Note

Methylation of carbohydrates bearing base-labile substituents, with diazomethane–boron trifluoride etherate. Part V*. A new synthesis of 4,6-di-*O*-methyl-D-mannose

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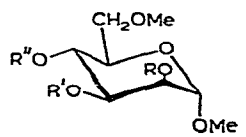
In previous articles[1–4] in this series, we reported that partially acylated carbohydrates could be methylated by the diazomethane–boron trifluoride etherate reagent without migration of the *O*-acyl groups. The procedure was successfully applied to partially *O*-acetylated[2,3] or *O*-benzoylated[4] monosaccharides.

We now describe an extension of the method in which the methylating agent is applied to a monosaccharide having *O*-(ethoxycarbonyl) groups in the molecule.

In an attempt to synthesize 2,6-di-*O*-methyl-D-mannose (D-curamicose)[5] starting from methyl 6-*O*-methyl-α-D-mannopyranoside[1] (**1**), we tried to protect selectively, with an acylating agent, the hydroxyl groups at C-3 and C-4 (both equatorially attached), leaving free the axially attached hydroxyl group at C-2.

In the literature, there exist a conflict regarding the selective esterification of D-mannose derivatives having a fixed conformation. In D-mannopyranose derivatives having the *C1* (D) conformation (in which the 2-hydroxyl group is axially attached), partial acetylation[6], esterification with nitric acid[7], or sulfonylation[7,8] lead to favored substitution at the equatorial hydroxyl groups, whereas benzoylation[9] causes substitution at the axial 2-hydroxyl group. On the other hand, sulfonylation of D-mannofuranose derivatives also gives substitution at the 2-hydroxyl group[10].



1 R=R'=R''=H
2 R=R'=COOEt; R''=H
3 R=R'=COOEt; R''=Me
4 R=R'=H; R''=Me

For our purpose, we chose ethyl chloroformate as the protecting agent, because of its known tendency to favor reaction with equatorial hydroxyl groups[11]. When compound **1** was treated with ethyl chloroformate in the proportion necessary to acylate two hydroxyl groups, a methyl di-*O*-(ethoxycarbonyl)-6-*O*-methyl-α-D-mannopyranoside was obtained. Analysis by p.m.r. spectroscopy at 100 MHz

*For Part IV, see ref. 1.

indicated that the new compound was methyl 2,3-di-*O*-(ethoxycarbonyl)-6-*O*-methyl-α-D-mannopyranoside (**2**), having the equatorial 4-hydroxyl group free. Hence, the substitution pattern is similar to that for benzoylation of methyl α-D-mannopyranoside[9].

To confirm the structure assigned to the new compound (**2**), it was methylated with diazomethane–boron trifluoride etherate, yielding methyl 2,3-di-*O*-(ethoxycarbonyl)-4,6-di-*O*-methyl-α-D-mannopyranoside (**3**), which, on treatment with potassium carbonate solution, afforded methyl 4,6-di-*O*-methyl-α-D-mannopyranoside[12] (**4**). Acid hydrolysis of compound **4** gave 4,6-di-*O*-methyl-D-mannose as a syrup, $[\alpha]_D^{20}$ +20.8° (in water), having spectral properties in agreement with those expected for the structure assigned.

Although the present method did not provide us with the 2,6-di-*O*-methyl-D-mannose desired (a compound which, in fact, has recently been synthesized by a different approach[13]), it proved that the methylating agent could be applied to carbohydrates having *O*-(ethoxycarbonyl) substituents without promoting migration or elimination of the base-labile protecting groups.

EXPERIMENTAL

P.m.r. spectra were recorded with Varian A-60 and XL-100 spectrometers, for solutions in chloroform-*d* or deuterium oxide. Preparative t.l.c. was conducted on silica gel (Merck). Solvents were removed under diminished pressure below 50°. Microanalyses were performed by A. Bernhardt Laboratory, West Germany.

