Carbohydrate Research, 83 (1980) 170–174
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Note

Selective benzylation of methyl 2-*O*-benzyl-α-L-fucopyranoside and benzyl 2,6-di-*O*-benzyl-β-D-galactopyranoside*

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(Received December 14th, 1979; accepted for publication, January 3rd, 1980)

Large amounts of methyl 2,4-di-*O*-benzyl-α-L-fucopyranoside (**4**) and methyl 2,3-di-*O*-benzyl-α-L-fucopyranoside (**6**) were needed in our laboratory for the preparation of deoxyfluoro sugars[2]. According to Dejter-Juszynski and Flowers[3], partial benzylation of methyl 2-*O*-benzyl-α-L-fucopyranoside (**1**) affords a mixture of such derivatives that can be separated by means of their monoacetates. They also reported that partial benzylation of the readily accessible methyl α-L-fucopyranoside gives the 2,4- and 3,4-dibenzyl ethers in the ratio of 3 : 2, and no 2,3 isomer could be detected in the reaction mixture. Recently, we studied selective monobenzylation of methyl 4-*O*-benzyl-α-L-rhamnopyranoside under different conditions[4], and we have now extended the use of similar methods for the selective benzylation of diol **1**. We also describe the selective benzylation of benzyl 2,6-di-*O*-benzyl-β-D-galactopyranoside[5] (**8**).

The reaction of diol **1** with trityl chloride in the presence of 4-(dimethylamino)pyridine[6] proceeded readily to give methyl 2-*O*-benzyl-3-*O*-trityl-α-L-fucopyranoside (**2**). The structure of **2** is based upon the observation that, under these conditions[6], an equatorial hydroxyl group is the more reactive towards trityl chloride. Prolonged treatment of benzyl 2,6-di-*O*-benzyl-β-D-galactopyranoside (**8**) with trityl chloride under similar conditions[6], followed by chromatography, gave the 3-*O*-trityl derivative (**9**) in 70% yield. Benzylation of compounds **2** and **9** in the presence of powdered potassium hydroxide, followed by removal of the trityl group with trifluoroacetic acid in chloroform, produced **4** and **11**, respectively. The derivatives were further converted into their monoacetates under the usual conditions with acetic anhydride–pyridine. The n.m.r. spectra of these monoacetates clearly established the presence of an equatorial acetoxyl group, suggesting that tritylation had occurred at the equatorial 3-hydroxyl group of **1** and **8**.

It has been well documented that a *cis*-diol can be effectively monobenzylated[7] by employing the dibutylstannylene derivative as a key intermediate. By this method, we were able to obtain the desired compound, namely, methyl 2,3-di-*O*-benzyl-α-L-

*Synthetic Studies in Carbohydrates, Part X. For Part IX, see ref. 1.
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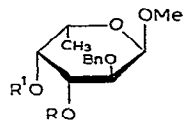
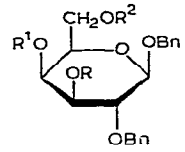


1 R = R^1 = H
2 R = Tr, R^1 = H
3 R = Tr, R^1 = Bn
4 R = H, R^1 = Bn
5 R = Ac, R^1 = Bn
6 R = Bn, R^1 = H
7 R = Bn, R^1 = Ac



8 R = R^1 = H, R^2 = Bn
9 R = Tr, R^1 = H, R^2 = Bn
10 R = Tr, R^1 = R^2 = Bn
11 R = H, R^1 = R^2 = Bn
12 R = Ac, R^1 = R^2 = Bn
13 R = R^2 = Bn, R^1 = H
14 R = R^2 = Bn, R^1 = Ac
15 R = R^1 = Bn, R^2 = H

fucopyranoside (**6**), from **1** in 54% yield. Under identical conditions, diol **8** afforded benzyl 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (**13**) in 50% yield. In another approach, on reaction with bis(tributylstannyl) oxide in toluene for 6 h, followed by the usual processing, the starting material **1** gave an oily, intermediate, stannylated product[8] which, when heated with α-bromotoluene (benzyl bromide) under nitrogen, gave the desired product **6**. In another experiment, on reaction with a slight excess of benzyl bromide by the phase-transfer catalysis procedure,[9] the readily accessible, crystalline benzyl 2,3-di-*O*-benzyl-β-D-galactopyranoside gave compound **13** (80% yield), and benzyl 2,3,4-tri-*O*-benzyl-β-D-galactopyranoside[10] (**15**) in a yield of 5%. It may also be mentioned that, according to our preliminary studies, alkylation of diol **1** by the phase-transfer catalysis method[9] was not selective for the preparation of methyl 2,3-di-*O*-benzyl-α-L-fucopyranoside (**6**). The structures assigned to monoacetyl derivatives **7** and **14**, obtained from **6** and **13**, were supported by the results of n.m.r. studies.

