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Note

Synthesis of 2,3-di-*O*-methyl- and 2,3,6-tri-*O*-methyl-D-mannitol*

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Permethylation of polysaccharides[1,2] is widely used to provide structural information Thus, it is necessary to have a broad list[3] of reference compounds with which to compare the methylated monosaccharides resulting from methanolysis or hydrolysis of the methylated polymer For structural determinations of mannose-containing polysaccharides, a large number of partially methylated D-mannose derivatives are available[3–18] However, for comparison by g l c, the 2,3-di- and 2,3,6-tri-methyl ethers of D-mannitol were required and have been prepared

During the course of the work, an improved method for the benzylidenation of methyl glycosides having *cis*-hydroxyl groups at C-2 and C-3 was developed Adjacent *cis*-hydroxyl groups are known to produce five-membered benzylidene acetals during formation of the more favored 4,6-*O*-benzylidene acetal[19] We found that rapid and preferential formation of the latter ring is obtained by use of a dry, weak cation-exchange resin as catalyst

Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**1**) was methylated[20] to give the 2,3-di-*O*-methyl derivative (**2**) This was debenzylidenated with trifluoroacetic acid–water[21] to give the 4,6-dihydroxy compound (**3**), which was sequentially converted into the 6-*O*-trityl derivative (**4**) and the 4-*O*-acetyl-6-*O*-trityl derivative (**5**) Compound **4** was isolated in high yields by purification on neutral alumina, as purification on silica gel was observed to produce detritylation[8,27] Detritylation of **5** occurred easily with aqueous trifluoroacetic acid to give methyl 4-*O*-acetyl-2,3-di-*O*-methyl-α-D-mannopyranoside (**6**) in 94% yield This reaction gave a better yield than other detritylation procedures[22,23] Compound **6** was methylated with diazomethane[10] and hydrolyzed to produce 2,3,6-tri-*O*-methyl-D-mannopyranose (**8**), which was reduced to the corresponding D-mannitol derivative (**9**)

2,3-Di-*O*-methyl-D-mannopyranose (**11**) was produced by acid hydrolysis of **3**, which gave a yield better than that of the hydrolysis of **2** The corresponding D-mannitol derivative (**12**) was obtained by reduction The time necessary to effect complete reduction of **8** and **11** was longer than the reduction time of D-mannose

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derivatives lacking a 3-methyl ether[24] After acetylation of the free hydroxyl groups of **9** and **12**, the respective acetates **10** and **13** had retention times on g l c as shown in Table I

TABLE I

RETENTION TIMES OF *O*-METHYL-D-MANNITOLS ON G L C [a]

O-Methyl groups	*O-Acetyl groups*	*Retention time*[b]
2,3,4,6	1,5	1 00
2,3,6	1,4,5	2 14
2,3	1,4,5,6	3 44

[a]G l c performed on a Varian aerograph, instrument, series 1800, equipped with a column (2 4 m) of Gas-Chrom Q (100–120 mesh) coated with 3% ECNSS-M, at 180°, with nitrogen (40 ml/min) as gas carrier[25] [b]Retention time relative to that of 1,5-di-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-D-mannitol

EXPERIMENTAL

General — Purity of products was determined by t l c on silica gel-coated glass plates (5 × 13 cm) irrigated with (A) 6 1 hexane–ethyl acetate, (B) 3 1 benzene–ethyl acetate, (C) 3 1 chloroform–acetone, (D) 6 1 chloroform–methanol, and (E) 3 1 chloroform–methanol Solvent ratios are based on volumes Components were located by spraying with 5% (v/v) sulfuric acid in ethanol and heating until permanent char spots were visible. Melting points were determined on a Fisher–Johns apparatus and are corrected N m r spectra were obtained with a Varian Associates T-60 A instrument I r spectra were obtained with a Perkin-Elmer Model 337 spectrophotometer Evaporations were done under reduced pressure at a bath temperature below 40° for organic solvents and at 45–50° for water Adsorption chromatography was performed on silica gel (Baker 3405) and neutral alumina (Woelm) Optical rotations were determined on a Perkin–Elmer Model 141 recording polarimeter connected with a circulating, constant-temperature bath maintained at 25° with a Valley Forge Temperature Programmer.

