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Note

Methylation of carbohydrates bearing base-labile substituents, with diazomethane–boron trifluoride etherate
Part IV*. An improved procedure for the synthesis of 6-*O*-methyl-D-mannose

E. G. CROS** AND E. M. GRUÑEIRO

Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Perú 222, Buenos Aires (Argentina)

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In connection with our work on the hydrolysis products from the antibiotic Curamycin[2], a sample of 6-*O*-methyl-D-mannose was needed. This compound had originally been prepared by Hudson *et al.*[3] by methylation of methyl 2,3,4-tri-*O*-acetyl-α-D-mannopyranoside with Purdie's reagents, followed by hydrolysis. From present knowledge[4], it is obvious that this procedure is unreliable, because of the acetyl migration that must occur in the basic medium used in the methylation. Dutton and Tanaka[5] could not obtain a good yield of 6-*O*-methyl-D-mannose by use of the method, and they correctly assumed that the very poor yield of desired product was due to acetyl migration. The title compound has recently been prepared[6] by direct methylation of methyl α-D-mannopyranoside, but the method does not afford the desired product in good yield.

We now report that, by use of diazomethane–boron trifluoride etherate as the methylating agent, no acetyl migration occurs, and the expected intermediate product is obtained in good yield.

Methyl α-D-mannopyranoside[7] (**1**) was tritylated and then acetylated in one step, to give methyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl-α-D-mannopyranoside (**2**), and this was detritylated, by use of a column of silica gel as the acidic catalyst[8], to methyl 2,3,4-tri-*O*-acetyl-α-D-mannopyranoside (**3**). Compound **3** was then methylated with diazomethane–boron trifluoride etherate as previously described[1], affording methyl 2,3,4-tri-*O*-acetyl-6-*O*-methyl-α-D-mannopyranoside (**4**). Deacetylation of compound **4** with sodium methoxide in methanol yielded methyl 6-*O*-methyl-α-D-mannopyranoside (**5**) which, on acid hydrolysis, gave 6-*O*-methyl-D-mannose (**6**) as a syrup, $[\alpha]_D^{25}$ +34.9 (10 min)→ +32.9° (8 h), having spectral properties in agreement with the structure assigned. The m.p. of the phenylosazone of **6** was in accord with reported values[3,5,6].

*For Part III, see ref. 1.
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EXPERIMENTAL

Melting points were determined with a Fisher–Johns apparatus and are uncorrected. I.r. spectra were recorded with a Perkin–Elmer "Infracord" spectrophotometer. N.m.r. spectra were recorded with a Varian A-60 spectrometer for solutions in $CDCl_3$ or D_2O. Microanalyses were performed by A. Bernhardt, W. Germany. Solvents were removed under diminished pressure below 50°.

Methyl 2,3,4-tri-O-acetyl-6-O-trityl-α-D-mannopyranoside (**2**). — A solution of methyl α-D-mannopyranoside[7] (**1**, 3.0 g) and chlorotriphenylmethane (4.65 g) in pyridine (15 ml) was heated for 3 h at 100°, and then kept overnight at room temperature. To the solution, acetic anhydride (12 ml) was added, and the mixture was kept for 24 h at room temperature. It was then poured onto ice–water, and the solid was filtered off, washed with water, and dried. The product was recrystallized from ether–petroleum ether and from ethanol, to give 7.3 g of **2**, m.p. 128–129°, $[\alpha]_D^{26}$ +44.6° (*c* 1.0, chloroform)[3]; its i.r. and n.m.r. spectra were in agreement with the structure assigned.

Methyl 2,3,4-tri-O-acetyl-α-D-mannopyranoside (**3**). — To a column of silica gel (Davison, grade 12, activity I) (100 g) was added a solution of compound **2** (1 g) in benzene (20 ml); the column was developed to its full length with benzene (100 ml), and kept for 24 h at room temperature. The column was then eluted with 1:9 (v/v) ethyl acetate–benzene (600 ml). The eluate was found (by t.l.c.) to contain triphenylmethanol and a trace of the starting material. The column was then eluted with 1:4 (v/v) methanol–ethyl acetate (800 ml). On evaporation of the solvent, the residue obtained crystallized on drying; it was recrystallized from ether–petroleum ether, yielding **3** (428 mg), m.p. 97–98°, $[\alpha]_D^{25}$ +54.9° (*c* 1.1, chloroform)[3]; its i.r. and n.m.r. spectra were in accordance with the structure assigned.

Methyl 2,3,4-tri-O-acetyl-6-O-methyl-α-D-mannopyranoside (**4**). — A solution of compound **3** (1.0 g) in dichloromethane (10 ml) was cooled to 0°; boron trifluoride etherate (0.05 ml) was added, and, while the temperature was kept at 0°, a solution of diazomethane in dichloromethane was added until a yellow color persisted in the solution. After 30 min at 0°, the precipitate of polymethylene was filtered off, and the filtrate was evaporated. The residue failed to crystallize, but it was purified by distillation at 70°/10^{-3} torr; the compound (850 mg) showed only one component by t.l.c., and had $[\alpha]_D^{26}$ +56.8° (*c* 1.2, chloroform); its i.r. spectrum showed no hydroxyl band; n.m.r. data: τ 8.02, 7.97, 7.87 (3-proton singlets, acetyl groups); τ 6.65 (2-proton multiplet, H-6); τ 6.62 (OMe at C-1) and 6.59 (OMe at C-6)[9]; τ 6.28 (broad signal, H-5); τ 5.29 (1-proton doublet, $J_{1,2}$ 1.5 Hz, H-1); and τ 4.85 (3-proton multiplet, H-2, H-3, H-4).

Anal. Calc. for $C_{14}H_{22}O_9$: C, 50.29; H, 6.63. Found: C, 50.51; H, 6.73.

Methyl 6-O-methyl-α-D-mannopyranoside (**5**). — To a solution of compound **4** (700 mg) in methanol (10 ml) was added M methanolic sodium methoxide (1 ml), and the solution was kept for 12 h at room temperature. The base was neutralized with Dowex 50W ion-exchange resin, the suspension was filtered off, and the filtrate was

evaporated. The gummy residue was purified by distillation at 75–80°/10^{-3} torr; the product (260 mg) showed only one component by t.l.c. and had $[\alpha]_D^{25}$ +78.8° (*c* 1.2, chloroform); n.m.r. data: τ 5.20 (1-proton doublet, $J_{1,2}$ 1.5 Hz, H-1); τ 6.56 (OMe at C-1) and 6.58 (OMe at C-6)[9].

Anal. Calc. for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 46.06; H, 7.73.

6-O-Methyl-D-mannose (**6**). — A solution of compound **5** (410 mg) in M hydrochloric acid (8 ml) was kept for 2 h at 100°, cooled, and made neutral with Dowex 1 ion-exchange resin; the suspension was filtered, and the filtrate was lyophilized. The gummy residue (342 mg) was homogeneous by t.l.c.; it had $[\alpha]_D^{25}$ +34.9 (10 min)→ +32.9° (8 h) (*c* 1.1, water). N.m.r. data: τ 4.77 (1-proton doublet, $J_{1,2}$ 1.0 Hz, H-1 of the β-D anomer); τ 5.20 (1-proton doublet, $J_{1,2}$ 1.5 Hz, H-1 of the α-D anomer); τ 6.58 (OMe). Its phenylosazone had m.p. 173–174°, undepressed on admixture with an authentic sample; lit.[3,5,6] m.p. 173–174°.

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