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Note

A convenient synthesis of *O*-α-L-rhamnopyranosyl-(1→4)-*O*-α-L-rhamnopyranosyl-(1→6)-D-galactopyranose nona-acetate

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O-α-L-Rhamnopyranosyl-(1→4)-*O*-α-L-rhamnopyranosyl-(1→6)-*O*-D-galactopyranose is the carbohydrate component of the flavone glycoside Xanthorhamnin A, isolated[1] from *Rhamnus petiolaris* (Bois). During our first synthesis[2] of the nona-acetate of this trisaccharide, starting from 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[3], all the intermediates were syrupy or amorphous products. We now report a new synthesis.

Hydrogenolysis of benzyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside[4] (**1**) with lithium aluminium hydride–aluminium chloride[5] gave benzyl 2,3,4-tri-*O*-benzyl-β-D-galactopyranoside (**2**, 91.8%). The structure of **2** was confirmed by conversion into the 6-*O*-methyl derivative (**3**). Another route for the synthesis of **2** has been published[6].

Reaction of **2** with acetobromorhamnose[7] (**4**) in benzene–nitromethane, in the presence of mercuric cyanide, gave benzyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-β-D-galactopyranoside (**5**, 70.5%), which was purified by short-column chromatography[8]. Saponification (Zemplén) of **5** gave a crystalline product (**6**), hydrogenolysis of which followed by acetylation afforded robinobiose hepta-acetate[9] (**7**). The structure of **7** has been proved by synthesis[10], and the configuration of the interglycosidic linkage confirmed[11].

The reaction of **6** with anhydrous acetone–sulphuric acid gave benzyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3-*O*-isopropylidene-α-L-rhamnopyranosyl)-β-D-galactopyranoside (**8**). The chemical shift (δ 3.37) of the signal for methoxyl protons in the n.m.r. spectrum of the 4-*O*-methyl derivative (**9**) of **8** was similar to that (δ 3.36) for the corresponding group in benzyl 2,3-*O*-isopropylidene-4-*O*-methyl-α-L-rhamnopyranoside (**11**) prepared by the methylation[14] of benzyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside[12] (**10**).

The condensation of **8** and **4**, under the conditions used for the preparation of **5**, gave **12** (79.6%). Saponification of **12**, followed by mild hydrolysis with acid, debenzylation, and acetylation, gave the title acetate (**13**), which was identical with the product of our first synthesis[2].

EXPERIMENTAL

Melting points were taken on a Kofler apparatus and are uncorrected. N.m.r. spectra were obtained with a Jeol MH-100 instrument, using Me_4Si as internal standard. I.r. spectra were obtained on a Perkin–Elmer 700 instrument. Optical rotations were measured with a POLAMAT (Zeiss) automatic polarimeter. T.l.c. was performed on Kieselgel-G (Merck); compounds were detected by charring with sulphuric acid.

*Benzyl 2,3,4-tri-*O*-benzyl-β-*D*-galactopyranoside* (**2**). — To a solution of **1** (3 g) in 1:1 ether–dichloromethane (160 ml), 1 g of $LiAlH_4$ was added in three portions with stirring, and the mixture was slowly heated to reflux. A solution of 3 g of $AlCl_3$ in ether (60 ml) was then added during 30 min, and boiling was continued for 2 h until **1** disappeared. After cooling, the excess of $LiAlH_4$ was decomposed with ethyl acetate, and water (15 ml) was then added. The organic layer was washed with water (2 × 50 ml), dried (Na_2SO_4), and concentrated, and the residue was recrystallized from cyclohexane (25 ml) to give **2** (2.75 g, 91.8%), m.p. 96°, $[\alpha]_D$ −49° (*c* 1.05, chloroform), R_F 0.55 (benzene–methanol, 97:3); lit.[6] m.p. 96–96.5°, $[\alpha]_D$ −46° (*c* 3, chloroform). N.m.r. data ($CDCl_3$): δ 7.45–7.10 (m, 20 H, aromatic), 5.10–4.47 (m, 9 H, benzyl and H-1), 4.08–3.10 (m, 6 H, H-2,3,4,5,6,6′), 1.53 (s, 1 H, OH).