Methyl 4,6-O-benzylidene-α-D-mannopyranoside (**1**) — Dry methyl α-D-mannopyranoside[26] (29.1 g, 0 15 mole) and IRC-50(H^+) resin (30 g) were suspended in freshly distilled benzaldehyde (300 g) containing hydroquinone (300 mg) under a stream of dry nitrogen The suspension was stirred (12 h, 125°) The cooled supernatant was decanted, and the same procedure was repeated The combined supernatants were chromatographed on neutral alumina (500 g) The excess benzaldehyde and methyl 2,3 4,6-di-*O*-benzylidene-α-D-mannopyranoside were eluted with benzene, pure **1** was eluted with 1 1 (v/v) acetone–methanol The dibenzylidene compound crystallized from acetone (8 9 g, 16%) and was homogeneous by t l c (A, R_F 0 36), m p 179–180°, lit [28] m p 174–178° Compound **1** was crystallized from benzene (33 5 g, 79%) and was homogeneous by t l c (C, R_F 0 39), m p 143–144°, $[\alpha]_D^{25}$ +70 2° (*c* 1 02, chloroform), lit [29] m p 140–141°, $[\alpha]_D^{25}$ +69 7°

Methyl 4,6-O-benzylidene-2,3-di-O-methyl-α-D-mannopyranoside (**2**) — Dry **1** (28 2 g, 0 10 mole) was methylated by treatment with sodium hydride–methyl iodide[20] Chromatography on neutral alumina gave pure[30] **2** (97%)

Methyl 2,3-di-O-methyl-α-D-mannopyranoside (**3**) — Compound **2** (15 5 g, 50 mmoles) was stirred (15 min, 0°) with 9 1 (v/v) trifluoroacetic acid–water (150 ml)[21] Chromatography of the impure syrup[21] on silica gel (200 g) using irrigant C gave pure[11] **3** (95%)

Methyl 2,3-di-O-methyl-6-O-trityl-α-D-mannopyranoside (**4**) — Dry **3** (5 6 g, 25 mmoles) and chlorotriphenylmethane (11 2 g, 0 04 mole) were stirred (30 h, 45°) in dry pyridine (90 ml) After isolation the cooled, washed[31] solution in benzene was adsorbed on neutral alumina (150 g), and pure[17] **4** (94%) was eluted with chloroform

Methyl 4-O-acetyl-2,3-di-O-methyl-6-O-trityl-α-D-mannopyranoside (**5**) — Dry **4** (10 2 g, 22 mmoles) was acetylated and isolated by standard procedure[32] Pure **5** (11 1 g, 99%), which crystallized from ethanol, was homogeneous by t l c (B, R_F 0 57), m p 205–206°, $[\alpha]_D^{25}$ +24 6° (*c* 1 28, chloroform)

Anal Calc for $C_{30}H_{34}O_7$ C, 71 13, H, 6 76 Found C, 71 12, H, 6 60

Methyl 4-O-acetyl-2,3-di-O-methyl-α-D-mannopyranoside (**6**) — Dry **5** (10 1 g, 20 mmoles) was detritylated (15 min, 0°) with 9 1 (v/v) trifluoroacetic acid–water (100 ml)[21] The isolated[21], impure syrup was chromatographed on silica gel (50 g) in 6 1 (v/v) chloroform-acetone solution Syrup **6** (5 5 g, 94%) was homogeneous by t l c (C, R_F 0 46), $[\alpha]_D^{25}$ +33 5° (*c* 1 63, chloroform)

Anal Calc for $C_{11}H_{20}O_7$ OMe, 35 23 Found OMe, 35 14

Methyl 4-O-acetyl-2,3,6-tri-O-methyl-α-D-mannopyranoside (**7**) — Dry **6** (3 9 g, 15 mmoles) was methylated with diazomethane in dichloromethane[10] Syrup **7** (4 1 g, 99%), isolated by the standard procedure[10], was homogeneous by t l c (C, R_F 0 72), $[\alpha]_D^{25}$ +58 8° (*c* 1 07, chloroform)

Anal Calc for $C_{12}H_{22}O_7$· OMe, 44 60 Found OMe, 44 39

2,3,6-Tri-O-methyl-D-mannopyranose (**8**) — Dry **7** (3 6 g, 13 mmoles) was stirred (30 h, 90°) in 1 5M sulfuric acid (40 ml) After neutralization (barium carbonate) and evaporation of the filtered solution to a syrup that was purified on silica gel (30 g) in 18 1 (v/v) chloroform–methanol, **8** (2 6 g, 89%) was homogeneous by t l c (D, R_F 0 52), $[\alpha]_D^{25}$ +14 7° (*c* 1 20, methanol), lit [33] $[\alpha]_D^{22}$ +15°

