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UNAMBIGUOUS SYNTHESES OF THE 3,4-DI- AND 3,4,6-TRI-METHYL ETHERS OF METHYL α-D-MANNOPYRANOSIDE*

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ABSTRACT

The unambiguous syntheses of methyl 3,4,6-tri-*O*-methyl-α-D-mannopyranoside (**6**) and methyl 3,4-di-*O*-methyl-α-D-mannopyranoside (**10**) were performed by routes involving methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**1**) to form methyl 2-*O*-*p*-tolylsulfonyl-D-mannopyranoside (**4**). Compound **4** directly led to **6**, and, *via* a 6-trityl derivative, to **10**.

INTRODUCTION

In a continuing effort to obtain reference compounds for structural determinations on mannans, two selectively methylated derivatives of methyl α-D-mannopyranoside have been prepared by unambiguous routes. The synthesis of methyl 3,4,6-tri-*O*-methyl-α-D-mannopyranoside (**6**) required the protection of the 2-hydroxyl group; this was achieved by first specifically benzoylating the 3-hydroxyl group of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside in a way analogous to that of Williams and Richardson[1]. The resulting monobenzoate **1** was then *p*-toluenesulfonylated to yield methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl-α-D-mannopyranoside (**2**); this was debenzoylated to yield **3**, and **3** was debenzylidenated to give the specifically protected methyl 2-*O*-*p*-tolylsulfonyl-α-D-mannopyranoside (**4**); compound **4** was permethylated, and the product (**5**) was deacylated to yield methyl 3,4,6-tri-*O*-methyl-α-D-mannopyranoside (**6**).

That the *p*-tolylsulfonyl group was on O-2 of **2** was shown in two ways. Firstly, the 3-*p*-toluenesulfonate corresponding to the mono-*p*-toluenesulfonate **3** has been reported, with a well-established structure[2]. The physical properties, particularly the

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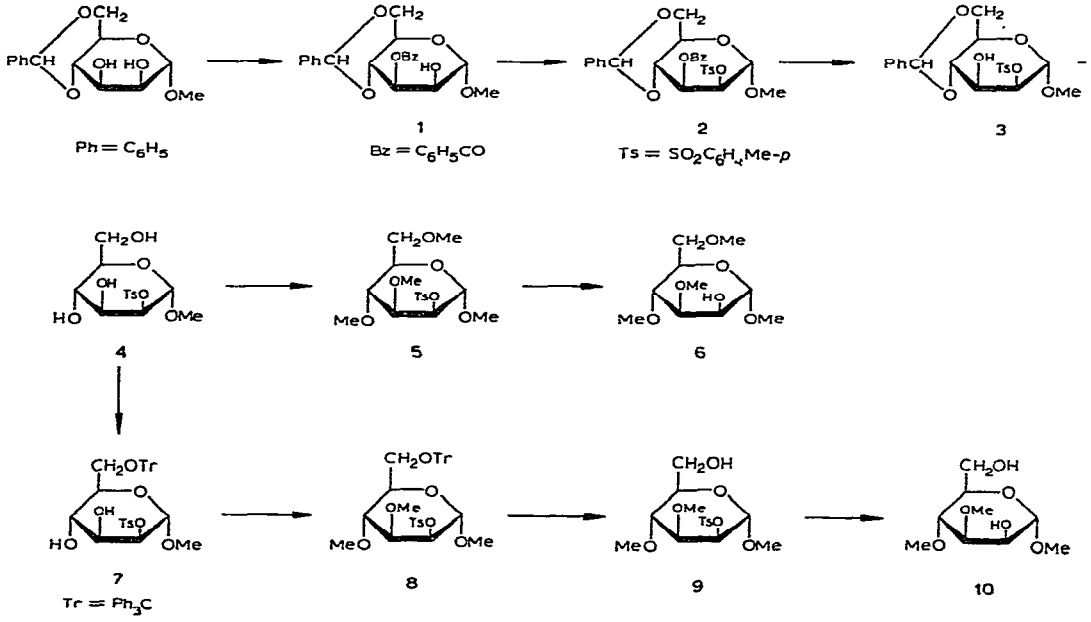
n.m.r. spectra, of the 3-ester and compound **3** are different. The chemical shift of the anomeric proton for compound **3** is displaced downfield, an effect expected when the *p*-tolylsulfonyl group is in an adjacent position. Secondly, three isomers of **6**, namely, the 2,3,4-, the 2,3,6-, and the 2,4,6-trimethyl ethers, have all been prepared by unambiguous routes[3,4]. The n.m.r. spectra of all four of these compounds were found to differ from each other; therefore, the *p*-tolylsulfonyl group in compounds **2** to **5** is on O-2, and the single, free hydroxyl group in **6** is on C-2.

