SIMPLE, UNAMBIGUOUS SYNTHESES OF 2,3,6- AND 2,4,6-TRI-*O*-METHYL-D-MANNOSE.

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ABSTRACT

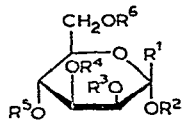
Methylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside, followed by removal of the benzylidene group, tritylation, tosylation, detritylation, methylation, and removal of the protective tosyl and methyl glycoside groups gave syrupy 2,3,6-tri-*O*-methyl-D-mannose, characterized by a crystalline di-*p*-nitrobenzoate. Monotosylation of the 4,6-*O*-benzylidene derivative gave a 3-*O*-tosyl derivative; hydrolysis of the benzylidene group, followed by methylation, and removal of the protective tosyl and methyl glycoside groups gave crystalline 2,4,6-tri-*O*-methyl-α,β-D-mannopyranose, characterized by a crystalline *N*-phenylglycosylamine.

INTRODUCTION

2,3,6-Tri-*O*-methyl-D-mannopyranose (7) was first obtained as a result of elucidation of the structure of (1→4)-linked galactomannans using the methylation procedure[1–4], and its structure was determined by Howarth, Hirst, and Streight[5]. This sugar was also obtained in the structure elucidation of benzoate esters of D-mannose[6]. 2,4,6-Tri-*O*-methyl-D-mannose (**13**) was obtained after methylation of galactomannans[7] and mannans[8] containing the (1→3) linkage.

The synthesis of 2,3,4-tri-*O*-methyl-D-mannopyranose (7) required the specific blocking of the hydroxyl group at C-4 which was first obtained by synthesis of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside[9,10]. Methylation of this derivative, followed by removal of the benzylidene group gave **1** which was tritylated at O-6 to give **2**, leaving the hydroxyl group at C-4 free for blocking. Tosylation of this hydroxyl group was readily obtained at a temperature of 50° or higher. Following removal of the trityl group of **3**, the resulting **4** was methylated with methyl iodide and silver oxide to give methyl 4-*O*-*p*-tolylsulfonyl-2,3,6-tri-*O*-methyl-α-D-mannopyranoside (**5**) in good yield (the efficient Hakomori methylation[11] could not be used, since sodium hydride readily removes the tosyl groups[12]). Detosylation was achieved with alcoholic sodium methoxide, a condition in which Walden inversion does not occur[13]. Hydrolysis of the methyl glycoside group of **6** with mineral acid gave pure, sirupy 2,3,6-tri-*O*-methyl-D-mannose (7) which was identical in all respects with the previously described [14,15] compounds.

In the preparation of 2,4,6-tri-*O*-methyl-D-mannose (**13**), monotosylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside was best achieved in pyridine solution at room temperature and took place preferentially, as might be expected, at the equatorial C-3 hydroxyl group[10,16]. After removal of the benzylidene group from **9** to give **10**, methylation with methyl iodide and silver oxide afforded methyl 2,4,6-tri-*O*-methyl-3-*O*-*p*-tolylsulfonyl-D-mannopyranoside (**11**) in very satisfactory yield. Removal of the tosyl group with alcoholic sodium methoxide, followed by hydrolysis of the methyl glycoside group of **12** with mineral acid gave 2,4,6-tri-*O*-methyl-D-mannopyranose (**13**) which crystallized from ether in two crystal forms (α and β anomers). The melting points of each anomer have been reported after a mechanical separation of the crystal forms[17]. Resolution of the two anomers could not be effected by t.l.c. (silica gel), paper chromatography, or g.l.c. The derived *N*-phenylglycosylamine (**14**) was identical in all respects with an authentic sample.



