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Note

Synthesis and methanolysis of 2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl bromide

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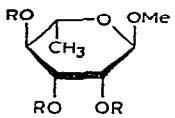
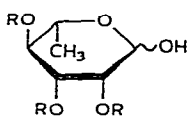
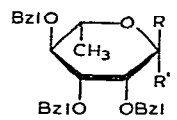
In continuation of our studies[1,2] on steric control in glycoside and oligosaccharide synthesis, we now report the preparation of 2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl bromide (**7**) and the reactions it undergoes with methanol under a variety of conditions.



1 R = H
2 R = Bzl



3 R = Bzl
4 R = H, Bzl$_2$



5 R = *p*-$NO_2C_6H_4CO_2$, R' = H
6 R = H, R' = *p*-$NO_2C_6H_4CO_2$
7 R = Br, R' = H

Methyl α-L-rhamnopyranoside (**1**) was benzylated with benzyl chloride and sodium hydroxide, and the syrupy product was hydrolyzed by boiling at reflux in 3:1 (v/v) *p*-dioxane–0.5M sulfuric acid. No attempt was made to optimize the reaction conditions and it turned out that neither reaction had gone to completion. Chromatographic separation of the product mixture furnished the fully benzylated but unhydrolyzed glycoside **2** as an analytically pure syrup, then the desired 2,3,4-tri-*O*-benzyl-L-rhamnose (**3**) in crystalline form, and finally, a crystalline di-*O*-benzyl-L-rhamnose (**4**). The yields were 32, 24, and 39%, respectively. *p*-Nitrobenzoylation of **3** gave 2,3,4-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-α-L-rhamnopyranose (**5**) and its β-anomer (**6**), both crystalline, in yields of 75 and 14%, respectively. Treatment of **5** with anhydrous hydrogen bromide in dichloromethane solution[1–5] afforded the title compound (**7**) as an oil showing $[\alpha]_D^{25}$ −119°.

Compound **7** was methanolyzed in dichloromethane solution under four different sets of conditions and the ratios of anomeric methyl glycosides produced

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were examined by n.m.r. spectroscopy, in the manner that has been described in our preceding study[2] on D-galactosyl halides. The conditions employed were the same, namely, reaction with methanol alone (in 70-fold molar excess), and with methanol in the presence of tetrabutylammonium bromide (4 mol. equiv.), mercuric cyanide (1.7 mol. equiv.), or silver tetrafluoroborate (2 mol. equiv.). The first three reactions were performed at room temperature, and the fourth at −78°.

The reaction with methanol alone proceeded practically without stereoselectivity, giving a ratio of α- to β-glycoside of 12:13. The polarimetrically determined[2,3] rate constant k was 2.4×10^{-3} [ln, sec^{-1}], $t_{0.5}$ was 300 sec. In the presence of tetrabutylammonium bromide (which was added with the aim of promoting anomerization[2,3,5,6] in 7), the product ratio shifted in favor of the α-L-glycoside (31:19), but this was not accompanied by any significant enhancement in the reaction velocity ($k = 2.5 \times 10^{-3}$ [ln, sec^{-1}]; $t_{0.5} = 275$ sec). Clearly, the effect of excess bromide ion was less pronounced than in the cases of the analogous tetra-*O*-benzyl-α-D-galactopyranosyl[2] and α-D-glucopyranosyl[3] bromides, where considerable rate increases and greater shifts in anomer ratios were observed. It would be consistent with our previous discussion[2] of the subject to conclude that, in the reaction of the L-rhamnose derivative 7, partial (α→β)-anomerization prior to methanolysis does not play a major role in contrast to the cases just mentioned. This is perhaps due to the increased anomeric effect which is known to be especially strong in sugars having, like 7, an axial C-2 substituent. Methanolysis by an SN2 or tight ion-pair mechanism should then lead to the β-L-glycoside predominantly, but since a substantial proportion of α-L-glycoside was formed, nevertheless, it appears possible that the displacement by methanol proceeds to a greater extent *via* a loose or solvent-separated ion-pair. A relatively facile formation of glycosyl carbonium-ion in the present instance may be promoted inductively through the electron-donating effect of the C-5 methyl group. By this mechanism, both glycoside anomers can arise, but equatorial attack of the nucleophile leading to the β-L anomer would involve an unfavorable transition-state owing to the anomeric effect.

