

## Reaction of Carbohydrates with Hydrogen Bromide. Preparation of Some 6-Deoxy-D-mannofuranoses

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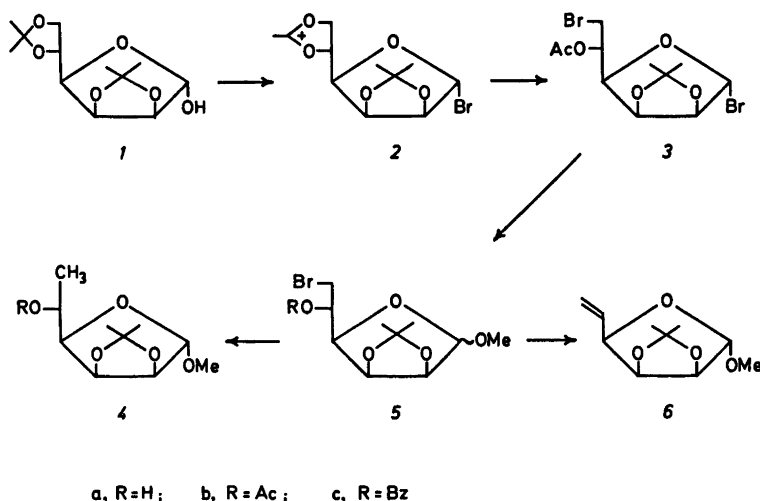
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Reaction of 2,3-5,6-di-*O*-isopropylidene- $\alpha$ -D-mannofuranose (*1*) with hydrogen bromide in acetic acid gave 5-*O*-acetyl-6-bromo-6-deoxy-2,3-*O*-isopropylidene- $\alpha$ -D-mannofuranosyl bromide (*3*). With methanol *3* gave the methyl furanoside (*5*) which was converted into methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene- $\alpha$ -D-mannofuranoside (*4c*) and into methyl 5,6-dideoxy-2,3-*O*-isopropylidene- $\alpha$ -D-*lyxo*-hex-5-enofuranoside (*6*). Hydrolysis of *4* gave D-rhamnose.

In a previous paper<sup>1</sup> the conversion of methyl 2,3,6-tri-*O*-benzoyl- $\alpha$ -D-galactopyranoside into tri-*O*-benzoyl-6-bromo-6-deoxy-D-galactofuranosyl bromide by treatment with hydrogen bromide in acetic acid (HBA) was described. The reaction was assumed to proceed *via* a ring-contraction to a furanose derivative, formation of a 5,6-benzoxonium ion, and subsequent reaction of the latter with bromide ions.

This reaction indicated that hexofuranoses might also yield 6-bromo-6-deoxy-derivatives by treatment with HBA and a number of compounds has now been studied in order to investigate this reaction. In the present paper the reaction of 2,3-5,6-di-*O*-isopropylidene- $\alpha$ -D-mannofuranose (*1*) with HBA is described.

When *1* was treated with HBA for 2 h at room temperature it was converted into a syrup which, as seen from NMR spectra, consisted almost exclusively of 5-*O*-acetyl-6-bromo-6-deoxy-2,3-*O*-isopropylidene- $\alpha$ -D-mannofuranosyl bromide (*3*). This product was not purified, but was only characterized through its <sup>1</sup>H and <sup>13</sup>C NMR spectra. Treatment of *3* with methanol in the presence of silver carbonate gave methyl 5-*O*-acetyl-6-bromo-6-deoxy-2,3-*O*-isopropylidene- $\beta$ -D-mannofuranoside (*5b*). When *3* was treated with methanol alone the corresponding



$\alpha$ -anomer was formed, presumably *via*  $\beta$ -5a and subsequent anomerization catalyzed by the liberated hydrogen bromide. The acidic conditions, arising in the latter reaction, also caused deacetylation of  $\alpha$ -5b and the crude  $\alpha$ -5a thus obtained was benzoylated. This gave crystalline methyl 5-O-benzoyl-6-bromo-6-deoxy-2,3-O-isopropylidene- $\alpha$ -D-mannofuranoside ( $\alpha$ -5c). Reduction of  $\alpha$ -5a with lithium aluminium hydride yielded the corresponding 6-deoxy-compound (4a), which was converted into the known<sup>2</sup> crystalline 5-O-benzoate (4c).

Hydrolysis of 4a with aqueous acid gave a 65% yield of D-rhamnose, thus confirming its structure. Alternatively, 1 could be converted into crystalline D-rhamnose in 30% overall yield *via* 3, 5, and 4 without purification of any of the intermediates.

Treatment of 5c with zinc in boiling acetic acid yielded the previously described<sup>3</sup> methyl 5,6-dideoxy-2,3-O-isopropylidene- $\alpha$ -D-lyxo-hex-5-enofuranoside (6).