	R^1	R^2	R^3	R^4	R^5	R^6
1	H	Me	Me	Me	H	H
2	H	Me	Me	Me	H	Tr
3	H	Me	Me	Me	Ts	Tr
4	H	Me	Me	Me	Ts	H
5	H	Me	Me	Me	Ts	Me
6	H	Me	Me	Me	H	Me
7	(H, OH)		Me	Me	H	Me
8	H	*p*-$NO_2C_6H_4CO$	Me	Me	*p*-$NO_2C_6H_4CO$	Me
9	H	Me	H	Ts	(PhCH)	
10	H	Me	H	Ts	H	H
11	H	Me	Me	Ts	Me	Me
12	H	Me	Me	H	Me	Me
13	(H, OH)		Me	H	Me	Me
14	(PhNH, H)		Me	H	Me	Me

Ts = tosyl; Tr = trityl

EXPERIMENTAL

General methods. — T.l.c. was performed on glass plates coated with silica gel (Baker, 3405). Column chromatographic separations were carried out on silica gel of the same type. G.l.c. analyses were carried out using a copper column, 3/16 in by 10 ft, containing 20% neopentylglycol succinate on HMDS–Chromosorb W, at 170° and a helium flow rate of 100 ml/min[18]. Melting points are uncorrected.

*Methyl 2,3-di-*O*-methyl-6-*O*-trityl-α-*D*-mannopyranoside* (**2**). — A solution of methyl 2,3-di-*O*-methyl-α-D-mannopyranoside[19] (**1**, 2.1 g) and chlorotriphenylmethane (2.8 g) in dry pyridine (20 ml) was heated for 2 h on a boiling water-bath. The solution was poured into ice–water, and the precipitate that formed chromatographed on silica gel (50 g). Triphenylmethanol and chlorotriphenylmethane were eluted with chloroform (1 liter), and the pure product **2** (3.3 g, 73%) was eluted with 19:1 chloroform–ethanol (500 ml). After crystallization from ethanol, it showed m.p. 172–174° (lit.[19]: m.p. 172–173°); t.l.c. in 19:1 chloroform–acetone, R_F 0.47.

Methyl 2,3-di-O-methyl-4-O-p-tolylsulfonyl-6-O-trityl-α-D-mannopyranoside (**3**). — A solution of **2** (3.2 g) and *p*-toluenesulfonyl chloride (3.0 g) in dry pyridine (20 ml) was kept for 3 days at 53°. The precipitate (**3**, 4.1 g, 95%) that formed upon pouring the solution into ice–water was washed thoroughly with water and found to be homogeneous on t.l.c in 19:1 chloroform–acetone, R_F 0.70. After recrystallization from ethanol, it showed m.p. 144–145°, $[\alpha]_D^{22}$ +36.5° (*c* 2.0, chloroform).

Anal. Calc. for $C_{35}H_{38}O_8S$: C, 67.9; H, 6.19; OMe, 15.05. Found: C, 67.9; H, 6.23; OMe, 14.90.

Methyl 2,3-di-O-methyl-4-O-p-tolylsulfonyl-α-D-mannopyranoside (**4**). — Compound **3** (4.0 g) was detritylated with a solution (30 ml) of hydrogen chloride (1%) in chloroform at 0° (1 h), followed by neutralization with sodium carbonate (2 g). The resulting product was fractionated on a silica gel column (50 g) by firstly eluting triphenylmethanol with chloroform (700 ml), and then the desired compound **4** (2.2 g, 91%) with 19:1 chloroform–ethanol (400 ml). Compound **4**, a syrup, was homogeneous on t.l.c. in 19:1 chloroform–acetone, R_F 0.15, and showed $[\alpha]_D^{22}$ +41° (*c* 2.5, chloroform).

Anal. Calc. for $C_{16}H_{24}O_8S$: OMe, 24.7. Found: OMe, 24.4.

Methyl 2,3,6-tri-O-methyl-4-O-p-tolylsulfonyl-α-D-mannopyranoside (**5**). — Compound **4** (2.0 g) was treated with methyl iodide (40 ml) and silver oxide (4 g) to give, after filtration and evaporation of the solvent, the fully methylated product (1.96 g, 96%) which crystallized from ethyl acetate. After recrystallization from petroleum ether, compound **5** had m.p. 91–92°, $[\alpha]_D^{22}$ +38° (*c* 1.0, chloroform); t.l.c. in 19:1 chloroform–acetone, R_F 0.3.

