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Note

Synthesis of the 2- and 3-methyl ethers of L-rhamnose and methyl α-L-rhamnopyranoside

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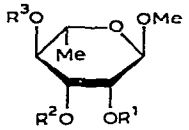
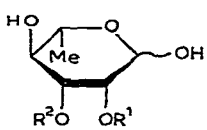
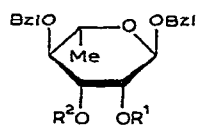
A recent synthesis[1] of methyl 2-*O*- (**1**) and 3-*O*-methyl-α-L-rhamnopyranoside (**2**) involved metal ion-catalysed monomethylation of methyl α-L-rhamnopyranoside with diazomethane followed by chromatography. We were not able to repeat the chromatographic separation of **1** and **2**, and we now report an alternative synthesis of these compounds, which are important reference compounds in the structural elucidation of microbial polysaccharides[2] and other natural products[1].



1 R^1 = Me, R^2 = R^3 = H
2 R^2 = Me, R^1 = R^3 = H
5 R^1 = Me, R^2 = H, R^3 = Bzl
6 R^1 = H, R^2 = Me, R^3 = Bzl
7 R^1 = R^2 = H, R^3 = Bzl
8 R^1 = R^3 = Bzl, R^2 = Me
9 R^1 = Me, R^2 = R^3 = Bzl



3 R^1 = Me, R^2 = H
4 R^1 = H, R^2 = Me



10 R^1 = Me, R^2 = H
11 R^1 = Bzl, R^2 = Me

The 4-benzyl ethers **5** and **6**, obtained[3] by treatment of methyl 4-*O*-benzyl-α-L-rhamnopyranoside (**7**) with methyl iodide in the presence of a tetrabutylammonium salt, can be separated[3] easily by chromatography on Kieselgel and are therefore readily accessible precursors for **1** and **2**. The minor product **6** can be prepared in a good yield by treatment[4] of the 2,3-*O*-dibutylstannylene derivative of **7** with methyl iodide. Hydrogenolysis of **5** and **6** gave **1** and **2**, respectively.

Partially protected derivatives of methyl α-L-rhamnopyranoside are available[3], having HO-2 or HO-3 unsubstituted. Hence, **1** can be prepared also from methyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside by methylation followed by hydrogenolysis,

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and **2**, likewise, from methyl 2,4-di-*O*-benzyl-3-*O*-methyl-α-L-rhamnopyranoside.

2-*O*-Methyl-L-rhamnose (**3**) can be prepared by hydrogenolysis of benzyl 4-*O*-benzyl-2-*O*-methyl-α-L-rhamnopyranoside[3] (**10**), and the 3-methyl ether (**4**) by hydrogenolysis of benzyl 2,4-di-*O*-benzyl-3-*O*-methyl-α-L-rhamnopyranoside (**11**) obtained by methylation of benzyl 2,4-di-*O*-benzyl-α-L-rhamnopyranoside[3].

EXPERIMENTAL

General methods. — Melting points (uncorrected) were determined on a Kofler hot-stage. T.l.c. was performed on Kieselgel (Merck, 5562) with *A*, light petroleum–ethyl acetate (3:2); *B*, benzene–methanol (3:1); *C*, benzene–methanol (100:3); and *D*, chloroform–methanol[1] (9:1); and detection with u.v. light or by charring with sulphuric acid. Optical rotations were measured with a Perkin–Elmer 241 automatic polarimeter. P.m.r. spectra (100 MHz) were recorded for solutions in $CDCl_3$ with a JEOL MH-100 spectrometer.

Methyl 4-O-benzyl-3-O-methyl-α-L-rhamnopyranoside[3] (**6**). — A solution of methyl 4-*O*-benzyl-α-L-rhamnopyranoside (265 mg) in dry methanol (10 ml) was stirred with dibutyltin oxide (270 mg) and boiled under reflux for 1 h, and then concentrated in a high vacuum. A solution of the resulting, slightly yellow syrup in *N*,*N*-dimethylformamide (5 ml) was stirred with methyl iodide (2 ml) at 45° overnight*. The mixture was concentrated and the residue was subjected to chromatography (solvents *A* or *B*), to give **6** (170 mg, 64%), $[\alpha]_D$ −80° (*c* 1.1, chloroform); lit.[3] $[\alpha]_D$ −83°.