Thus the simple treatment of the readily available diisopropylidene derivative with hydrogen bromide offers a convenient route to a number of D-mannofuranose derivatives and to 5,6-unsaturated compounds.

The first step in the conversion of 1 into 3 must be loss of the 5,6-isopropylidene group and formation of 2,3-O-isopropylidene-D-mannofuranose. This was confirmed by the fact that methyl 2,3-O-isopropylidene- $\alpha$ -D-mannofuranoside also gave 3 in high yield when treated with HBA. The next step is probably acetylation at C5 or C6 and subsequent formation of the acetoxonium ion (2). The latter finally reacts with bromide ions to give 3.<sup>1,4</sup>

## EXPERIMENTAL

Melting points are uncorrected. Preparative thin layer chromatography (TLC) was performed on 20  $\times$  40 cm plates using 1 mm layers of Merck silica gel PF<sub>254</sub>. <sup>1</sup>H NMR spectra were measured at 270 MHz and <sup>13</sup>C NMR spectra at 22.63 MHz on Bruker instruments using deuteriochloroform as solvent and TMS as internal reference.

5-O-Acetyl-6-bromo-6-deoxy-2,3-O-isopropylidene- $\alpha$ -D-mannofuranosyl bromide (3). To a 33% solution of hydrogen bromide in acetic acid (25 ml) was added 2,3-5,6-di-O-isopropylidene- $\alpha$ -D-mannofuranose (1)<sup>5</sup> (5.0 g) and the mixture was stirred at room temperature for 2 h. It was then diluted with dichloromethane (100 ml) and

washed with water and aqueous NaHCO<sub>3</sub>, dried (MgSO<sub>4</sub>) and evaporated. The syrupy residue (7.5 g), (~100%) consisted of almost pure 3 as seen from <sup>1</sup>H and <sup>13</sup>C NMR spectra. It was not purified further. <sup>1</sup>H NMR:  $\delta$  6.39 (H1), 5.15 (H2), 4.85 (H3), 4.49 (H4), 5.27 (H5), 3.86 (H6), 3.59 (H6');  $J_{12}$  0 Hz,  $J_{23}$  5.8,  $J_{34}$  3.8,  $J_{45}$  8.5,  $J_{56}$  2.8,  $J_{56'}$  4.1,  $J_{66'}$  11.6. <sup>13</sup>C NMR: 91.5 ppm (C1), 89.5 (C2), 81.1 (C3), 77.7 (C4), 67.6 (C5), 32.5 (C6).

Methyl 5-O-acetyl-6-bromo-6-deoxy-2,3-O-isopropylidene- $\beta$ -D-mannofuranoside ( $\beta$ -5b). A solution of crude 3 (1.8 g) in methanol (20 ml) was stirred with silver carbonate (2.5 g) overnight at room temperature. Filtration and evaporation gave 1.45 g of crude product. Purification by TLC using ether-pentane (3:1) as eluent gave 968 mg (62%) of  $\beta$ -5b as a syrup,  $[\alpha]_D^{20} + 10.7^\circ$  (c 0.4, CHCl<sub>3</sub>). Anal. C<sub>12</sub>H<sub>19</sub>BrO<sub>6</sub>: C, H, Br. <sup>1</sup>H NMR:  $\delta$  4.70 (H1), 4.66 (H2), 4.72 (H3), 3.98 (H4), 5.22 (H5), 3.88 (H6), 3.72 (H6');  $J_{12}$  3.6 Hz,  $J_{23}$  6.3,  $J_{34}$  4.4,  $J_{45}$  8.4,  $J_{56}$  3.0,  $J_{56'}$  3.6,  $J_{66'}$  11.4. <sup>13</sup>C NMR: 103.5 ppm (C1), 79.3 (C2), 78.5 (C3), 75.2 (C4), 69.0 (C5), 33.3 (C6).

Methyl 5-O-benzoyl-6-bromo-6-deoxy-2,3-O-isopropylidene- $\alpha$ -D-mannofuranoside ( $\alpha$ -5c). A solution of 3 (7.5 g) in methanol (100 ml) was kept at room temperature for 24 h. Pyridine (5 ml) was then added and the solution was evaporated. The residue was dissolved in chloroform and washed with 4 N hydrochloric acid and with aqueous NaHCO<sub>3</sub>, dried and evaporated. The residue (5.9 g, ~100%) consisted of methyl 6-bromo-6-deoxy-2,3-O-isopropylidene- $\alpha$ -D-mannofuranoside ( $\alpha$ -5a) as seen from <sup>1</sup>H and <sup>13</sup>C NMR spectra.