Compound **4** was also used for preparing methyl 3,4-di-*O*-methyl-α-D-mannopyranoside, by tritylation to give **7**, followed by permethylation to **8** and removal of the protecting groups to give **10**. Compound **7** has been reported[5] as a minor by-product of a partial *p*-toluenesulfonylation in a sequence for synthesis of 2,4-di-*O*-methyl-α-D-mannose[6]. From relative rates of electrophoretic migration, Murty and Siddiqui[6] inferred that one component in the sulfonylation product was *p*-toluenesulfonylated at O-2. The present work confirms their assignment of the position of the *p*-tolylsulfonyl group.



EXPERIMENTAL

General. — N.m.r. spectra of compounds dissolved in chloroform-*d* were obtained at 100 MHz with a Varian HA-100 spectrometer, with tetramethylsilane as the internal standard. Only pertinent parts of the n.m.r. spectra are presented, the rest also being in accord with the structures presumed. Optical rotations were determined with a Bendix NPL polarimeter. Melting points are uncorrected.

In thin-layer chromatography (t.l.c.), each product gave a single spot clearly separated from that for the starting material. Plates (silica gel) were developed with various concentrations (1:100 to 1:10) of methanol–chloroform, and zones were made visible by spraying with 1:10 methanol–sulfuric acid and heating. The R_F values were found to be in inverse relationship to the number of hydroxyl groups in each compound. All tritylated compounds turned yellow before charring. Precoated plates (0.2 cm thick) of Silica Gel F-254 (E. Merck, Darmstadt) were used for preparative t.l.c., with detection either by u.v. fluorescence-quenching or by exposure to iodine vapors. Fractions were eluted with 1:20 methanol–chloroform.

Solutions were evaporated under diminished pressure at 45°. Pyridine was dried over calcium hydride.

Purdie methylations were performed by refluxing in methyl iodide (10 ml/g of sugar) and adding silver oxide (1 g/g of sugar) at 30-min intervals until t.l.c. showed a single, faster-moving component.

Photolysis[7,8] was performed with a Hanovia high-pressure, mercury-vapor, quartz-jacketed, 450-W immersion-lamp (Ace Glass, Vineland, N.J.); nitrogen was bubbled through the reaction mixture kept at ~30°.

The composition of all mixed solvents is expressed in terms of volume/volume.

Methyl 3-O-benzoyl-4,6-O-benzylidene-α-D-mannopyranoside (**1**). — Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside[6] (9.00 g) and pyridine (300 ml) in a round-bottomed flask equipped with a side-arm dropping-funnel were placed in a Dewar flask partially filled with acetone and supported by a magnetic stirrer. By careful addition of Dry Ice, the temperature of the bath was adjusted to −45°. Benzoyl chloride (4.08 ml) in pyridine (20 ml) was added dropwise, with stirring, during 30 min at −45°, and then the temperature was allowed to rise to room temperature during ~6–8 h. The mixture was evaporated in a rotary evaporator, and the residue dried by addition and evaporation of toluene (3 × 30 ml). An essentially quantitative reaction resulted, with only traces of starting material and of the dibenzoate. The product was purified by chromatography on a column of silica gel (1.2 kg) in pure chloroform, by elution with 1:50 methanol–chloroform, to yield 10.5 g (90%) of **1**, m.p. 131–132°, $[\alpha]_D^{25}$ −24° (*c* 1.3, chloroform); n.m.r. data: τ 1.95 (m, 2 H, *ortho* benzoyl protons), 2.65 (m, 8 H, *meta* and *para* benzoyl protons plus aromatic benzylidene protons), 4.43 (s, 1 H, benzylidene proton), 4.54 (d, *J* 4, 1 H, H-3), 5.27 (d, *J* 2, 1 H, H-1), and 6.62 (s, 3 H, CH_3O).