EXPERIMENTAL

General. — Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 241 polarimeter. I.r. spectra were recorded with a Perkin–Elmer Model 297 spectrometer, and n.m.r. spectra with a Varian A-100 spectrometer at 100 MHz, with chloroform-*d* as the solvent and Me_4Si as the internal standard. Ascending t.l.c. was conducted on plates coated with a layer (0.25 mm) of Silica Gel HF-254 (Merck, Darmstadt); the components were located by exposure to u.v. light. Elementary analyses were performed by Robertson Laboratory, Florham Park, NJ, U.S.A.

Methyl 2-O-benzyl-3-O-trityl-α-L-fucopyranoside (**2**). — A solution of **1** (2.68 g, 0.01 mol), chlorotriphenylmethane (3.07 g, 0.01 mol), triethylamine (2.5 mL), and 4-(dimethylamino)pyridine (100 mg) in dichloromethane (100 mL) was stirred for three days at 60° under nitrogen. The cloudy, yellow solution was poured into ice–

water, and the mixture extracted with dichloromethane. The extracts were combined, washed with ice–water, dried (Na_2SO_4), and evaporated, giving a yellowish solid that was chromatographed on silica gel by elution with 5:1 (v/v) hexane–ethyl acetate. The unreacted trityl chloride emerged first from the column, followed by **2** (3.57 g, 70%), m.p. 61–62°, $[\alpha]_D^{25}$ −48.6° (*c* 1, chloroform).

Anal. Calc. for $C_{33}H_{34}O_5$: C, 77.62; H, 6.71. Found: C, 77.45; H, 6.73.

Methyl 2,4-di-O-benzyl-3-O-trityl-α-L-fucopyranoside (**3**). — To a stirred solution of **2** (2.55 g) and KOH (1.05 g) in $HCONMe_2$ (28 mL) was added benzyl bromide (1.0 mL) dropwise, and stirring was continued for three days. The milky solution was then poured into ice–water, and the mixture extracted with $CHCl_3$ (5 × 50 mL). The extracts were combined, washed with water (3 × 50 mL), dried (Na_2SO_4), and evaporated; the residue was chromatographed on a column of silica gel by elution with 4:1 hexane–ethyl acetate, to give syrupy **3** (1.95 g, 65% yield), whose i.r. spectrum showed complete absence of hydroxyl group.

Methyl 2,4-di-O-benzyl-α-L-fucopyranoside (**4**). — A solution of compound **3** (1.5 g) in $CHCl_3$ (50 mL) was treated with trifluoroacetic acid (5 mL) with continuous stirring, the progress of the reaction being monitored by t.l.c. After detritylation was complete, the solution was evaporated, and the residue dried by successive addition and evaporation of toluene (4 × 25 mL), to give the alcohol **4**; after purification by chromatography on a column of silica gel, yield 60%, $[\alpha]_D^{25}$ −68.1° (*c* 1, chloroform); ν_{max}^{film} 3500 cm^{-1} (OH).

Methyl 3-O-acetyl-2,4-di-O-benzyl-α-L-fucopyranoside (**5**). — A solution of **4** (1.0 g) in 1:1 acetic anhydride–pyridine (10 mL) was kept overnight at room temperature, and then poured onto crushed ice. The mixture was extracted with $CHCl_3$, and the extracts were combined, washed with water, dried (Na_2SO_4), and evaporated, to give chromatographically homogeneous **5** as a viscous syrup, $[\alpha]_D^{25}$ −91.4° (*c* 1, chloroform); n.m.r. data ($CDCl_3$): δ 7.34 (10 H, 2 Ph), 3.38 (3 H, OMe), 1.97 (3 H, *eq* OAc), and 1.15 (d, *J* 6.5 Hz, 3 H, CH-Me); these data are comparable to those reported in the literature[3].

Methyl 2,3-di-O-benzyl-α-L-fucopyranoside (**6**). — A mixture of compound **1** (1.68 g, 10 mmol) and bis(tributylstannyl) oxide (4.47 g, 7.5 mmol) in toluene (50 mL) was boiled at 135° under reflux with continuous removal of water (7 h), to give, after evaporation of the toluene, an oily intermediate[8] which was heated with benzyl bromide (15 mL) under nitrogen for 24 h at 100°. The mixture was cooled, and co-evaporated several times with water and then with toluene, to give a syrup which was purified by column chromatography by elution with 4:1 (v/v) hexane–ethyl acetate, affording **6** in 60% yield (2.14 g), m.p. 81–82°, $[\alpha]_D^{25}$ −62.1° (*c* 1, chloroform); n.m.r. data: δ 7.34 (10 H, 2 Ph), 3.38 (3 H, OMe), and 1.16 (d, *J* 6.5 Hz, 3 H, CH-Me).

In another experiment[7], a suspension of compound **1** (1.3 g, 5 mmol) and dibutyltin oxide (1 g, 4 mmol) in absolute methanol was boiled under reflux for 3 h, cooled, and evaporated under diminished pressure. The resulting methyl 2-*O*-benzyl-3,4-di-*O*-(dibutylstannylene)-α-L-fucopyranoside was dried, and then heated with benzyl bromide (0.72 mL, 6 mmol) in *N*,*N*-dimethylformamide (15 mL) for 3 h at

90°. The solvent was removed under diminished pressure, and chromatography of the residue on a column of silica gel gave, in 54% yield (0.9 g), a pure compound that was identical to compound **6** on the basis of spectral data.