In even greater contradistinction to the results obtained[2,7] with the aforementioned α-D-*galacto* and α-D-*gluco* bromides, metal salt-assisted methanolysis of 7 lacked the very high stereoselectivity (90–100%) that had furnished β-pyranosides under the same conditions and that has been attributed to direct displacement, with inversion, aided by a "push-pull" process. Thus, the α to β ratio generated by 7 in the presence of mercuric cyanide was 37:63, and it was even reversed to 3:2 in the presence of silver tetrafluoroborate. Again, this suggests that a free carbonium-ion mechanism contributes to a considerable, if not major extent, to the course of these reactions of 7.

As has been pointed out[2,8], steric control in certain types of methanolysis is more difficult to achieve in the galactopyranose than in the glucopyranose series. The present results indicate that a further loss in stereoselectivity is conditioned by the structural features of the rhamnopyranose system. Of course, this applies only when a non-participating substituent has been placed at C-2, as for the purpose of generating

1,2-*cis* glycosides. 1,2-*trans* Glycosides are obtainable stereospecifically from peracetylglycosyl halides, and this holds also for the synthesis of α-L-rhamnopyranosides[9]. Perhaps the moderate β selectivity noted above for the reaction of 7 in the presence of mercuric cyanide can be utilized for the synthesis of less readily accessible β-L-rhamnopyranosides.

EXPERIMENTAL

Benzylation of methyl α-L-rhamnopyranoside and subsequent hydrolysis. — A suspension of fine-powdered methyl α-L-rhamnopyranoside[10] (**1**, 10 g) and sodium hydroxide (22 g) in benzyl chloride (120 ml) was stirred for 6 h at 120–130°. After cooling, chloroform (200 ml) was added and the mixture was filtered. The filtrate was washed several times with water and evaporated, finally at 2 mm Hg. Residual benzyl chloride was removed by steam distillation, and the remaining oil was boiled at reflux for 4 days in *p*-dioxane–0.5M sulfuric acid (480 ml, 3:1). The cooled hydrolyzate was neutralized with barium carbonate, filtered, and evaporated. The residue was dissolved in chloroform and the solution washed several times with water, dried, and evaporated. The crude product, which showed three well-separated spots in t.l.c. (47:3, v/v, benzene–methanol), was chromatographed on a column of silica gel (250 g) with 10:1 (v/v) benzene–ether as eluent. Chromatographically homogeneous products eluted from the column were **2** (8 g, 32%), **3** (5.8 g, 24%), and **4** (7.6 g, 39%), in that order.

Methyl 2,3,4-tri-O-benzyl-α-L-rhamnopyranoside (**2**). — This product was a colorless syrup that failed to crystallize; $[\alpha]_D^{20}$ −27.8° (*c* 1.9, chloroform); n.m.r. data (100 MHz, chloroform-*d*): δ 7.25 (s, 15 H, 3 Ph), 3.28 (s, 3 H, OCH_3), and 1.32 (d, 3 H, *J* 5.5 Hz, *C*–CH_3).

Anal. Calc. for $C_{28}H_{32}O_5$ (448.5): C, 74.91; H, 7.19. Found: C, 74.76; H, 7.06.

2,3,4-Tri-O-benzyl-L-rhamnopyranose (**3**). — Crystallized from ether–petroleum ether (b.p. 60–80°), it gave needles, m.p. 90–92°, $[\alpha]_D^{20}$ −15.4° (*c* 1.6, chloroform). The n.m.r. spectrum suggested that, in chloroform-*d* solution, **3** was a mixture of anomers sine the *C*–CH_3 signal near δ 1.29 consisted of 4 lines; no OMe signal was present.

