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Note

Synthesis of some mono-*O*-benzyl- and penta-*O*-methyl-*myo*-inositols*

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Glycosides of *myo*-inositol are common in Nature (compare, *e.g.*, ref. 1). In structural studies of these and of other *myo*-inositol derivatives, access to the six different penta-*O*-methyl-*myo*-inositols would be of value. Ballou and Lee[2] have characterized the two *meso*- and the two racemic forms of pentamethyl ethers in mixtures by g.l.c. For the synthesis of these ethers, the corresponding mono-*O*-benzyl ethers would be suitable starting materials. They would also be useful intermediates in the synthesis of different natural *myo*-inositol derivatives. Different mono-*O*-benzyl ethers of *myo*-inositol have been prepared by Angyal *et al.*[3,4], and the four chiral *mono-O*-benzyl ethers by Shvets *et al.*[5,6]. In the present communication, syntheses of 1(3)- (**14**), 4(6)- (**9**), and 5-mono-*O*-benzyl-*myo*-inositol (**8**), and of the two *meso* and the two racemic forms of penta-*O*-methyl-*myo*-inositol are reported.

Treatment of *myo*-inositol with 1-ethoxycyclohexene and a catalytic amount of *p*-toluenesulfonic acid in *N,N*-dimethylformamide yielded a mixture of dicyclohexylidene derivatives that was fractionated by crystallization and chromatography on silica gel columns. The 1,2:3,4- (**1**), 1,2:4,5- (**7**), and 1,2:5,6-di-*O*-cyclohexylidene-*myo*-inositol (**4**), previously prepared and characterized by Angyal *et al.*[7], were obtained in yields of 19, 26, and 38%, respectively (only one enantiomer is given in the Scheme).

Partial benzylation of **1** using phase-transfer catalysis[8] in order to obtain good yields of monobenzyl ethers gave a mixture of the 5- and the 6-benzyl ethers (**2** and **3**, respectively). These were separated by chromatography on a silica gel column and hydrolyzed to give 5-*O*-benzyl-*myo*-inositol (**8**) and 4(6)-*O*-benzyl-*myo*-inositol[4] (**9**), respectively.

*Dedicated to Professor Raymond U. Lemieux.
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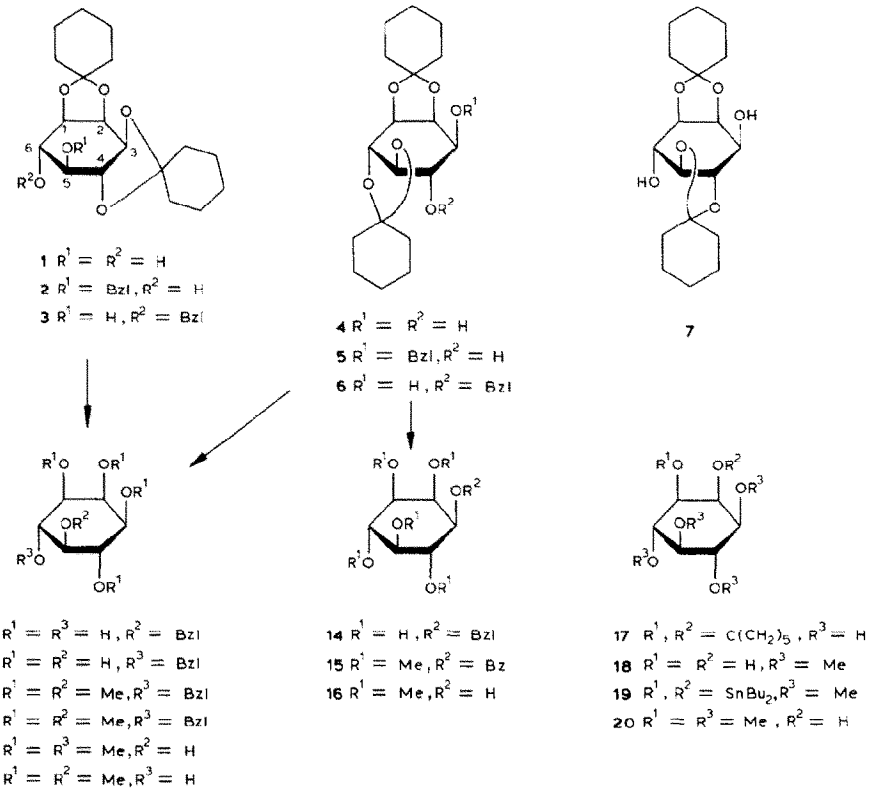