*Benzyl 2,3,4-tri-*O*-benzyl-6-*O*-methyl-β-*D*-galactopyranoside* (**3**). — A mixture of 0.5 g of **2**, methyl iodide (0.7 ml), Ag_2O (0.7 g), and *N*,*N*-dimethylformamide (10 ml) was stirred for 24 h. The reaction mixture was then diluted with chloroform (50 ml) and filtered. The filtrate was washed successively with 1% aqueous KCN (3 × 20 ml) and water (2 × 20 ml), dried ($CaCl_2$), and concentrated. Crystallisation of the residue from cyclohexane (6 ml) afforded **3** (0.42 g, 82.3%), m.p. 80–81°, $[\alpha]_D$ −30° (*c* 1.25, chloroform), R_F 0.73 (benzene–methanol, 97:3).

Anal. Calc. for $C_{35}H_{38}O_6$: C, 75.76; H, 6.90. Found: C, 75.47; H, 6.63.

N.m.r. data ($CDCl_3$): δ 7.55–7.12 (m, 20 H, aromatic), 5.17–4.35 (m, 9 H, benzyl and H-1), 4.10–3.95 (m, 6 H, H-2,3,4,5,6,6′), 3.33 (s, 3 H, OMe).

*Benzyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-acetyl-α-*L*-rhamnopyranosyl)-β-*D*-galactopyranoside* (**5**). — A solution of **2** (5.4 g, 10 mmol) in benzene (70 ml) and nitromethane (70 ml) was concentrated at atmospheric pressure to 50 ml. After cooling to 40°, $Hg(CN)_2$ (2.78 g, 11 mmol) and 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl bromide[7] (**4**; 3.88 g, 11 mmol) were added and the mixture was stirred at 40° for 2 h until **2** disappeared. The filtered mixture was concentrated at 40° and the residue was extracted with chloroform (200 ml). The filtered extract was washed successively with 5% aqueous KI (5 × 40 ml) and water (2 × 50 ml), dried (Na_2SO_4), and concentrated. The syrupy residue was eluted from Kieselgel G (250 g) with benzene–methanol (95:5) to give **5** (5.73 g, 70.5%), $[\alpha]_D$ −64° (*c* 2.1, chloroform), R_F 0.80 (benzene–methanol, 95:5).

Anal. Calc. for $C_{46}H_{52}O_{13}$: C, 67.97; H, 6.46. Found: C, 68.12; H, 6.42.

N.m.r. data ($CDCl_3$): δ 7.20–7.00 (m, 20 H, aromatic); 5.14–3.25 (m, 20 H, benzyl and ring protons); 2.04, 1.96, 1.90 (3 s, 9 H, 3 AcO); 1.03 (d, 3 H, *J* 6.5 Hz, Me).

Benzyl 2,3,4-tri-O-benzyl-6-O-α-L-rhamnopyranosyl-β-D-galactopyranoside (**6**). — Compound **5** (5 g) was saponified with 0.1M methanolic sodium methoxide (5 ml) in methanol (100 ml). After neutralization with acetic acid, the reaction mixture was concentrated, and the residue was recrystallized from ethanol (25 ml) to give **6** (3.86 g, 91.4%), m.p. 139–142°, $[\alpha]_D$ −12° (*c* 1, pyridine), R_F 0.70 (benzene–methanol, 8:2).

Anal. Calc. for $C_{40}H_{46}O_{10}$: C, 69.94; H, 6.75. Found: C, 69.25; H, 6.28.

N.m.r. data (Me_2SO-d_6): δ 7.44–7.04 (m, 20 H, aromatic), 5.00–3.40 (m, 20 H, benzyl and ring protons), 3.26 (broad, 3 H, 3 HO), 3.10 (d, 3 H, *J* 6.5 Hz, Me).

1,2,3,4-Tetra-O-acetyl-6-O-(2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl)-D-galactopyranose (**7**, *robinobiose hepta-acetate*). — A solution of **6** (1 g) in 100 ml of ethyl acetate containing 5% of glacial acetic acid was hydrogenolysed in the presence of 10% palladium-on-carbon (200 mg) for 24 h. The filtered mixture was then concentrated and traces of water were removed from the residue by repeated distillation of benzene therefrom. The syrupy residue was then conventionally acetylated with acetic anhydride (10 ml) and pyridine (10 ml). Crystallisation of the product from 70% ethanol gave **7** (0.68 g, 75%), m.p. 79–83°, $[\alpha]_D$ −9° (*c* 1, chloroform), R_F 0.50 (benzene–methanol, 9:1), lit.[9] m.p. 84.5–85°, $[\alpha]_D$ −8.9° (chloroform).