Anal. Calc. for $C_{27}H_{30}O_5$ (434.5): C, 74.63; H, 6.96. Found: C, 74.39; H, 6.85.

Di-O-benzyl-L-rhamnose (**4**). — This compound crystallized in needles from ether, m.p. 129–130°; $[\alpha]_D^{20}$ +39° (*c* 2, chloroform). The n.m.r. spectrum indicated an intensity ratio of 10:3 for the aromatic and C–Me proton signals.

Anal. Calc. for $C_{20}H_{24}O_5$ (344.4): C, 69.75; H, 7.02. Found: C, 69.73; H, 6.90.

2,3,4-Tri-O-benzyl-1-O-p-nitrobenzoyl-α-L-rhamnopyranose (**5**) *and β-anomer* (**6**). — A solution of **3** (3.35 g) in dry pyridine (40 ml) was cooled to 0° and *p*-nitrobenzoyl chloride (5 g) was added. The mixture was kept overnight at room temperature, then poured into ice–water (500 ml). The sticky precipitate formed was washed with water and dissolved in dichloromethane. The solution was washed rapidly with ice-cold 0.6M hydrochloric acid followed by water, sodium hydrogencarbonate solution, and water. After being dried (magnesium sulfate), it was evaporated to give an oil which

was passed through a column of silica gel (150 g). Elution with 99:1 (v/v) benzene–ether gave first the α-anomer **5** (3.4 g, 76%), which crystallized from ether–petroleum ether, m.p. 109–110°, $[\alpha]_D^{20}$ −60.9° (*c* 1.85, chloroform). Subsequently, the β-anomer **6** (0.63 g, 14%) was eluted and crystallized from carbon tetrachloride–petroleum ether, m.p. 128–130°, $[\alpha]_D^{20}$ +33.8° (*c* 2, chloroform).

Anal. Calc. for $C_{34}H_{33}NO_8$ (583.6): C, 69.97; H, 5.70; N, 2.40. Found for **5**: C, 69.77; H, 5.88; N, 2.51. Found for **6**: C, 69.82; H, 5.84; N, 2.54.

2,3,4-Tri-O-benzyl-α-L-rhamnopyranosyl bromide (**7**). — Compound **5** (1.05 g) was dissolved, at room temperature, in dry dichloromethane (50 ml) saturated with dry hydrogen bromide gas. A precipitate of *p*-nitrobenzoic acid was formed almost at once, and after 10 min the reaction was complete according to t.l.c. in 5:1 (v/v) benzene–ether. The precipitated acid (289 mg, 96%) was collected on a glass filter, the filtrate was evaporated, and three portions of dichloromethane were added to and then evaporated from the amorphous residue, which was finally dried *in vacuo*. The material (0.9 g) gave a single spot in t.l.c. and showed $[\alpha]_D^{20}$ −119° (*c* 1.7, dichloromethane). The n.m.r. spectrum in chloroform-*d* showed an anomeric proton doublet (*J* 2 Hz) at δ 6.4 and a *C*–CH_3 doublet (*J* 6 Hz) at δ 1.35.

Methanolysis. — Methanolysis of **7** (100 mg) with methanol (0.50 ml) in dichloromethane (4.5 ml) without additive and with added tetrabutylammonium bromide (200 mg) or mercuric cyanide (91 mg) at room temperature, or with silver tetrafluoroborate (76 mg) at −78°, was performed exactly as described[2] for similar experiments in the D-*galacto* series. The ratio of anomeric glycosides formed was determined, after processing[2], by integration of the OMe signals at δ 3.28 (α-anomer) and δ 3.50 (β-anomer), in chloroform-*d* solution (100 MHz n.m.r. spectra with 100-Hz sweep-width).

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