Similar benzylation of **4** yielded the 1(3)- and the 4-benzyl ethers (**5** and **6**, respectively), which were hydrolyzed to give 1(3)-*O*-benzyl-*myo*-inositol[3] (**14**) and 4(6)-*O*-benzyl-*myo*-inositol (**9**) respectively, the latter indistinguishable from the sample obtained from **3**. The melting points of the three monobenzyl *myo*-inositols agreed with literature values[3,4]. Each of the three mono-*O*-benzyl-*myo*-inositols was methylated according to Hakomori[9], and the benzyl group removed by catalytic hydrogenation, yielding 1,2,3,4,6- (**12**), 1,2,3,4,5- (**13**), and 1,2,4,5,6-penta-*O*-methyl-*myo*-inositol (**16**). The remaining 1,3,4,5,6-pentamethyl ether (**20**) was prepared from 1,2-*O*-cyclohexylidene-*myo*-inositol[7] (**17**) by methylation, followed by removal of the acetal group by acid hydrolysis[10] to give the 1,4,5,6-tetra-*O*-methyl ether **18**. Selective methylation of the dibutyl stannate at the equatorial[11] OH-1 gave crystalline 1,3,4,5,6-penta-*O*-methyl-*myo*-inositol (**20**). The four pentamethyl ethers were well separated, as their acetates, by g.l.c. on an SP-1000 glass capillary column (Table I).

On methylation analysis of an α-L-fucopyranosyl-*myo*-inositol isolated from urine[12], the penta-*O*-methyl-*myo*-inositol obtained had a retention time of 0.93 relative to that of 1,5-di-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-D-glucitol, demonstrating that the L-fucosyl group was linked to O-4(6) of *myo* inositol.

TABLE I

GAS-LIQUID CHROMATOGRAPHY OF THE ACETYLATED PENTA-*O*-METHYL-*myo*-INOSITOLS[a]

O-Methyl derivatives	T[b]
1,3,4,5,6 (**20**)	0.29
1,2,4,5,6 (**16**)	0.34
1,2,3,4,5 (**13**)	0.93
1,2,3,4,6 (**12**)	0.84

[a]On an SP1000 glass-capillary column at 190°. [b]Retention time relative to that of 1,5-di-*O*-acetyl-2,3,4,6-tri-*O*-methyl-D-glucitol (retention time 12.4 min).

EXPERIMENTAL

General methods. — Melting points are corrected. Evaporations were performed at bath temperatures <40°. For t.l.c., Merck plates (silica gel F_{254}) were used. Compounds were located by quenching of u.v. fluorescence or by charring with sulfuric acid. For column chromatography, Merck silica gel 60 (40–63 μm) was used. The loadings on columns were 1:50–100. The light petroleum used boiled between 40–60°. The ^{1}H- and ^{13}C-n.m.r. spectra were recorded for all substances and were in agreement with the postulated structures.