Benzoylation with benzoyl chloride in pyridine in the usual manner and crystallization from pentane gave 4.0 g (52%) of  $\alpha$ -5c, m.p. 50–55°C. Two recrystallizations from pentane gave the pure product, m.p. 56–57°C,  $[\alpha]_D^{20} + 27.8^\circ$  (c 2.7, CHCl<sub>3</sub>). Anal. C<sub>17</sub>H<sub>21</sub>BrO<sub>6</sub>: C, H, Br. <sup>1</sup>H NMR:  $\delta$  4.93 (H1), 4.59 (H2), 4.77 (H3), 4.39 (H4), 5.44 (H5), 4.00 (H6), 3.87 (H6');  $J_{12}$  0 Hz,  $J_{23}$  5.9,  $J_{34}$  3.6,  $J_{45}$  8.5,  $J_{56}$  2.9,  $J_{56'}$  3.3,  $J_{66'}$  11.3. <sup>13</sup>C NMR: 106.9 ppm (C1), 84.9 (C2), 79.1 (C3), 78.1 (C4), 69.5 (C5), 33.7 (C6).

Methyl 5-O-benzoyl-6-deoxy-2,3-O-isopropylidene- $\alpha$ -D-mannofuranoside (4c). A solution of  $\alpha$ -5c (3.8 g) in ether (30 ml) was treated with LiAlH<sub>4</sub> (400 mg) in ether (30 ml) for 24 h at room temperature. The mixture was worked up by careful addition of ethyl acetate followed by 1 N sulfuric acid, separation of the ether phase and extraction of the aqueous phase with ether. The combined ether solutions were washed with aqueous NaHCO<sub>3</sub>, dried and evaporated to give 2.28 g (82%) of crude methyl 6-deoxy-2,3-O-isopropylidene- $\alpha$ -D-mannofuranoside (4a) as a syrup. Benzoylation with benzoyl chloride in pyridine gave the benzoate 4c which was crystallized from pentane, yield 2.11 g (51%), m.p. 72–74°C,  $[\alpha]_D^{20} + 19.7^\circ$  (c 2.3, CHCl<sub>3</sub>) (reported<sup>2</sup> m.p. 75–76°C,  $[\alpha]_D^{20} + 19.9^\circ$ ).<sup>13</sup>C

NMR: 107.2 ppm (C1), 84.9 (C2), 79.5 (C3), 81.7 (C4), 69.0 (C5), 17.5 (C6).

*D-Rhamnose*. Crude **4a** (1.55 g) was stirred at 100 °C for 1 h with 15 ml 0.5 N hydrochloric acid. The solution was then neutralized with "Amberlite" IR-4B and evaporated to dryness. The residue (834 mg, 65 %) was recrystallized from ethanol-ether to give 554 mg (41 %) of *D-rhamnose monohydrate*, m.p. 87–89 °C, undepressed in admixture with an authentic sample.

Alternatively **1** (25 g) was treated with HBA as described above. The crude dibromo-compound (**3**) was treated with methanol to give  $\alpha$ -**5a**, which was reduced with  $\text{LiAlH}_4$  to give crude  $\alpha$ -**4a**. Hydrolysis as described above gave 7 g crude product and crystallization from ethanol-ether gave 5.2 g (28 %) of *D-rhamnose*, m.p. 87 °C.

*Methyl 5,6-dideoxy-2,3-O-isopropylidene- $\alpha$ -D-lyxo-hex-5-enofuranoside* (**6**). A solution of **5c** (550 mg) in acetic acid (5 ml) was boiled for 1 h with zinc dust (500 mg). The mixture was then filtered and the filtrate was poured into water. The product was extracted with chloroform and the extract was washed with water, aqueous  $\text{NaHCO}_3$ , dried and evaporated. The residue was purified by TLC (ether-pentane 1:2) to give pure **6** (130 mg, 57 %) as a syrup,  $[\alpha]_{\text{D}}^{20} + 28.0^\circ$  (c 0.7,  $\text{CHCl}_3$ ) (reported  $[\alpha]_{\text{D}} + 27.8^\circ$ ). Anal.  $\text{C}_{16}\text{H}_{24}\text{O}_4$ : C, H.  $^1\text{H}$  NMR:  $\delta$  4.90 (H1), 4.57 (H2), 4.67 (H3), 4.37 (H4), 6.00 (H5), 5.40 (H6), 5.32 (H6');  $J_{12}$  0 Hz,  $J_{23}$  6.0,  $J_{34}$  3.8,  $J_{45}$  7.3,  $J_{56}$  17.5,  $J_{56'}$  10.5,  $J_{66'}$  1.8,  $J_{46}$  1.0,  $J_{46'}$  0.9.  $^{13}\text{C}$  NMR 107.2 ppm (C1), 81.6, 81.2 (C2) (C3), 85.4 (C4), 132.4 (C5), 119.1 (C6).

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