2,3,6-Tri-O-methyl-D-mannitol (**9**) — A solution of **8** (2 2 g, 0 01 mole) was reduced (16 h) with sodium borohydride[24] (0 57 g, 15 mmoles) After neutralization with IR-120(H^+) resin, the usual treatment gave **9** (2 2 g. 99%), crystallized from ethyl acetate It was homogeneous by t l c (D, R_F 0 44), m p 81–82°, $[\alpha]_D^{25}$ +40 6° (*c* 1 43, methanol)

Anal. Calc for $C_9H_{20}O_6$ C, 48 20, H, 8 99. Found C, 48 25; H, 8 98

1,4,5-Tri-O-acetyl-2,3,6-tri-O-methyl-D-mannitol (**10**) — Dry **9** (2 0 g, 9 mmoles) was acetylated and isolated in the same manner as **5** Syrup **10** (3 1 g, 98%) was homogeneous by t l c (B, R_F 0 34), $[\alpha]_D^{25}$ +48 0° (*c* 1 18, chloroform)

Anal. Calc for $C_{15}H_{26}O_9$ OAc, 36 86, OMe, 26.57. Found· OAc, 36 75: OMe, 26 50

2,3-Di-O-methyl-D-mannopyranose (**11**) — Dry **3** (4.5 g, 20 mmoles) was stirred (30 h, 90°) in 1.5M sulfuric acid (45 ml). Pure **11** (3.6 g, 87%), isolated in the same manner as **8**, was homogeneous by t.l.c. (E, R_F 0.51), $[\alpha]_D^{25}$ +9.27° (*c* 1.46, methanol), lit.[33] $[\alpha]_D$ +6.0.

2,3-Di-O-methyl-D-mannitol (**12**) — Dry **11** (3.1 g, 15 mmoles) was reduced[24] (16 h) with sodium borohydride (0.76 g, 20 mmoles). Compound **12** (3.1 g, 99%), isolated in the same manner as **8** and crystallized from ethyl acetate, was homogeneous by t.l.c. (E, R_F 0.46), m.p. 113–114°, $[\alpha]_D^{25}$ +11.0° (*c* 1.14, methanol), lit.[30] m.p. 101–102°).

Anal. Calc. for $C_8H_{18}O_6$: C, 45.71; H, 8.63. Found: C, 45.94; H, 8.66.

1,4,5,6-Tetra-O-acetyl-2,3-di-O-methyl-D-mannitol (**13**) — Dry **12** (2.1 g, 10 mmoles) was acetylated and isolated in the same manner as **5**. Syrup **13** (3.7 g, 98%) was homogeneous by t.l.c. (B, R_F 0.42), $[\alpha]_D^{25}$ +42.5° (*c* 1.92, chloroform).

Anal. Calc. for $C_{16}H_{26}O_{10}\cdot$ OAc, 45.50, OMe, 16.40. Found: OAc, 45.61, OMe, 16.48.

2,3,6-Tri-O-methyl-1,4-di-O-(p-nitrobenzoyl)-α-D-mannopyranose (**14**) — Dry **8** (0.222 g, 1 mmole) and freshly recrystallized *p*-nitrobenzoyl chloride (0.953 g, 5 mmoles) were stirred (8 h, 50°) in dry pyridine (10 ml). The product was isolated in the same manner as **5**. After crystallization from methanol, **14** (0.499 g, 96%) was homogeneous by t.l.c. (B, R_F 0.52), m.p. 187–188°, $[\alpha]_D^{25}$ +34.3° (*c* 1.82, chloroform), lit.[17] m.p. 188°, $[\alpha]_D^{22}$ +34°.

2,3-Di-O-methyl-1,4,6-tri-O-(p-nitrobenzoyl)-α-D-mannopyranose (**15**) — Dry **11** (0.416 g, 2 mmoles) and freshly recrystallized *p*-nitrobenzoyl chloride (1.85 g, 10 mmoles) were stirred (8 h, 50°) in dry pyridine (20 ml). The product was isolated in the same manner as **5**. After crystallization from methanol, **15** (1.29 g, 98%) was homogeneous by t.l.c. (B, R_F 0.64), m.p. 191–192°, $[\alpha]_D^{25}$ +44.3° (*c* 1.74, chloroform), lit.[11] m.p. 194–195°, $[\alpha]_D^{25}$ +42°.

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