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Note

A facile synthesis of methyl 2,3-di-*O*-benzyl-α-L-rhamnopyranoside*

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Recent investigations related to the synthesis of complex saccharides[2–4] and modified sugar analogs[5,6] strongly indicate the advisability of using partially *O*-benzylated carbohydrate derivatives as the key intermediates. As a result, different approaches are being developed for the preparation of such suitable "aglycons" having persistent, protecting groups. Our continued interest in the synthesis of such valuable intermediates has led to preparation of the title compound.

The use of dibutylstannylene derivatives obtainable from *cis*-diols, introduced by Wagner *et al.*[7], has been successfully used for monoalkylation of starting diol derivatives[8–10]. Recently, it has been reported that methyl α-D-mannopyranoside or methyl 6-*O*-trityl-α-D-mannopyranoside provides the corresponding, 3-*O*-alkylated derivative in satisfactory yield[11]. In experiments based upon these findings, we have observed that, on reaction with dibutyltin oxide in absolute methanol, methyl α-L-rhamnopyranoside (**1**) gives the tin derivative which, on treatment with benzyl bromide (α-bromotoluene), produces compound **2**, the 3-benzyl ether, as a crystalline material. Compound **2** was clearly distinguishable from methyl 4-*O*-benzyl-α-L-rhamnopyranoside[12], and we did not observe the formation of any methyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside[10], indicating that the free 4-hydroxyl group in the tin derivative did not undergo alkylation. The n.m.r. spectrum of the diacetate (**3**) of **2**, prepared by a conventional method from **2**, showed the presence of an axial acetoxyl group at δ 2.12, and an equatorial acetoxyl group at δ 2.02, further supporting the observation that under these conditions, alkylation of the dibutylstannylene derivative occurs exclusively at O-3.

Phase-transfer catalysis, introduced by Garegg *et al.*[13] in the field of carbohydrate chemistry, offers another elegant method for selective monoalkylation of a diol. It has been suggested that alkylation of the 2-hydroxyl group of a glycopyranoside is favored, due to its enhanced acidity. For example, various 4,6-di-*O*-protected

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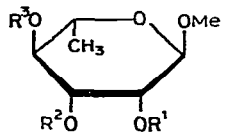

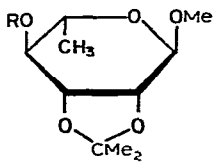

1 $R^1 = R^2 = R^3 = H$
2 $R^1 = R^3 = H$, $R^2 = Bn$
3 $R^1 = R^3 = Ac$, $R^2 = Bn$
4 $R^1 = R^2 = Bn$, $R^3 = H$
5 $R^1 = R^2 = Bn$, $R^3 = Ac$
8 $R^1 = R^2 = H$, $R^3 = All$
9 $R^1 = R^2 = Bn$, $R^3 = All$

6 R = H
7 R = All

All = $CH_2CH{=}CH_2$; Bn = $PhCH_2$

aglycons having free 2- and 3-hydroxyl groups have been subjected to alkylation by the phase-transfer-catalysis technique, to give the corresponding 2-*O*-alkylated derivatives as the major products[13]. Thus, the reaction of **2** with benzyl bromide in a mixture of dichloromethane and aqueous sodium hydroxide in the presence of tetrabutylammonium hydrogensulfate for 6 days gave a crude product which, on chromatography on a column of silica gel, produced the title compound (**4**) in 52% yield. The n.m.r. spectrum of the acetate (**5**) of **4** clearly showed the presence of an equatorial acetoxyl group.

An authentic sample of **4** was obtained by benzylation of methyl 4-*O*-allyl-α-L-rhamnopyranoside (**8**), followed by deallylation[14]. Compound **7** was prepared from methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside[15] (**6**) by the usual method. Starting from benzyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside, Lipták *et al.*[14] reported the preparation of benzyl 2,3-di-*O*-benzyl-α-L-rhamnopyranoside. It is obvious that the present approach offers a simple method for the preparation of the title compound in two steps. However, it may be briefly mentioned that, according to our preliminary findings, reaction of methyl α-L-fucopyranoside with dibutyltin oxide, followed by alkylation, did not proceed to give the corresponding 3-*O*-alkylated derivative.