Anal. Calc. for $C_{17}H_{26}O_8S$: C, 52.29; H, 6.71; OMe, 31.7. Found: C, 52.60; H, 6.76; OMe, 31.1.

Methyl 2,3,6-tri-O-methyl-α-D-mannopyranoside (**6**). — Compound **5** (1.94 g) was dissolved in a solution (50 ml) of sodium methoxide in methanol[20] (2.5 g sodium dissolved in 50 ml dry methanol). The mixture was heated for 12 h at reflux, after which water (25 ml) was added and the organic solvent was distilled off. Extraction with chloroform (5 × 25 ml) and evaporation gave a syrup (1.1 g, 94%) which was homogeneous on t.l.c. in butanone–water azeotrope, R_F 0.52, and had the same retention time (17.2 min) in g.l.c. as authentic **6**, obtained by methylation of guar gum; $[\alpha]_{22}^{D}$ +32° (*c* 2.8, chloroform).

Anal. Calc. for $C_{10}H_{20}O_6$: OMe, 52.7. Found: OMe, 52.2.

2,3,6-Tri-O-methyl-D-mannose (**7**). — A solution (25 ml) of compound **6** (1.0 g) in 0.5M sulfuric acid was heated for 11 h at reflux. After neutralization with barium carbonate, the filtrate was evaporated to give sirupy **7** (0.93 g, 97%) which was identical in all respects with an authentic sample prepared by methylation and hydrolysis of guar gum; paper chromatography on Whatman No. 1 paper with butanone–water, R_F 0.50; t.l.c. in butanone–water, R_F 0.40; g.l.c. of per(trimethylsilyl) derivative, retention time 4.8 min; $[\alpha]_D^{22}$ −11° (*c* 2.0, water); lit.[15,16]: $[\alpha]_D$ −10°.

To a portion (220 mg) of **6** in dry pyridine (5 ml) was added *p*-nitrobenzoyl chloride (10% molar excess). The mixture was heated for 30 min at 70° and then the

excess of aroyl halide was decomposed with saturated sodium hydrogen carbonate (30 ml). The product, 2,3,6-tri-*O*-methyl-1,4-di-*O*-*p*-nitrobenzoyl-α-D-mannopyranose (**8**) had, after recrystallization from methanol, m.p. and mixed m.p. 188°, $[\alpha]_D^{22}$ +34° (*c* 1.0, chloroform); lit.[21] : $[\alpha]_D$ +33°, m.p. 187–188°.

*Methyl 4,6-benzylidene-3-*O-p-*tolylsulfonyl-α-*D-*mannopyranoside* (**9**). — A solution (70 ml) of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (4.5 g) and *p*-toluenesulfonyl chloride (3.5 g) in dry pyridine (70 ml) was kept for 12 h at room temperature. The reaction mixture was poured into ice–water, and the product extracted with chloroform (5 × 30 ml). After evaporation of the solvent, the residue was chromatographed on a silica gel column (60 g), in chloroform, to remove the impurities. Elution with 20:1 chloroform–acetone gave **9**, first obtained as a syrup which crystallized by addition of petroleum ether (6.1 g, 90%). After recrystallization from petroleum ether–chloroform it had m.p. 155–156°, $[\alpha]_D^{22}$ +24.5° (*c* 1.0, chloroform); lit.[10]: m.p. 151–153°, $[\alpha]_D^{17}$ +21° (*c* 2.57, chloroform).

Anal. Calc. for $C_{21}H_{24}O_8S$: C, 57.79; H, 5.54 Found: C, 57.65; H, 5.56.

