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A SYNTHESIS OF METHYL 4,6-DI-*O*-METHYL-α-D-MANNOPYRANOSIDE

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ABSTRACT

A new route is described for preparing methyl 4,6-di-*O*-methyl-α-D-mannopyranoside (**5**) *via* methyl 2,3-di-*O*-*p*-tolylsulfonyl-α-D-mannopyranoside (**3**) as an intermediate. The retention of the mannopyranoside configuration and ring form was confirmed by proton n.m.r. spectroscopy and by m.s. of peracetylated aldononitrile derivatives. Mass-spectral fragmentation-pathways previously proposed were confirmed for 5-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-, 2,5-di-*O*-acetyl-3,4,6-tri-*O*-methyl-, and 3,5-di-*O*-acetyl-2,4,6-tri-*O*-methyl-D-mannononitrile.

INTRODUCTION

We report a rapid and simple route to methyl 4,6-di-*O*-methyl-α-D-mannopyranoside. Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**1**), a readily available starting-material[1], has previously been shown to be readily ditosylated to yield methyl 4,6-*O*-benzylidene-2,3-di-*O*-*p*-tolylsulfonyl-α-D-mannopyranoside[2] (**2**), which in turn can be debenzylidenated to give methyl 2,3-di-*O*-*p*-tolylsulfonyl-α-D-mannopyranoside (**3**). Compound **3** has stable protective groups on O-2 and O-3, allowing a wide variety of functional groups to be introduced at O-4 and O-6. Compound **3** was readily permethylated with Purdie's reagents or with diazomethane–boron trifluoride to give methyl 4,6-di-*O*-methyl-2,3-di-*O*-*p*-tolylsulfonyl-α-D-mannopyranoside (**4**).

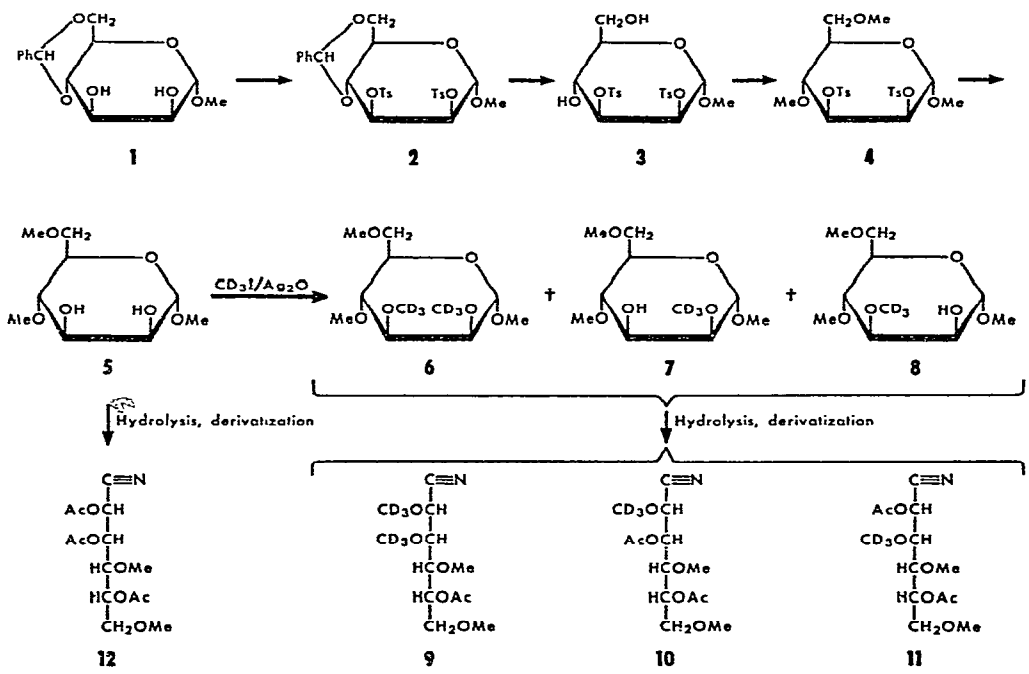
Tosyl groups have previously been removed without inversion by photolysis as reported by Zen *et al.*[3] for the general case and by one of us for an analogous mannopyranoside containing only one tosyl group[4]. To the best of our knowledge, the photolytic removal of tosyl groups has only been achieved with sugars that have stable functional groups adjacent to the tosyl group. We wished to ascertain not only whether adjacent tosyl groups could be removed without degradation, but also whether the carbon atoms to which the tosyloxy groups are attached retain their configurations.

*Mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products not mentioned.

Compound **4** was readily detosylated photolytically to yield a chromatographically pure, single product, **5**, with migration on silica gel (t.l.c.) identical to that of the 4,6-dimethyl ether (a mixture of methyl ethers of methyl α-D-mannopyranoside can readily be separated by t.l.c. on silica gel with methanol–chloroform, to give four components corresponding to the tetra- and the collective tri-, di-, and mono-*O*-methyl derivatives). Additional evidence that this compound was a di-*O*-methyl derivative was provided by n.m.r. spectroscopy, which showed three clearly distinguishable methyl singlet peaks.

Compound **5** was shown by two independent methods to retain the *manno* configuration. Firstly, compound **5** was permethylated by Purdie's reagents to yield a product having a n.m.r. spectrum identical to that of methyl tetra-*O*-methyl-α-D-mannopyranoside. This spectrum is considered diagnostic, as the chemical shift of each methyl group of an *O*-methylated hexose depends on the configuration and conformation[5] of the compound.

Secondly, compound **5** was partially methylated with trideuteriomethyl iodide in the presence of silver oxide, to give a mixture of dimethyl-di- (**6**) and -mono-(trideuteriomethyl) ethers (**7** and **8**). This mixture was hydrolyzed to the free sugars, and these were derivatized to the corresponding peracetylated aldononitriles (**9**, **10**, and **11**) according to a previously established program[6] (see Scheme 1). G.l.c. of this mixture showed only three well-defined peaks, with relative retention-times cor-



Scheme 1

responding to those of the peracetylated aldononitrile derivatives of 2,3,4,6-tetra-, 2,4,6-tri-, and 3,4,6-tri-*O*-methyl-D-mannose—proof that the original compound **5** had the mannopyranoside configuration and ring structure. In addition, for each compound analyzed by m.s., the fragment ions assigned to the parts of the molecule containing the deuteriomethyl groups[6] were shifted higher by three mass units than those of the ions from the corresponding, nondeuteriomethylated, reference compounds.

Compound **5** was hydrolyzed and the product derivatized to the peracetylated aldononitrile, whose g.l.c. retention-time differed from those of the other peracetylated dimethyl ethers of D-mannononitrile, and whose mass spectrum was in complete agreement with that expected for 2,3,5-tri-*O*-acetyl-4,6-di-*O*-methyl-D-mannononitrile (**12**) (see Scheme 1).

On this basis, we conclude that the tosyl groups can be readily removed from a tosylated sugar having adjacent secondary tosyl groups, with no inversion of configuration. Our work also confirmed the mass-spectral fragmentation-pathways proposed[6] for 5-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-D-mannononitrile, 2,5-di-*O*-acetyl-3,4,6-tri-*O*-methyl-D-mannononitrile, and 3,5-di-*O*-acetyl-2,4,6-tri-*O*-methyl-D-mannononitrile.

EXPERIMENTAL

General. — N.m.r. spectra were recorded, for solutions in chloroform-*d*, at 100 MHz with a Varian HA-100 spectrometer, with tetramethylsilane ($\tau = 10.0$) as the internal standard. Optical rotations were determined with a Bendix NPL polarimeter.

In t.l.c., each product gave a single spot clearly separated from that for the starting material. Plates (silica gel) were developed with methanol–chloroform, and spots were made visible by spraying with 1:10 methanol–sulfuric acid and heating. Precoated plates (0.2 cm thick) of Silica Gel F-254 (E. Merck, Darmstadt) were used for preparative t.l.c., with detection by exposure to iodine vapor.

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.

Photolysis[3] 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°.

Mass spectra were recorded at 70 eV with a duPont 21-492-1 mass spectrometer. All samples were introduced into a Packard 7401 gas chromatograph coupled to the mass spectrometer by means of a jet separator. Glass columns (1.83 m × 3.18 mm), packed with 5% of 1,4-butanediol succinate on Supelcoport, were operated at 180–200°. The temperature of the transfer lines from the gas chromatograph to the mass spectrometer was held at 220°.