EXPERIMENTAL

General. — Melting points were determined with a Fisher–Johns apparatus and are uncorrected. I.r. spectra were recorded with a Perkin–Elmer model 297 spectrometer, and n.m.r. spectra with a Varian XL-100 spectrometer at 100 MHz, with Me_4Si as the internal standard. Ascending t.l.c. was conducted on plates coated with a layer (0.25 mm) of silica gel CC-7 (Mallinckrodt); the components were located by exposure to u.v. light, or by spraying with 5% sulfuric acid in ethanol and heating. Optical rotations were measured with a Perkin–Elmer model 241 polarimeter. Elementary analyses were performed by Robertson Laboratory, Florham Park, New Jersey, U.S.A.

Methyl 3-O-benzyl-α-L-rhamnopyranoside (**2**). — A mixture of compound **1** (2.0 g) and dibutyltin oxide (2.79 g) in absolute methanol (200 mL) was refluxed for 4 h, and then the solvent was evaporated under diminished pressure. The resulting methyl 2,3-*O*-(dibutylstannylene)-α-L-rhamnopyranoside was dried, and then heated with benzyl bromide (2 mL) in *N,N*-dimethylformamide (50 mL) for 3 h at 110°. The mixture was cooled, and evaporated under diminished pressure, to give compound **2**, which was purified by chromatography on a column of silica gel, with elution with 1:1 hexane–ethyl acetate; yield (1.5 g, 50%), m.p. 80°, $[\alpha]_D$ −26.1° (*c* 1, chloroform); n.m.r. data: δ 1.30 (d, 3 H, *J* 5 Hz, Me), 3.36 (s, 3 H, OCH_3), and 7.2–7.5 (m, 5 H, Ph).

Anal. Calc. for $C_{14}H_{20}O_5$: C, 62.57; H, 7.51. Found: C, 62.53; H, 7.51.

Methyl 2,4-di-O-acetyl-3-O-benzyl-α-L-rhamnopyranoside (**3**). — Conventional acetylation of **2** (100 mg) with acetic anhydride (1 mL) in pyridine (3 mL), and elution of the product from a column of silica gel using 1:7 ethyl acetate–hexane, gave syrupy compound **3** in 90% yield; $[\alpha]_D$ −2.5° (*c* 1, chloroform); n.m.r. data: δ 1.2 (d, 3 H, *J* 5 Hz, Me), 2.02 (s, 3 H, Ac-*eq*), 2.14 (s, 3 H, Ac-*ax*), 3.36 (s, 3 H, OCH_3), and 7.2–7.5 (m, 5 H, aromatic).

Methyl 4-O-allyl-2,3-O-isopropylidene-α-L-rhamnopyranoside (**7**). — A suspension of compound **6** (4.08 g, 18.75 mmol), barium oxide (12.5 g), and barium hydroxide octahydrate (3.75 g) in dry *N,N*-dimethylformamide (125 mL) was vigorously stirred for 6 h in the presence of allyl bromide (3.13 mL, 2 equiv.). After dilution with chloroform (500 mL), aqueous 35% acetic acid (150 mL) was added, and the solution was stirred for 15 min at room temperature. The chloroform layer was separated, successively washed with sodium hydrogencarbonate solution and water, dried (K_2CO_3), and evaporated. The residue was purified by chromatography on a column of silica gel with elution with 6:1 hexane–ethyl acetate, to give **7** (3.67 g, 76%) $[\alpha]_D$ −45.6° (*c* 0.5, chloroform); R_F 0.9 (4:1 hexane–ethyl acetate); n.m.r. data: δ 1.30 (d, 3 H, *J* 5 Hz, Me), 1.36 and 1.54 (2 s, 6 H, CMe_2), 3.38 (s, 3 H, OCH_3), 4.88 (s, 1 H, H-1), 5.04–5.44 (m, 2 H, allyl $=CH_2$), and 5.76–6.14 (m, 1 H, allyl -CH=).