Anal. Calc. for $C_{21}H_{22}O_7$: C, 65.27; H, 5.74. Found: C, 65.22; H, 5.82.

Methyl 3-O-benzoyl-4,6-O-benzylidene-2-O-p-tolylsulfonyl-α-D-mannopyranoside (**2**). — A solution of *p*-toluenesulfonyl chloride (12 g) in pyridine (35 ml) was added to a solution of **1** (11.0 g) in pyridine (60 ml) cooled in an ice bath. After 1 day at 0° and 3 days at 25°, the solution was diluted with pyridine and made neutral by addition of potassium hydrogen carbonate (30 g); this mixture was evaporated to dryness, and re-evaporated with successive additions of toluene (2 × 150 ml) and then ethanol (2 × 150 ml), and the residue was dissolved in water–chloroform. The chloroform phase was dried (sodium carbonate), evaporated, and the residue heated with ethanol

(200 ml). The ethanol-insoluble crystals consisted of pure **2** (8.3 g), and, on combination with crystals (0.5 g) from the cooled filtrate, gave a total yield of 8.8 g (57%), m.p. 214–215°, $[\alpha]_D^{25}$ −35° (*c* 1.0, chloroform); n.m.r. data: τ 2.6 (m, 14 H, Ar-*H*), 4.40 (s, 1 H, nonaromatic benzylidene proton), 4.55 (d, *J* 10, 1 H, H-3), 5.06 (m, 2 H, H-1 and H-2), 6.58 (s, 3 H, CH_3O), and 7.88 (s, 3 H, Ar-CH_3).

Anal. Calc. for $C_{28}H_{28}O_9S$: C, 62.21; H, 5.22. Found: C, 62.40; H, 5.45.

Methyl 4,6-O-benzylidene-2-O-p-tolylsulfonyl-α-D-mannopyranoside (**3**). — Compound **2** (8.0 g) in methanol (400 ml) containing barium oxide (1 g) was boiled under reflux for 25 min. The mixture was evaporated to dryness, and the residue dissolved in water–chloroform. The chloroform phase was dried (sodium carbonate), evaporated (6.8 g), and the residue used directly for preparation of compound **4**.

A small sample was purified by preparative t.l.c. (1:50 methanol–chloroform) to yield amorphous **3**, $[\alpha]_D^{25}$ −25° (*c* 0.5, chloroform); n.m.r. data: τ 2.14 [d, *J* 10, 2 H, *ortho p*-tolylsulfonyl (tosyl) protons], 2.68 (m, 7 H, *meta* tosyl protons and aromatic benzylidene protons), 5.19 (d, *J* 2, 1 H, H-1), 5.27 (m, 1 H, H-2), 6.66 (s, 3 H, CH_3O), and 7.58 (s, 3 H, Ar-CH_3).

Anal. Calc. for $C_{21}H_{24}O_8S$ C, 57.79; H, 5.54. Found C, 57.82; H, 5.68.

For n.m.r. comparison, methyl 4,6-*O*-benzylidene-3-*O*-*p*-tolylsulfonyl-α-D-mannopyranoside was prepared according to Buchanan and Schwarz[2]. N.m.r. data: τ 2.30 (d, *J* 10, 2 H, *meta* tosyl protons), 2.72 (m, 7 H, *meta* tosyl protons and aromatic benzylidene protons), 4.62 (s, 1 H, nonaromatic benzylidene proton), 5.22 (m, 1 H, H-3), 5.25 (d, *J* 2, 1 H, H-1), 6.66 (s, 3 H, CH_3O), and 7.72 (s, 3 H, Ar-CH_3).