*Methyl 3-*O-p-*tolylsulfonyl-α-*D-*mannopyranoside* (**10**). — Compound **9** (5 g) was heated for 3 h at reflux in a mixture (18:8:1, v/v) of acetone–water–M hydrochloric acid to remove the benzylidene group. Completion of the reaction was ascertained by t.l.c. in 19:1 chloroform–acetone. After neutralization with barium carbonate (10 g) followed by filtration, the solvent was evaporated under reduced pressure. The aqueous solution (20 ml) of the residue was extracted with chloroform (2 × 10 ml) to remove the benzaldehyde and impurities. The solvent was evaporated and the residue was extracted with chloroform (100 ml). Evaporation under reduced pressure gave a syrupy product (3.6 g, 92%) which crystallized from benzene. After recrystallization from chloroform–petroleum ether, **10** had m.p. 87–90°, $[\alpha]_D^{22}$ +51° (*c* 1.0, chloroform); lit.[10]: m.p. 90–100°, 120–121.5°, $[\alpha]_D^{17}$ +35° (*c* 2, water).

Anal. Calc. for $C_{14}H_{20}O_8S$: C, 48.27; H, 5.79. Found: C, 48.15; H, 5.75.

*Methyl 2,4,6-tri-*O-*methyl-3-*O-p-*tolylsulfonyl-α-*D-*mannopyranoside* (**11**). — Compound **10** (3.0 g) was methylated with methyl iodide (40 ml) and silver oxide (4 g) in the usual manner to give, after five such treatments with fresh reagents, the fully methylated **11** (no hydroxyl group absorption in i.r. spectrum) (3.1 g, 94%) which was recrystallized from ether, m.p. 118–120°, $[\alpha]_D^{22}$ +44° (*c* 1.0, chloroform).

Anal. Calc. for $C_{17}H_{26}O_8S$: C, 52.29; H, 6.71; OMe, 31.7. Found: C, 52.15; H, 6.78; OMe, 31.3.

*Methyl 2,4,6-tri-*O-*methyl-α-*D-*mannopyranoside* (**12**). — Compound **11** (2.0 g) was detosylated as described previously to give a syrup (1.1 g, 92%) which was homogeneous on t.l.c. in butanone–water azeotrope, R_F 0.55. It had identical g.l.c. retention time (14 min) and specific rotation, $[\alpha]_D^{22}$ +51° (*c* 2.0, chloroform), as **12** obtained by partial methylation of methyl α-D-mannopyranoside[22] (separated from the product mixture by preparative g.l.c.).

Anal. Calc. for $C_{10}H_{19}O_6$: C, 51.06; H, 8.08; OMe, 52.7. Found: C, 51.04; H, 8.09; OMe, 52.3.

*2,4,6-Tri-*O-*methyl-*D-*mannopyranose* (**13**). — A solution of compound **12**

(1.0 g) in 0.5M sulfuric acid (25 ml) was heated for 6 h at 100°. Neutralization with barium carbonate, followed by filtration and evaporation of the solvent under reduced pressure gave a syrup (0.94 g, 98%) which crystallized upon addition of ethyl acetate. Recrystallization from ether gave a mixture of two crystalline forms (α and β anomers), m.p. 53–57°, $[\alpha]_D^{22}$ +15.1° (*c* 0.8, water), G.l.c. of the per(trimethylsilyl) derivative showed one component (α and β anomers do not separate under the conditions used) which had an identical retention time (4.2 min) as authentic **13**.

Anal: Calc. for $C_9H_{17}O_6$: C, 48.43; H, 8.52; OMe, 41.8. Found: C, 48.41; H, 8.50; OMe, 41.3.

N-*Phenyl-2,4,6-tri*-O-*methyl*-D-*mannopyranosylamine* (**14**). — A portion (0.1 g) of **13** was treated with aniline, as described previously, to give **14**. After recrystallization from ether, the *N*-phenylglycosylamine had m.p. 133–134°, $[\alpha]_D^{22}$ −149°→+8° (after 24 h, *c* 1.0, methanol); lit.[17] : m.p. 134°, $[\alpha]_D$ −150°→+8° (methanol).

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