*Methyl 4,6-*O*-benzylidene-2,3-di-*O*-p-tolylsulfonyl-α-D-mannopyranoside* (**2**). — A solution of *p*-toluenesulfonyl chloride (11 g) in pyridine (30 ml) was added to a

solution of cold methyl 4,6-*O*-benzylidene-α-D-mannopyranoside[1] (**1**, 3.5 g) in pyridine (30 ml). After 12 h at room temperature, the solution was warmed for 48 h at 50°, diluted with pyridine (20 ml), and made neutral with solid potassium hydrogen carbonate. This mixture was dissolved in water plus chloroform. The chloroform phase was dried (sodium carbonate), evaporated to the minimum volume, and re-evaporated with toluene (2 × 100 ml). The residue was crystallized twice from ethanol to yield the chromatographically pure compound **2** (5.7 g, 78%), m.p. 163–164°, $[\alpha]_D^{33}$ −5.5° (*c* 1.9, chloroform), R_F 0.5 (chloroform), R_F 0.9 (1:20 methanol–chloroform); lit.[2] m.p. 163–164°, $[\alpha]_D^{20}$ −5.3° (*c* 2.25, chloroform); n.m.r. data: τ 2.16 (d, *J* 8, 2 H, C-3 *ortho* tosyl protons), 2.49 (d, *J* 8, 2 H, C-2 *ortho* tosyl protons), 2.8 (m, 9 H, *meta* tosyl protons and aromatic benzylidene protons), 4.68 (s, 1 H, nonaromatic benzylidene proton), 5.03 (d, *J* 2, 1 H, anomeric proton), 5.14 (q, *J* 2, and *J* 4, 1 H, H-2), 5.37 (q, *J* 4, and *J* 8, 1 H, H-3), 5.8–6.4 (m, 4 H, H-4,5,6), 6.66 (s, 3 H, methyl aglycon protons), 7.58 (s, 3 H) and 7.76 (s, 3 H, tosyl methyl protons).

Methyl 2,3-di-O-p-*tolylsulfonyl*-α-D-*mannopyranoside* (**3**). — A solution of compound **2** (2.6 g) in acetic acid (70 ml) plus water (5 ml) was heated for 1 h at 80°, cooled, evaporated to the minimum volume, and then successively re-evaporated with water (2 × 100 ml) and ethanol (100 ml). The amorphous product was dried overnight in a vacuum desiccator at 45° to yield chromatographically pure compound **3** (2.1 g, 95%), $[\alpha]_D^{33}$ −14.5° (*c* 1.5, chloroform); R_F 0.3 (1:20 methanol–chloroform); n.m.r. data: τ 2.30 (t, *J* 8, 4 H, *ortho* tosyl protons), 2.71 (d, *J* 8, 4 H, *meta* tosyl protons), 5.16 (s, 1 H, anomeric proton), 5.38 (m, 2 H, H-2,3), 6.2 (m, 4 H, H-4,5,6), 6.65 (s, 3 H, methyl aglycon protons), and 7.60 (s, 6 H, tosyl methyl protons).

Methyl 4,6-di-O-*methyl-2,3-di*-O-p-*tolylsulfonyl*-α-D-*mannopyranoside* (**4**). — Amorphous compound **3** (1.30 g) was methylated with Purdie's reagents, the suspension was filtered, and the filtrate was evaporated to yield chromatographically pure compound **4** (1.35 g, 98%), $[\alpha]_D^{33}$ +3.5° (*c* 3.3, chloroform); R_F 0.8 (1:20 methanol–chloroform), R_F 0.95 (1:9 methanol–chloroform); n.m.r. data: τ 2.24 (m, 4 H, *ortho* tosyl protons), 2.70 (m, 4 H, *meta* tosyl protons), 5.20 (d, *J* 2, 1 H, anomeric proton), 5.3 (m, 2 H, H-2,3), 6.3–6.7 (m, 4 H, H-4,5,6), 6.68 (s, 3 H, methyl aglycon protons), 6.72 (s, 3 H) and 6.88 (s, 3 H, methyl ether protons), and 7.58 (s, 6 H, tosyl methyl protons).