Methyl 2-O-p-tolylsulfonyl-α-D-mannopyranoside (**4**). — Compound **3** (6.6 g) in acetic acid (400 ml)/water (30 ml) was heated for 55 min at 65–70°, evaporated, re-evaporated with water (30 ml × 2), and the residue dissolved in water–chloroform. The aqueous phase was combined with aqueous extracts of the chloroform solution, and evaporated to dryness to yield **4** (4.85 g; 94% yield, based on **2**), m.p. 149–150°, $[\alpha]_D^{25}$ +50° (*c* 3.4, water); τ 2.16 (d, *J* 8, 2 H, *ortho* tosyl protons), 2.68 (d, *J* 10, 2 H, *meta* tosyl protons), 5.28 (d, *J* 1, 1 H, anomeric proton), 5.38 (s, 1 H, H-2), 6.71 (s, 3 H, methyl aglycon protons), and 7.59 (s, 3 H, tosyl methyl protons).

Anal. Calc. for $C_{14}H_{20}O_8S$: C, 48.27; H, 5.79. Found: C, 48.40; H, 5.86.

Methyl 3,4,6-tri-O-methyl-2-O-p-tolylsulfonyl-α-D-mannopyranoside (**5**). — Compound **4** (2.00 g) was methylated with Purdie's reagents, the suspension filtered, and the filtrate evaporated, to give 2.20 g of amorphous **5** (98% yield), $[\alpha]_D^{25}$ +6° (*c* 5.6, chloroform); τ 2.15 (d, *J* 8, 2 H, *ortho* tosyl protons), 2.68 (d, *J* 10, 2 H, *meta* tosyl protons), 5.23 (d, *J* 2, 1 H, anomeric proton), 5.30 (m, 1 H, H-2), 6.88 (s, 3 H, methoxyl and methyl aglycon protons), and 7.57 (s, 3 H, tosyl methyl protons).

Anal. Calc. for $C_{17}H_{26}O_8S$: C, 52.29; H, 6.71. Found: C, 51.94; H, 6.73.

Methyl 3,4,6-tri-O-methyl-α-D-mannopyranoside (**6**). — A solution of compound **5** (1.0 g) in methanol (250 ml) containing sodium (70 mg) was subjected to photolysis for 30 min. The mixture was then evaporated, and the residue dissolved in chloroform–water. The chloroform phase was dried (sodium sulfate), filtered, and the filtrate evaporated to give 0.52 g of amorphous **6** (yield 87%), $[\alpha]_D^{25}$ +8° (*c* 1.2, chloroform);

τ 5.25 (d, *J* 2, 1 H, H-1), 6.5 (s, 3 H), 6.46 (s, 3 H), 6.60 (s, 3 H), 6.64 (s, 3 H, C*H*$_3$O), and 7.58 (s, 1 H, O*H*).

Anal. Calc. for $C_{10}H_{20}O_6$: C, 50.83; H, 8.53. Found: C, 50.64; H, 8.63.

For purposes of n.m.r. comparison, the following compounds (previously reported) were reprepared.

Methyl 2,3,4-tri-*O*-methyl-α-D-mannopyranoside[3]. — τ 5.24 (d, *J* 2, 1 H, H-1), 6.46 (s, 3 H), 6.52 (s, 6 H), 6.64 (s, 3 H, C*H*$_3$O), and 7.87 (s, 1 H, O*H*).

Methyl 2,4,6-tri-*O*-methyl-α-D-mannopyranoside[4]. — τ 5.20 (d, *J* 2, 1 H, H-1), 6.46 (s, 3 H), 6.54 (s, 3 H), 6.60 (s, 3 H), 6.65 (s, 3 H, C*H*$_3$O), and 7.56 (s, 1 H, O*H*).

Methyl 2,3,6-tri-*O*-methyl-α-D-mannopyranoside[9]. — τ 5.20 (d, *J* 2, 1 H, H-1), 6.55 (s, 6 H), 6.61 (s, 3 H), 6.62 (s, 3 H, C*H*$_3$O), and 7.14 (s, 1 H, O*H*).