Methyl 3-O-methyl-α-L-rhamnopyranoside (**2**). — Methylation (MeI and Ag_2O in *N*,*N*-dimethylformamide) of methyl 2,4-di-*O*-benzyl-α-L-rhamnopyranoside[3] and chromatography of the product (solvent *A*) gave the 3-*O*-methyl derivative **8**, $[\alpha]_D$ −29° (*c* 0.9, chloroform). P.m.r. data: δ 1.30 (d, 3 H, $J_{5,6}$ 6 Hz, Me), 3.28 (s, 3 H, OMe), 3.76 (m, 1 H, H-2), 4.72 (b, 1 H, H-1), 4.52–4.96 (m, 4 H, 2 CH_2-Ph), and 7.34 (m, 10 H, 2 Ph). Hydrogenolysis (10% Pd/C) of **6** or **8** in ethanol, with chromatography of the product on Kieselgel H (solvent *D*), gave **2**, $[\alpha]_D$ −60° (*c* 1.2, chloroform); lit.[1] $[\alpha]_D$ −61°.

Methyl 2-O-methyl-α-L-rhamnopyranoside (**1**). — Methylation of methyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside[3], as described above, with chromatography of the product (solvent *A* or *C*), gave the syrupy 2-*O*-methyl derivative **9**, $[\alpha]_D$ −38° (*c* 1.8, chloroform). P.m.r. data: δ 1.33 (d, 3 H, $J_{5,6}$ 6 Hz, Me), 3.32 (s, 3 H, OMe), 3.50 (s, 3 H, OMe), 3.86 (dd, 1 H, $J_{2,3}$ ~3, $J_{3,4}$ ~9 Hz, H-3), 4.70 (b, 1 H, H-1), 4.78 (q, 4 H, 2 CH_2-Ph), and 7.36 (m, 10 H, 2 Ph). Hydrogenolysis of **5** or **9** and chromatography of the product, as described above, gave **1**, $[\alpha]_D$ −37° (*c* 1.3, chloroform); lit.[1] $[\alpha]_D$ −49°.

2-O-Methyl-L-rhamnose (**3**). — Hydrogenolysis of benzyl 4-*O*-benzyl-2-*O*-

Note added in proof.* Methylation can also be effected at 35–40° in the absence of *N*,*N*-dimethylformamide, to give **6 in 70% yield.

methyl-α-L-rhamnopyranoside[3] (**10**) and chromatography of the product (solvent *B*) gave syrupy **3**, $[\alpha]_D$ +25° (*c* 0.3, water); lit.[5] m.p. 113–114°, $[\alpha]_D$ +31°; lit.[6] $[\alpha]_D$ +24°.

3-O-Methyl-L-rhamnose (**4**). — Methylation of benzyl 2,4-di-*O*-benzyl-α-L-rhamnopyranoside[3], as described above for **8**, gave the 3-*O*-methyl derivative (**11**) as a syrup, $[\alpha]_D$ −51° (*c* 1.3, chloroform). P.m.r. data: δ 1.30 (d, 3 H, $J_{5,6}$ 6 Hz, Me), 3.40 (s, 3 H, OMe), 3.42–3.90 (m, 4 H, H-2,3,4,5), 4.32–4.96 (m, 7 H, 3 CH_2Ph, H-1), and 7.25–7.75 (m, 15 H, 3 Ph). Hydrogenolysis of **11** and chromatography of the product (solvent *B*) gave **4**, m.p. 109–111°, $[\alpha]_D$ +30° (*c* 0.6, water); lit.[7] m.p. 115°, $[\alpha]_D$ +39.1°; lit.[8] m.p. 110–112.5°, $[\alpha]_D$ +32°.

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