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Note

Evidence of acetyl migration during the methylation of methyl 2,3,4-tri-*O*-acetyl-D-mannose with diazomethane–boron trifluoride etherate

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As we had a need to prepare 6-*O*-methyl-D-mannose, we proceeded by using the method of Gros and coworkers which utilized methyl 2,3,4-tri-*O*-acetyl-α-D-mannopyranoside, with diazomethane–boron trifluoride etherate as the methylating agent[1,2]. This synthesis was found to be superior to earlier methods[3] that involved either the cumbersome separation of a mixture of mono-, di-, and tri-methyl ethers obtained from partial methylation of methyl α-D-mannopyranoside or a low-yield, selective methylation with unavoidable acetyl migration[4,5]. Gros and coworkers claimed that no acetyl migration occurred during their process[1,2].

In this study we succeeded in preparing methyl 2,3,4-tri-*O*-acetyl-6-*O*-methyl-D-mannopyranoside by the procedure of Gros and coworkers[1,2] in high yield, but the methylation step was not entirely problem-free as had been claimed as there was evidence of acetyl migration in the diazomethane–boron trifluoride etherate methylation step. Herein is reported the identification of the by-products from this procedure, and it is established that the acetyl groups do migrate to a small extent, even under these mild conditions.

In our synthesis[1], we started with methyl D-mannopyranoside (**1**, Scheme 1), and by the sequence of (*i*) tritylation, (*ii*) acetylation, (*iii*) detritylation, and (*iv*) methylation, we were able to obtain separately, by column chromatography, the anomeric compounds methyl 2,3,4-tri-*O*-acetyl-6-*O*-methyl-α-D-mannopyranoside (**7**, slower migrating on t.l.c.) and methyl 2,3,4-tri-*O*-acetyl-6-*O*-methyl-β-D-mannopyranoside (**7**, faster migrating on t.l.c.). In this separation, a small amount of a middle fraction was isolated which principally contained the slower moving compound and two other positional isomers. This was confirmed by converting the mixture to the corresponding (1-^{2}H) alditol acetates and analyzing these by g.l.c. and by g.l.c.–m.s.[6,7]. The major product was 1,2,3,4,5-penta-*O*-acetyl-6-*O*-methyl-D-(1-^{2}H)mannitol (**11**); minor products were 1,2,3,4,6-penta-*O*-acetyl-5-*O*-methyl-D-(1-^{2}H)mannitol (**12**) and 1,2,3,5,6-penta-*O*-ace-

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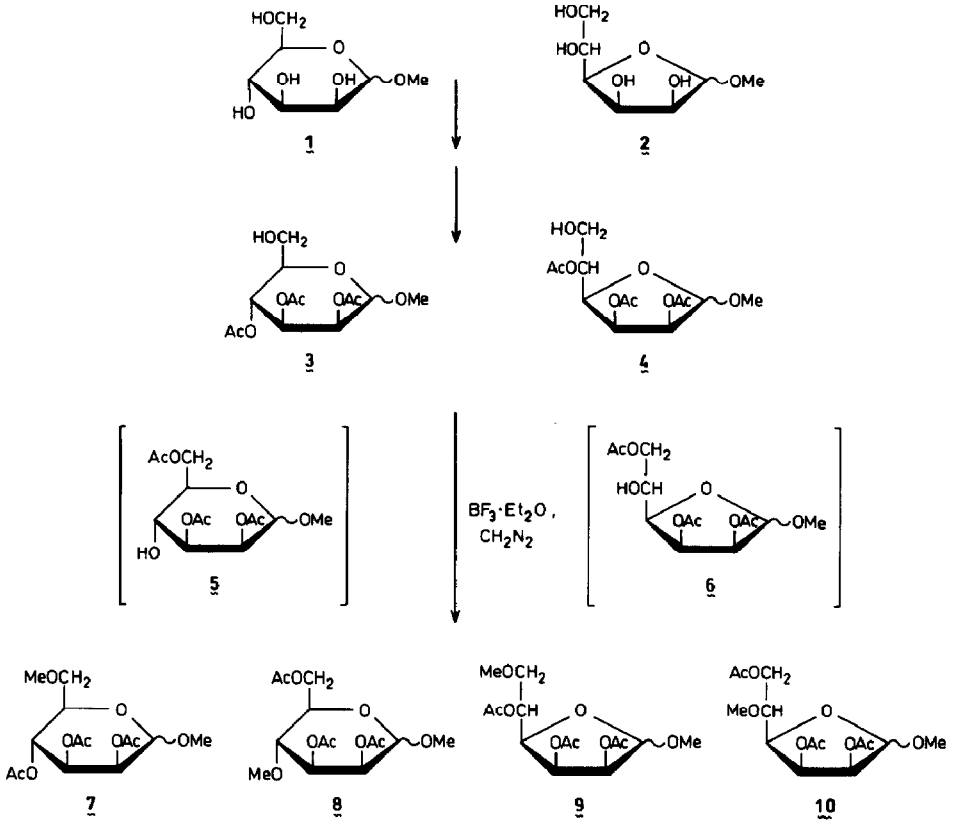

AcOCH,D
AcOCH
AcOCH
HCOAc
HCOAc
CH_2OMe

11

AcOCH,D
AcOCH
AcOCH
HCOAc
HCOMe
CH_2OAc

12

AcOCH,D
AcOCH
AcOCH
HCOMe
HCOAc
CH_2OAc

13

Scheme 1.