*Methyl 2-*O-p-*tolylsulfonyl-6-*O-*trityl-*α-D-*mannopyranoside* (7). — A solution of compound **4** (1.02 g) and chlorotriphenylmethane (0.91 g) in pyridine (4 ml) was kept for 3 days at room temperature. Potassium hydrogen carbonate (0.45 g) was added to the mixture, which was then evaporated, and the residue re-evaporated with toluene (2 × 15 ml) and ethanol (2 × 15 ml). T.l.c. of the crude product revealed a single (charring) component, and it was used without further purification for preparing compound **8**. An analytical sample was obtained by purifying by preparative t.l.c. (3:97 methanol–chloroform), to yield amorphous **7**, $[\alpha]_D^{25}$ +6° (*c* 5.6, chloroform); τ 2.18 (d, *J* 8, 2 H, *ortho* tosyl protons), 2.7 (m, 17 H, *meta* tosyl, and trityl protons), 5.26 (d, *J* 2, 1 H, H-1), 5.34 (m, 1 H, H-2), 6.70 (s, 3 H, C*H*$_3$O), and 7.61 (s, 3 H, Ar-C*H*$_3$).

Anal. Calc. for $C_{33}H_{34}O_8S$: C, 67.10; H, 5.80. Found: C, 67.43; H, 6.04.

*Methyl 3,4-di-*O-*methyl-2-*O-p-*tolylsulfonyl-6-*O-*trityl-*α-D-*mannopyranoside* (**8**). — Crude compound **7** was methylated with Purdie's reagents plus 0.6 g of potassium hydrogen carbonate, the suspension filtered, and the filtrate evaporated. T.l.c. of the crude product showed a single (charring) component, and it was used without further purification for preparing compound **9**. An analytical sample was obtained by purifying by preparative t.l.c. (1:99 methanol–chloroform), and recrystallizing from ethanol to give compound **8**, m.p. 154–155°, $[\alpha]_D^{25}$ +3° (*c* 1.3, chloroform); τ 2.11 (d, *J* 8, 2 H, *ortho* tosyl protons), 2.7 (m, 17 H, Ar-*H*, 5.09 (d, *J* 2, 1 H, H-1), 5.17 (m, 1 H, H-2), 6.66 (s, 3 H, C*H*$_3$O), and 7.64 (s, 3 H, Ar-*H*).

Anal. Calc. for $C_{35}H_{38}O_8S$: C, 67.94; H, 6.19. Found: C, 67.43; H, 6.04.

*Methyl 3,4-di-*O-*methyl-2-*O-p-*tolylsulfonyl-*α-D-*mannopyranoside* (**9**). — Into a solution of crude compound **8** in chloroform (10 ml) containing a trace of water was passed gaseous hydrogen chloride for 10 min. Solid potassium carbonate was then added portionwise until gas evolution ceased. The mixture was filtered, the filtrate evaporated, and the product purified by preparative t.l.c. (1:20 methanol–chloroform) to yield amorphous **9**, 0.52 g (51%, based on **4**), $[\alpha]_D^{25}$ +7.6° (*c* 5.3, chloroform); τ 2.18 (d, *J* 8, 2 H, *ortho* tosyl protons), 2.50 (d, *J* 8, 2 H, *meta* tosyl protons), 5.21 (d, *J* 2, 1 H, H-1), 5.33 (q, 1 H, H-2), 6.56 (s, 3 H), 6.70 (s, 3 H), 6.96 (s, 3 H, C*H*$_3$O), 7.58 (s, 3 H, Ar-*H*), and 7.91 (s, 1 H, O*H*).

*Methyl 3,4-di-*O-*methyl-*α-D-*mannopyranoside* (**10**). — A solution of compound **9**

(0.45 g) in methanol (250 ml) containing sodium (30 mg) was photolyzed for 20 min. The mixture was evaporated, and the product purified by preparative t.l.c. (1:20 methanol–chloroform) to give amorphous **10**, 0.163 g (62% yield), $[\alpha]_D^{25}$ +86° (*c* 1.4, chloroform); τ 5.23 (d, *J* 2, 1 H, H-1), 6.50 (s, 3 H), 6.56 (s, 3 H), 6.64 (s, 3 H, CH_3O), and 7.6 (s, 2 H, O*H*).

Anal. Calc. for $C_9H_{18}O_6$: C, 48.64; H, 8.16. Found: C, 48.42; H, 8.20.

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