Methyl 2,3-di-O-(ethoxycarbonyl)-6-O-methyl-α-D-mannopyranoside (**2**). — Methyl 6-*O*-methyl-α-D-mannopyranoside[1] (**1**) (100 mg) was dissolved in a mixture of chloroform (2 ml) and pyridine (1 ml), and the solution was cooled to 0°. To this solution, ethyl chloroformate (0.18 ml) was added dropwise with continuous stirring. When the addition was complete, the mixture was kept for 1 min at 0°, and treated with cold water until the white precipitate dissolved. The organic layer was successively washed with cold 2M hydrochloric acid (3 × 1 ml), cold 2M sodium hydrogen carbonate (1 × 1 ml), and cold water (3 × 1 ml), dried (magnesium sulfate), and evaporated; the residue was purified by preparative t.l.c., and then by distillation (90–95°/10^{-3} torr), yielding 49 mg of **2**, $[\alpha]_D^{21}$ +10.3° (*c* 1, chloroform); its i.r. spectrum showed hydroxyl (3400 cm^{-1}) and carbonyl (1740 cm^{-1}) absorption; p.m.r. data (chloroform-*d*): τ 8.70 (6-proton triplet, *J* 7 Hz, CH_3–CH_2–), 6.62 (3-proton singlet, OMe), 6.60 (3-proton singlet, OMe), 6.30 (4-proton multiplet, H-4, H-5, H-6), 5.84 (2-proton quartet, *J* 7 Hz, CH_3–CH_2–), 5.80 (2-proton quartet, *J* 7 Hz, CH_3–CH_2–), 5.24 (1-proton doublet, $J_{1,2}$ 1.5 Hz, H-1), 5.00 (1-proton quartet, $J_{2,3}$ 3 Hz, $J_{3,4}$ 9 Hz, H-3), and 4.90 (1-proton quartet, $J_{2,1}$ 1.5 Hz, $J_{2,3}$ 3 Hz, H-2).

Anal. Calc. for $C_{14}H_{24}O_{10}$: C, 47.72; H, 6.87. Found: C, 47.75; H, 6.82.

Methyl 2,3-di-O-(ethoxycarbonyl)-4,6-di-O-methyl-α-D-mannopyranoside (**3**). — A solution of compound **2** (243 mg) in dichloromethane (5 ml) was cooled to 0°; boron trifluoride etherate (0.02 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 2 h at 0°, the precipitate of polymethylene was filtered off, and the filtrate was evaporated. The residue (207 mg) failed to crystallize, but it was purified by distillation (twice) at 75°/10^{-3} torr; the compound (179 mg) showed only one component by t.l.c., and had $[\alpha]_D^{22}$ +21.8° (*c* 1, chloroform); its i.r. spectrum showed no hydroxyl band; p.m.r. data (chloroform-*d*): τ 8.69 (6-proton triplet, *J* 7 Hz, CH_3–CH_2–), 6.62 (3-proton singlet, OMe), 6.58 (3-proton singlet, OMe), 6.52 (3-proton singlet, OMe), 6.36 (4-proton multiplet, H-4, H-5, H-6), 5.81 (2-proton quartet, *J* 7 Hz, CH_3–CH_2–), 5.78 (2-proton quartet, *J* 7 Hz, CH_3–CH_2–), 5.22 (1-proton doublet, $J_{1,2}$ 1.5 Hz, H-1), and 4.94 (2-proton multiplet, H-2, H-3).

Anal. Calc. for $C_{15}H_{26}O_{11}$: C, 49.17; H, 7.15. Found: C, 49.35; H, 7.29.

Methyl 4,6-di-O-methyl-α-D-mannopyranoside (**4**). — A solution of compound **3** (70 mg) in methanol (3 ml) was treated with 10% potassium carbonate solution (1.7 ml), and the mixture was kept for 30 min at 60° and then for 24 h at room temperature. The methanol was evaporated by means of a stream of warm air, and the residue was filtered through a column of Dowex 50W ion-exchange resin (H^+, 2.5 ml). The resin was eluted with water (25 ml), and the eluate was lyophilized. The residue (42 mg) showed only one component by t.l.c., but was further treated by preparative t.l.c.; it then had $[\alpha]_D^{21}$ +81.3° (*c* 1, methanol); lit.[12] $[\alpha]_{5780}^{20}$ +80.5° (in water); p.m.r. data (D_2O): τ 6.61 (3-proton singlet, OMe at C-6), 6.57 (3-proton singlet, OMe at C-1)[14], 6.45 (3-proton singlet, OMe at C-4)[14], and 5.41 (1-proton doublet, $J_{1,2}$ 1.5 Hz, H-1).

4,6-Di-O-methyl-D-mannose. — A solution of compound **4** (25 mg) in 4% hydrochloric acid (2.5 ml) was heated under reflux for 5 h, cooled, made neutral with Dowex-1 ion-exchange resin (OH^-), filtered, and the filtrate lyophilized. The residue (18 mg) showed only one component by t.l.c., and had $[\alpha]_D^{21}$ +20.8° (*c* 1, water); lit.[12] $[\alpha]_{5780}^{22}$ +20° (in water); p.m.r. data (D_2O): τ 6.60 (3-proton singlet, OMe at C-6)[14], and 6.43 (3-proton singlet, OMe at C-4)[14].

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