monotoluenesulfonylation of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**1**) as reported by Bladon and Owen[4], to afford compound **2** in crystalline form.

Deacetonation of compound **2** by the method of Christensen and Goodman[5] gave **3** in good yield.

In the n.m.r. spectra of compounds **3** and **4**, the H-3 signals resonated at δ 5.15 and 5.85, respectively. The absence of any other signals at similar low field rules out the possibility of substitution at any other secondary carbon atom in compound **4**. The relatively high yield (38%) of compound **4** also accords with the expected preferential reaction at carbons 1 and 6.

EXPERIMENTAL

General methods. — Melting points (corrected) of the analyzed samples were measured on a Nalge–Axelrod micro hot-stage; others (uncorrected) were measured using a Mettler automatic apparatus, and are indicated with no melting interval. N.m.r. spectra (60 MHz) were recorded and integrated at 37° with a Varian A-60D spectrometer. An internal reference (sodium 4,4-dimethyl-4-silapentane-1-sulfonate) was used, and the sample concentration was 6–8% in deuterium oxide. I.r. spectra (KBr pellets) were recorded on a Perkin–Elmer Model 337 spectrometer. Evaporations were conducted *in vacuo*, below 38°.

Improved preparation of 1,2:5,6-di-O-isopropylidene-3-O-p-tolylsulfonyl-D-mannitol (**2**). — To a stirred, ice–water-cooled solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**1**, 22.5 g, 85 mmoles) in anhydrous pyridine (150 ml) was added a solution of *p*-toluenesulfonyl chloride (16.4 g, 86 mmoles) in anhydrous pyridine (50 ml), dropwise during 1 h.

The mixture was kept with stirring for 1 h at 0° and then for 30 h at room temperature. Pyridine was evaporated off, and the residual syrup was taken up in chloroform (300 ml) and washed successively with cold 3M hydrochloric acid, 5% aqueous sodium hydrogen carbonate, and finally with water. The dried (sodium sulfate) solution was evaporated, and the residual syrup crystallized from isopropyl ether (100 ml)–hexane (20 ml), yielding 17.2 g of a white solid, m.p. 85–98°. Recrystallization from isopropyl ether afforded 10.5 g (29%) of plates; m.p. 103.1°; ν_{max}^{KBr} 3405 (HO), 1600 (C=C), and 1157 cm^{-1} (S=O); lit.[4] m.p. 100°, $[\alpha]_D^{19}$ −27° (*c* 0.9, chloroform). Compound **2** decomposed on being kept for 1 week at room temperature.

3-O-p-Tolylsulfonyl-D-mannitol (**3**). — Compound **2** (5.0 g, 14 mmoles) was dissolved in trifluoroacetic acid–water (50 ml; 9:1, v/v) and the resulting solution was stirred for 10 min at room temperature. The solution was evaporated to a syrup, which was treated with dry ether (40 ml). The syrup dissolved partially, and the undissolved portion, on crystallization from ethyl acetate, gave compound **3**, m.p. 80–82° (0.50 g). Further crystals of compound **3** could be obtained from the ethereal solution. The total yield was 1.71 g (43%).

A sample of this product was recrystallized from ethyl acetate, m.p. 81–82.5°; ν_{max}^{KBr} 3500–3300 (HO), 1600 (C=C), and 1170 cm^{-1} (S=O); n.m.r. (δ): 2.46 (3 H, *s*, CH_3 of Ts), 3.30–4.25 (7 H, m), 5.14 (1 H, doublet of doublets, H-3), 7.57 and 7.98 (4 H, AB pattern, J_{AB} 9 Hz, aromatic).

Anal. Calc. for $C_{13}H_{20}O_8S$: C, 46.42; H, 5.99; S, 9.53. Found: C, 46.44; H, 5.90; S, 9.51.

1,3,6-Tri-O-p-tolylsulfonyl-D-mannitol (**4**). — To a stirred, ice-cooled solution of 3-*O*-*p*-tolylsulfonyl-D-mannitol (6.0 g, 18 mmoles) in anhydrous pyridine (30 ml), *p*-toluenesulfonyl chloride (7.5 g, 39 mmoles) in anhydrous pyridine (60 ml) was added dropwise during 1 h. The solution was stirred for 1 h at 0°, and then for 30 h at room temperature.

Pyridine was evaporated off, and the resulting syrup was dissolved in chloroform (250 ml) and the solution was treated as described for compound **2**. The syrup obtained after evaporation of solvent was dissolved in benzene–ethyl acetate (4:1, v/v) and the solution chromatographed on a column (45 × 5 cm) of Woelm silica gel. The same solvent was used as eluent, and 25-ml fractions were collected.

Fractions 32–61 yielded, after evaporation and recrystallization of the residue from benzene, compound **4** (4.16 g, 38%) as needles, m.p. 141–143°. A sample was recrystallized from the same solvent, giving m.p. 142–143°; ν_{max}^{KBr} 3550, 3400 (HO), 1600 (C=C), and 1170 cm^{-1} (S=O); n.m.r. (δ): 2.31 (3 H, s, CH_3 of Ts), 4.20–5.10 (7 H, m), 5.85 (1 H, doublet of doublets, H-3), 7.15–8.15 (12 H, m, aromatic).

Anal. Calc. for $C_{27}H_{32}O_{12}S_3$: C, 50.28; H, 5.01; S, 14.91. Found: C, 50.43; H, 5.06; S, 14.98.

Compounds **3** and **4** were unstable on storage and their specific rotations were not recorded.

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