Methyl 4-O-allyl-α-L-rhamnopyranoside (**8**). — Compound **7** (2.5 g) in chloroform (100 mL) was stirred with trifluoroacetic acid (10 mL) for 45 min at room temperature. Evaporation, followed by several additions and evaporations of toluene, gave a thick syrup which was purified by chromatography on a column of silica gel, to give **8** in 85% yield; $[\alpha]_D$ −66.6° (*c* 0.5, chloroform); ν_{max}^{film} 3400 (OH) and 3080, 1650, and 930 cm^{-1} (CH_2 =CH-).

Methyl 4-O-allyl-2,3-di-O-benzyl-α-L-rhamnopyranoside (**9**). — A suspension of compound **8** (2.5 g), barium oxide (4.0 g), and barium hydroxide octahydrate (1.3 g) in dry *N,N*-dimethylformamide (65 mL) and benzyl bromide (4.2 mL, 4 equiv.) was stirred vigorously for 24 h. Treatment as for the preparation of **7** gave compound **9**, which was purified by chromatography on a column of silica gel, with elution with 7:1 hexane–ethyl acetate, to afford pure compound **9**, yield (3.2 g, 70%); $[\alpha]_D$ −27.1° (*c* 1, $CHCl_3$); i.r., complete absence of hydroxyl groups; n.m.r. data:

δ 1.32 (d, 3 H, *J* 5 Hz, Me), 3.32 (s, 3 H, OCH_3), 5.1–5.4 (m, 2 H, allyl $=CH_2$), 5.76–6.16 (m, 1 H, allyl -CH=), and 7.2–7.5 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{24}H_{30}O_5$: C, 72.33; H, 7.59. Found: C, 72.38; H, 7.58.

*Methyl 2,3-di-*O*-benzyl-α-*L*-rhamnopyranoside* (**4**). — A mixture of **3** (1.88 g, 7 mmol) in dichloromethane (125 mL), 5% sodium hydroxide (10 mL), benzyl bromide (1.44 mL, 12 mmol), and tetrabutylammonium hydrogensulfate (0.8 g, 1.4 mmol) was refluxed for 6 days, and cooled, and the two layers were separated. The organic layer was washed with water (3 × 40 mL), dried (anhydrous sodium sulfate), and evaporated, to give a syrup that was purified by chromatography on a column of silica gel with elution with 4:1 hexane–ethyl acetate to afford **4** (1.3 g, 52%); $[\alpha]_D$ +14.5° (*c* 1, chloroform); n.m.r. data: δ 1.34 (d, 3 H, *J* 5 Hz, Me), 3.36 (s, 3 H, OCH_3), and 7.2–7.5 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.27; H, 7.30.

An authentic sample of methyl 2,3-di-*O*-benzyl-α-L-rhamnopyranoside was obtained by deallylation[14] of compound **9**. Compound **4** was identical with an authentic sample of the title compound on the basis of optical rotation, and i.r. and p.m.r. data.

*Methyl 4-*O*-acetyl-2,3-di-*O*-benzyl-α-*L*-rhamnopyranoside* (**5**). — Conventional acetylation of **4** (100 mg) with acetic anhydride (1 mL) in pyridine (2 mL), and elution of the product from a column of silica gel with 7:1 hexane–ethyl acetate gave **5** (95 mg) in 85% yield; $[\alpha]_D$ −26.4° (*c* 1, chloroform); n.m.r. data: δ 1.22 (d, 3 H, *J* 5 Hz, Me), 2.02 (s, 3 H, Ac-*eq*), 3,34 (s, 3 H, OCH_3), and 7.2–7.5 (m, 10 H, 2 Ph).

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