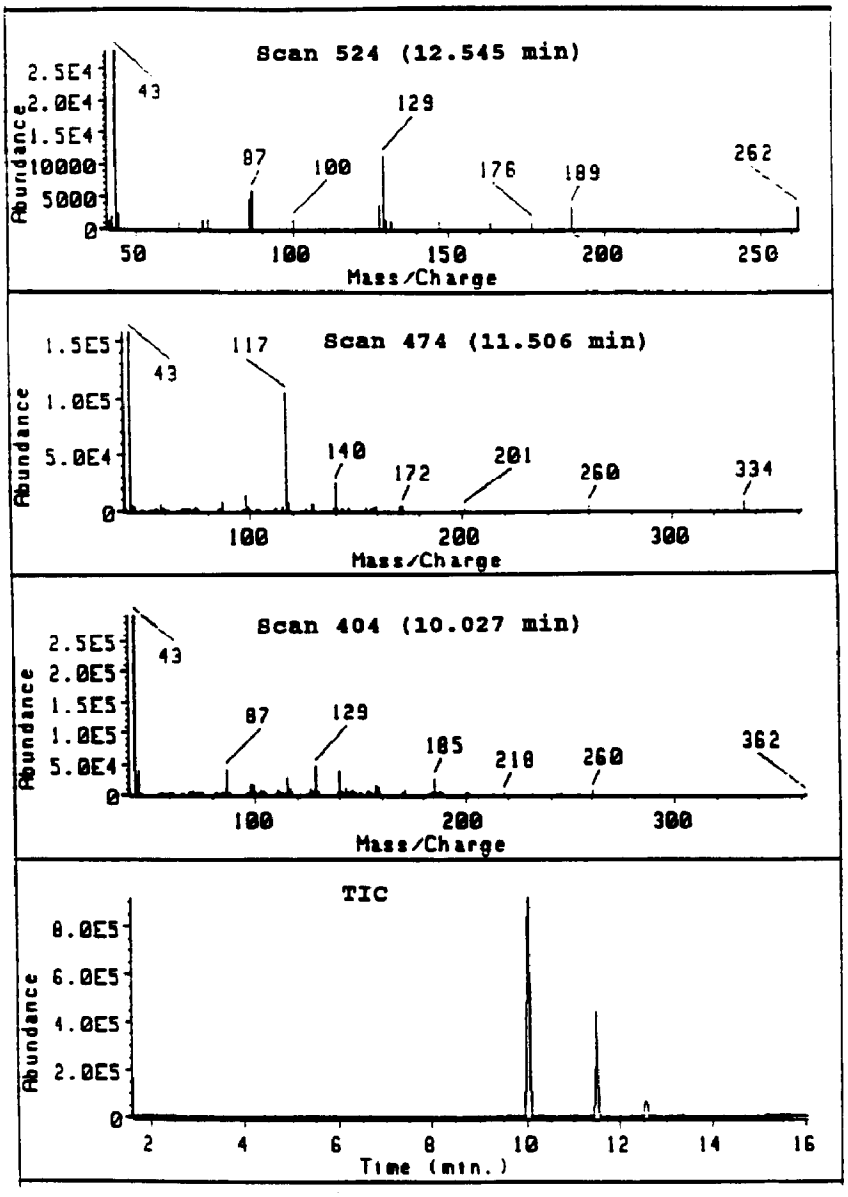

Fig. 1. G.l.c.–m.s. of 1,2,3,4,5-penta-*O*-acetyl-6-*O*-methyl-D-(1-^{2}H)mannitol (T_R 10.027 min), 1,2,3,4,6-penta-*O*-acetyl-5-*O*-methyl-D-(1-^{2}H)mannitol (T_R 11.506 min), and 1,2,3,5,6-penta-*O*-acetyl-4-*O*-methyl-D-(1-^{2}H)mannitol (T_R 12.545 min) [Column DB-23, 15 m (J&W Scientific); oven 80° for 2 min, increased to 170° at 30°/min, and then heated at 4°/min to 240°; mass-selective detector (H.P.)].

tyl-4-*O*-methyl-D-(1-^{2}-H)mannitol (**13**) (Fig. 1). Compounds **12** and **13** were derived from **10** and **8**, respectively.