*1,2:3,4-Di-O-cyclohexylidene-*myo*-inositol* (**1**), *1,2:4,5-di-O-cyclohexylidene-*myo*-inositol* (**7**), *and 1,2:5,6-di-O-cyclohexylidene-*myo*-inositol* (**4**). — A solution of *myo*-inositol (9 g, 50 mmol), 1-ethoxycyclohexane[13] (16.5 g, 130 mmol), and *p*-toluenesulfonic acid monohydrate (0.25 g, 1.3 mmol) in *N,N*-dimethylformamide (125 mL) was heated at 95–100° for 2 h. The mixture was cooled to room temperature, diluted with dichloromethane (250 mL), and washed with a saturated solution of aqueous sodium hydrogencarbonate (100 mL) and with water (2 × 100 mL). The dichloromethane layer was evaporated to a syrup which, after dissolution in acetone–light petroleum, gradually deposited crystalline **7** (4.5 g, 13 mmol, 26%), m.p. 172–174° (lit.[7] m.p. 174°). The remaining acetone–light petroleum mother liquor was evaporated to a syrup, which was chromatographed on silica gel (2:1 chloroform–acetone) to yield **1** (3.2 g, 9.4 mmol, 19%), m.p. 157–159° (from light petroleum) (lit.[7] m.p. 158°); and **4** (6.4 g, 19 mmol, 38%), m.p. 130–131° (from light petroleum) (lit.[7] m.p. 133°).

*5-O-Benzyl-1,2:3,4-di-O-cyclohexylidene-*myo*-inositol* (**2**) *and 6-O-benzyl-1,2:3,4-di-O-cyclohexylidene-*myo*-inositol* (**3**). — Aqueous sodium hydroxide (125 mL of a 5% solution) was added to a solution of 1,2:3,4-di-*O*-cyclohexylidene-*myo*-inositol (**1**) (2.5 g, 7 mmol), tetrabutylammonium hydrogensulfate (2.5 g, 7 mmol), and benzyl bromide (2.0 g, 12 mmol) in dichloromethane (125 mL). The mixture was boiled overnight under reflux, cooled to room temperature, and the two layers were separated. The dichloromethane layer was washed with water and evaporated. Chromatography on silica gel (15:1 chloroform–acetone) yielded syrupy **2** (0.6 g, 1.3 mmol, 18%), and **3** (1.1 g, 2.6 mmol, 36%), m.p. 125–126° (from diethyl ether–light petroleum).

1(3)-O-Benzyl-2,3:4,5-(1,2:5,6)-di-O-cyclohexylidene-myo-*inositol* (**5**)* *and 4-O-benzyl-1,2:5,6-di-O-cyclohexylidene*-myo-*inositol* (**6**). — Benzylation of **4** (5.0 g, 15 mmol) was performed as described for **1**, yielding the syrupy products **5** (1.6 g, 3.7 mmol, 25%) and **6** (3.6 g, 8.4 mmol, 57%).

1(3)-O-Benzyl-myo-*inositol* (**14**). — The syrupy product **5** (1.6 g, 3.7 mmol) was treated with 80% aqueous acetic acid (100 mL) for 1 h at 95–100°. The solution was evaporated and the resulting crystalline residue recrystallized from ethanol to yield **14** (0.75 g, 2.8 mmol, 75%), m.p. 203–205° (lit.[3] m.p. 203–206°).

4(6)-O-Benzyl-myo-*inositol* (**9**). — Compound **6** (3.6 g, 8.4 mmol) was treated with aqueous acetic acid and processed as described for the preparation of **14**, yielding **9** (1.4 g, 5.2 mmol, 62%), m.p. 165–167° (from ethanol) (lit.[4] m.p. 169–170°). Compound **9** was also obtained from **3** in an analogous manner.

5-O-Benzyl-myo-*inositol* (**8**). — Compound **2** (300 mg, 0.7 mmol) was treated with aqueous acetic acid and processed as described for the preparation of **14**, yielding **8** (140 mg, 0.5 mmol 74%), m.p. 281–283° (ethanol–water).

1(3)-O-Benzyl-2,3,4,5,6-(1,2,4,5,6)-penta-O-methyl-myo-*inositol* (**15**)*. — A solution of sodium methylsulfinylmethanide, prepared from sodium hydride (1 g) and dimethyl sulfoxide (20 mL), was added to **14** (540 mg, 2 mmol) in dimethyl sulfoxide (10 mL). The precipitated sodium salt was solubilized by ultrasonic treatment for 1 h. The reaction mixture was cooled to 0°, and methyl iodide (10 mL) was added, followed by ultrasonic treatment for further 30 min. The dimethyl sulfoxide solution was diluted with water (50 mL) and extracted with diethyl ether (2 × 25 mL). The diethyl ether extracts were dried (silica gel) and evaporated to a syrup, which was chromatographed on silica gel (4:1 chloroform–acetone) to yield **15** as a chromatographically homogenous syrup (410 mg, 1.2 mmol, 60%).