Methyl 4-O-acetyl-2,3-di-O-benzyl-α-L-fucopyranoside (**7**). — Compound **7** was prepared from **6** (500 mg) as described for **5**. After purification by column chromatography, a syrup was obtained in a yield of 70%; $[\alpha]_D^{25}$ −52.8° (*c* 1, chloroform) (lit.[3] $[\alpha]_D$ −46° in chloroform); n.m.r. data: δ 7.32 (10 H, 2 Ph), 3.38 (3 H, OMe), 2.14 (3 H, *ax* OAc), and 1.14 (d, *J* 6.5 Hz, 3 H, CH-Me), comparable to data reported in the literature[3].

Benzyl 2,6-di-O-benzyl-3-O-trityl-β-D-galactopyranoside (**9**). — Tritylation of benzyl 2,6-di-*O*-benzyl-β-D-galactopyranoside (2.7 g) as described for the α-L-*fuco* analog gave **9** (2.9 g, 70%); $[\alpha]_D^{25}$ −15.7° (*c* 1, chloroform); R_F 0.65 (5:1 hexane–ethyl acetate).

Benzyl 2,4,6-tri-O-benzyl-3-O-trityl-β-D-galactopyranoside (**10**). — Benzylation of compound **9** (2.31 g) as described for the α-L-*fuco* analog gave compound **10** as a syrup (72% yield); $[\alpha]_D^{25}$ −17.5° (*c* 1, chloroform); its i.r. spectrum showed no band for hydroxyl group.

Anal. Calc. for $C_{53}H_{50}O_6$: C, 81.30; H, 6.44. Found: C, 81.24; H, 6.48.

Benzyl 2,4,6-tri-O-benzyl-β-D-galactopyranoside (**11**). — Compound **10** (1.5 g) was detritylated as described for the α-L-*fuco* analog, to give compound **11** as a syrup (60% yield); $[\alpha]_D^{25}$ +16.5° (*c* 1, chloroform); ν_{max}^{film} 3480 (OH) and 3050, 1600, 740, and 700 cm^{-1} (aromatic).

Anal. Calc. for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71. Found: C, 75.58; H, 6.71.

Benzyl 3-O-acetyl-2,4,6-tri-O-benzyl-β-D-galactopyranoside (**12**). — Treatment of compound **11** (500 mg) with Ac_2O–pyridine as described for the α-L-*fuco* analog gave compound **12** (498 mg, 90%); $[\alpha]_D^{25}$ +8.2° (*c* 1, chloroform); R_F 0.72 (4:1 hexane–ethyl acetate); n.m.r. data ($CDCl_3$): δ 7.32 (20 H, 4 Ph) and 1.9 (s, 3 H, *eq* OAc).

Benzyl 2,3,6-tri-O-benzyl-β-D-galactopyranoside (**13**). — Selective benzylation[7] of **8** (2.25 g, 5 mmol) as described for the α-L-*fuco* analog gave compound **13** (1.35 g) in 50% yield; $[\alpha]_D^{25}$ −27.8° (*c* 1, chloroform).

A mixture of benzyl 2,3-di-*O*-benzyl-β-D-galactopyranoside (0.79 g, 1.75 mmol) in dichloromethane (30 mL), 5% sodium hydroxide (2.5 mL), benzyl bromide (0.36 mL, 3 mmol), and tetrabutylammonium hydrogensulfate (0.12 g, 3.5 mmol) was boiled under reflux for 2 days, cooled, washed with water (4 × 20 mL), dried (Na_2SO_4), and evaporated. The syrupy residue was purified by chromatography on a column of silica gel by elution with 4:1 hexane–ethyl acetate, to give **13** in 80% yield (0.760 g); t.l.c. in 4:1 hexane–ethyl acetate, R_F 0.38. It was a pure compound which was identical to compound **13** on the basis of spectral data.

On elution with 3:1 hexane–ethyl acetate, compound **15** was obtained as a solid which was recrystallized from chloroform–hexane, yield 50 mg (5.3%); m.p. 84–85°, $[\alpha]_D^{25}$ −46.5° (*c* 1, chloroform); lit.[10] m.p. 96–96.5°, $[\alpha]_D$ −46.1° in chloroform.

Anal. Calc. for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71. Found: C, 75.56; H, 6.70.

Benzyl 4-O-acetyl-2,3,6-tri-O-benzyl-β-D-galactopyranoside (**14**). — Compound **13** (600 mg) was acetylated as described for the α-L-*fuco* analog, to give compound **14** in 80% yield; $[\alpha]_D^{25}$ −7.9° (*c* 1, chloroform); R_F 0.69 (4 : 1 hexane–ethyl acetate); n.m.r. data ($CDCl_3$): δ 7.32 (20 H, 4 Ph) and 2.1 (s, 3 H, *ax* OAc).

ACKNOWLEDGMENTS

The authors thank Mrs. Onda Simmons for recording the n.m.r. spectra. This work was supported by Grant No. R01-CA 24051-01, awarded by the National Cancer Institute, DHEW.

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