Methyl 4,6-di-O-*methyl*-α-D-*mannopyranoside* (**5**). — A solution of compound **4** (1.0 g) in methanol (250 ml) containing sodium (100 mg) was subjected to photolysis (quartz vessel with no filter) for 45 min, and concentrated to 25 ml to yield a solid (300 mg). The solution was evaporated to an oil. Both fractions contained a major component with the R_F value (t.l.c.) of a di-*O*-methylated sugar. On the basis of t.l.c. charring, the oil contained most of the carbohydrate. The oil was then purified by preparative t.l.c. to yield compound **5** (253 mg, 61%), $[\alpha]_D^{33}$ +81.5° (*c* 2.8, water); lit.[7] $[\alpha]^{20}$ +80.5° (*c* 1.2, water); R_F 0.3 (1:9 methanol–chloroform); n.m.r. data: τ 5.31 (s, 1 H, anomeric proton), 6.1–6.5 (m, 6 H, H-2,3,4,5,6), 6.50 (s, 3 H), 6.61 (s, 3 H) and 6.69 (s, 3 H, methyl ether and methyl aglycon protons), and 7.3 (s, 2 H, hydroxyl protons). Permethylated samples of methyl α-D-mannopyranoside and of

compound **5** gave identical n.m.r. spectra. N.m.r. data for methyl 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranoside: τ 5.25 (d, *J* 2, 1 H, anomeric proton), 6.42 (m, 6 H, H-2,3,4,5,6), 6.52 (s, 3 H), 6.54 (s, 3 H), 6.56 (s, 3 H), 6.62 (s, 3 H), and 6.66 (s, 3 H, five Me ether and aglycon groups).

Partial deuteriomethylation with Purdie's reagents was performed on **5** (10 mg), the reaction being monitored by t.l.c. on silica gel (1:10 methanol–chloroform). The resulting mixture of products was hydrolyzed with M hydrochloric acid for 1 h at 100°, and the products derivatized, and subjected to g.l.c.–m.s.[6]. Three peaks emerged, with retention times (relative to that of the peracetylated aldononitrile derivative of 2,3,4,6-tetra-*O*-methyl-D-mannopyranose as unity) of 1.00 (peak A), 1.59 (peak B), and 1.89 (peak C). Peak A (**9**) gave a mass spectrum identical to that of 5-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-D-mannononitrile, except that fragment ions *m/e* 145 and 205 were shifted to *m/e* 148 and 208. Peak B (**10**) gave a mass spectrum identical to that of 3,5-di-*O*-acetyl-2,4,6-tri-*O*-methyl-D-mannononitrile, except that fragment ion *m/e* 186 was shifted to *m/e* 189. Peak C (**11**) gave a mass spectrum identical to that of 2,5-di-*O*-acetyl-3,4,6-tri-*O*-methyl-D-mannononitrile, except that the fragment ions *m/e* 126, 142, 145, 186, and 205 were respectively shifted to *m/e* 129, 145, 148,189, and 208. All mass-spectral data were in agreement with the fragmentation pathways previously established for these compounds[6].

These results confirmed that compound **5** was partially deuteriomethylated to a mixture of methyl 2,3-di-*O*-(deuteriomethyl)-4,6-di-*O*-methyl-α-D-mannopyranoside (**6**), methyl 2-*O*-(deuteriomethyl)-4,6-di-*O*-methyl-α-D-mannopyranoside (**7**), and methyl 3-*O*-(deuteriomethyl)-4,6-di-*O*-methyl-α-D-mannopyranoside (**8**), which was then hydrolyzed, and the sugars derivatized to a mixture of 5-*O*-acetyl-2,3-di-*O*-(deuteriomethyl)-4,6-di-*O*-methyl-D-mannononitrile (**9**), 3,5-di-*O*-acetyl-2-*O*-(deuteriomethyl)-4,6-di-*O*-methyl-D-mannononitrile (**10**), and 2,5-di-*O*-acetyl-3-*O*-(deuteriomethyl)-4,6-di-*O*-methyl-D-mannononitrile (**11**) (see Scheme 1).

Compound **5** was hydrolyzed, and the sugar was converted into the peracetylated aldononitrile (**12**), which was injected into the programmed g.l.c.–m.s. instrument. It yielded a single peak having a relative retention-time of 2.45, and major fragment-ions of *m/e* 87, 101, 112, 129, 154, 161, 173, 184, and 214. A complete listing has already been given of the relative intensities of the fragment ions in this mass spectrum, as well as a description of the fragmentation pathways[6].

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