Formation of these by-products can be deduced by considering some mechanistic aspects in sugar chemistry. To begin with, the starting material, methyl D-mannopyranoside (**1**), could be contaminated with a tiny amount of furanoside **2**. In turn, com-

pounds **1** and **2** produced **3** and **4**, respectively, during the course of the synthesis. In the methylation step using boron trifluoride etherate, acetyl migration from the secondary to the primary alcohol could occur even by way of a very minor pathway due to the close proximity of the acetyl and hydroxyl groups (Considering the $^4C_1$ conformation of **3**), giving rise to a tiny amount of **5** from **3**. The formation of **6** from **4** could also be explained in a similar manner. As a result, in the methylation step, the major product, methyl 2,3,4-tri-*O*-acetyl-6-*O*-methyl-D-mannopyranoside (**7**), was found to be associated with tiny amounts of methyl 2,3,6-tri-*O*-acetyl-4-*O*-methyl-D-mannopyranoside (**8**), methyl 2,3,5-tri-*O*-acetyl-6-*O*-methyl-D-mannofuranoside (**9**), and methyl 2,3,6-tri-*O*-acetyl-5-*O*-methyl-D-mannofuranoside (**10**). Compounds **7** and **9**, and **8** and **10** produced, upon reduction which sodium borodeuteride, followed by acetylation, **11**, **13** and **12**, respectively.

This study confirms that acetyl migration did occur in small amounts in the diazomethane–boron trifluoride etherate methylation and the structures of the by-products are confirmed.

EXPERIMENTAL

General methods. — Melting points were determined on an electrothermal melting point apparatus and are uncorrected. The ^{1}H-n.m.r. spectra were recorded on an IBM WP 270 SY instrument at 270 MHz in deuterochloroform (tetramethylsilane as internal standard) unless otherwise stated. The i.r. spectra were recorded on an IBM IR/32 (F.t.-i.r.) spectrophotometer. Low-ionization mass spectra were obtained by chemical ionization with methane as reagent gas on a Finnigan 4021 spectrometer. G.l.c.–m.s. of the partially methylated (1-^{2}H)alditol acetates was performed in a Hewlett–Packard 5970 M.S.D. instrument using a DB-23 column (J&W Scientific). The oven temperature was initially maintained at 80° for 2 min, increased to 170° at 30°/min, and then heated to 240° at 4°/min. Column chromatography was performed on Silica Gel 60 (70–230 mesh, E. Merck), and thin-layer chromatography (t.l.c.) was carried out on Silica Gel G plates (0.25 mm thickness, E. Merck).

*Preparation of methyl 2,3,4,-tri-*O*-acetyl-6-*O*-methyl-*D*-mannopyranoside* (**7**). — Compound **7** was prepared according to the method of Gros[1]. Pure α-**7**: R_F 0.26; ^{1}H-n.m.r.: δ 2.00 (s, 3 H), 2.05 (s, 3 H), 2.15 (s, 3 H), 3.39 (s, 3 H), 3.41 (s, 3 H), 3.48–3.50 (m, 2 H), 3.86–3.91 (m, 1 H), 4.72 (s, 1 H), 5.22–5.37 (m, 3 H), and β-**7**: R_F 0.30; ^{1}H-n.m.r.: δ 2.03 (s, 3 H), 2.06 (s, 6 H), 3.39 (s, 3 H), 3.41 (s, 3 H), 3.61 (dd, 1 H), *J* 11.0, *J* 4.7 Hz), 3.86 (dd, 1 H), *J* 11.0, *J* 2.6 Hz), 4.43 (dd, 1 H, *J* 9.35, *J* 3.50 Hz), 5.02 (d, 1 H, *J* 3.2 Hz), 5.18 (dd, 1 H, *J* 4.8, *J* 3.2 Hz), 5.24 (ddd, 1 H, *J* 9.1, *J* 4.7, *J* 2.7 Hz), 5.54 (dd, 1 H, *J* 5.0, *J* 3.6 Hz) amomers were separated by column chromatography over silica gel and eluted with 1:1 ethyl acetate–hexane. In this separation some middle fractions were separately collected. These were shown to contain mostly the α anomer contaminated with some positional isomers, as determined by the following experiment.

Preparation of the partially methylated alditol acetates (**11**, **12**, *and* **13**). — A small amount of the middle fractions from above (~2 mg) was hydrolyzed with 2M trifluoro-

acetic acid (2 mL) for 1.5 h at 110°. After evaporation of the solvents, the products were reduced with sodium borodeuteride (3 mg) in M ammoniun hydroxide (1 mL) for 1 h. Excess borodeuteride was decomposed with acetic acid, and the boric acid was removed by repeated evaporation of dry methanol from the residue. The crude product was acetylated with acetic anhydride (1 mL) in pyridine (1 mL) for 0.5 h at 110°. After the usual work up, the partially methylated alditol acetates were subjected to G.l.c.–m.s. analysis as described in the General Methods section.

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