4(6)-O-Benzyl-1,2,3,5,6-(1,2,3,4,5)-penta-O-methyl-myo-*inositol* (**11**)*. — This compound was prepared, as described for **15**, from **9** (270 mg, 1 mmol). The crystalline product was recrystallized from light petroleum to yield pure **11** (180 mg, 0.5 mmol, 51%), m.p. 81–82°.

Anal. Calc. for $C_{18}H_{28}O_6$: C, 63.5; H, 8.29. Found: C, 63.4; H, 8.19.

5-O-Benzyl-1,2,3,4,6-penta-O-methyl-myo-*inositol* (**10**). — This compound was prepared, as described for **15**, from **8** (100 mg, 0.4 mmol). The crystalline residue was recrystallized from light petroleum to give pure **10** (100 mg, 0.3 mmol, 79%), m.p. 77–79°.

1,3,4,5,6-Penta-O-methyl-myo-*inositol* (**20**). — A suspension of 1,4,5,6-tetra-*O*-methyl-*myo*-inositol[10,14] (**18**) (500 mg, 2.1 mmol) and dibutyltin oxide (550 mg, 2.2 mmol) in methanol (25 mL) was heated under reflux for 30 min (clear solution), and then the solvent was removed under diminished pressure. The resulting syrup, 1,2-*O*-dibutylstannylene-3,4,5,6-tetra-*O*-methyl-*myo*-inositol (**19**) was taken up in *N,N*-dimethylformamide (10 mL) and treated with methyl iodide (2 mL). The mixture was stirred overnight at room temperature, when t.l.c. (2:1 chloroform–

*The numbering in parentheses indicates the filiation with the starting material.

acetone) showed complete disappearance of the starting material. The mixture was evaporated to dryness, and then chromatographed on a silica gel column, in the solvent system used for t.l.c., to yield **20** (480 mg, 1.9 mmol, 91%), m.p. 82–83° (from diethyl ether–light petroleum).

Anal. Calc. for $C_{11}H_{22}O_6$: C, 52.8; H, 8.86. Found: C, 52.9; H, 8.51.

1,2,4,5,6-Penta-O-*methyl*-myo-*inositol* (**16**). — Syrupy **15** (400 mg, 1.2 mmol) was hydrogenated at room temperature and atmospheric pressure, in ethanol (20 mL) and in the presence of palladium-on-charcoal (10%, 400 mg). When the hydrogen consumption had ceased, the catalyst was removed by filtration, and the filtrate was evaporated to a crystalline residue that was recrystallized (from light petroleum) to yield **16** (210 mg, 0.8 mmol, 71%), m.p. 89–90°.

Anal. Calc. for $C_{11}H_{22}O_6$: C, 52.8; H, 8.86. Found: C, 52.9; H, 8.48.

1,2,3,4,5-Penta-O-*methyl*-myo-*inositol* (**13**). — Compound **11** (260 mg, 0.8 mmol) was hydrogenated, as described for the preparation of **16**, to yield **13** as a chromatographically homogeneous syrup (186 mg, 0.7 mmol, 97%).

1,2,3,4,6-Penta-O-*methyl*-myo-*inositol* (**12**). — Compound **10** (100 mg, 0.3 mmol) was hydrogenated as described for the preparation of **16**, except that ethyl acetate (10 mL) was used as solvent, to yield **12** (70 mg, 0.3 mmol, 96%), m.p. 85–87° (from light petroleum).

Anal. Calc. for $C_{11}H_{22}O_6$: C, 52.8; H, 8.86. Found: C, 53.0; H, 8.53.

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