Benzyl 2,3,4-tri-O-benzyl-6-O-(2,3-O-isopropylidene-α-L-rhamnopyranosyl)-β-D-galactopyranoside (**8**). — A solution of 3.3 g of **6** in anhydrous acetone (90 ml) containing 0.27 ml of conc. sulphuric acid was stored at room temperature. After 2 h, t.l.c. indicated the absence of **6**, and the mixture was neutralized with ammonium hydroxide and concentrated. The residue was extracted with hot cyclohexane (50 ml), and the product obtained on cooling the extract was recrystallized from cyclohexane (35 ml) to yield **8** (2.88 g, 82.5%), m.p. 116–118°, $[\alpha]_D$ −49° (*c* 1.06, chloroform), R_F 0.45 (benzene–methanol, 95:5).

Anal. Calc. for $C_{43}H_{50}O_{10}$: C, 71.05; H, 6.93. Found: C, 70.81; H, 6.68.

N.m.r. data ($CDCl_3$): δ 7.40–7.12 (m, 20 H, aromatic); 5.00–3.24 (m, 21 H, benzyl, ring protons, and OH); 1.46, 1.28 (2 s, 6 H, CMe_2); 1.12 (d, 3 H, *J* 6.5 Hz, Me).

Compound **8** (200 mg) was methylated[13] with *N*,*N*-dimethylformamide (5 ml), methyl iodide (0.5 ml), and NaH (50 mg). The product was purified by p.l.c. (benzene–methanol, 97:3) to give syrupy benzyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3-*O*-isopropylidene-4-*O*-methyl-α-L-rhamnopyranosyl)-β-D-galactopyranoside (**9**; 110 mg, 54%), $[\alpha]_D$ −50° (*c* 0.85, chloroform). N.m.r. data ($CDCl_3$): δ 7.40–7.12 (m, 20 H, aromatic); 3.37 (s, 3 H, OMe); 1.52, 1.34 (2 s, 6 H, CMe_2); 1.28 (d, 3 H, *J* 6.5 Hz, Me).

Benzyl 2,3,4-tri-O-benzyl-6-O-[2,3-O-isopropylidene-4-O-(2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranosyl]-β-D-galactopyranoside (**12**). — A solution of **8** (1.98 g, 2.7 mmol) in benzene (30 ml) and nitromethane (30 ml) was concentrated to 20–25 ml at atmospheric pressure. The mixture was cooled to 40°, and $Hg(CN)_2$ (0.76 g, 3.1 mmol) and **4** (1.06 g, 3.1 mmol) were added with stirring. Stirring was continued at 40° for 2 h and then at room temperature for 16 h. The filtered solution was concentrated *in vacuo*, and a solution of the residue in chloroform (100 ml) was

washed successively with 5% aqueous KI (3 × 20 ml) and water (3 × 20 ml), dried, and concentrated. The syrupy residue was crystallized from ethanol (12 ml) to give **12** (2.15 g, 79.6%), m.p. 126–128°, $[\alpha]_D$ −79° (*c* 1.2, chloroform), R_F 0.6 (benzene–methanol, 97:3).

Anal. Calc. for $C_{55}H_{66}O_{17}$: C, 66.12; H, 6.65. Found: C, 66.83; H, 6.32.

N.m.r. data ($CDCl_3$): δ 7.40–7.12 (m, 20 H, aromatic); 5.28–3.26 (m, 25 H, benzyl, anomeric, and ring protons); 2.08, 2.00, 1.92 (3 s, 9 H, 3AcO); 1.46, 1.26 (2 s, 6 H, CMe_2); 1.17, 1.06 (2 d, 6 H, *J* 6.5 Hz, 2Me).

*1,2,3,4-Tetra-*O*-acetyl-6-*O*-[2,3-di-*O*-acetyl-4-*O*-(2,3,4-tri-*O*-acetyl-α-*L*-rhamnopyranosyl)-α-*L*-rhamnopyranosyl]-*D*-galactopyranose* (**13**). — Compound **12** (2 g) was saponified with a mixture of 0.1M methanolic sodium methoxide (2 ml) and methanol (50 ml). After neutralization of the mixture with acetic acid and concentration, the isopropylidene group of the product was hydrolysed with 50% acetic acid (50 ml) at 80° for 12 h. Traces of water and acetic acid were removed by the repeated addition and distillation of benzene. The residue was then dissolved in ethanol (100 ml) containing 10% of water and hydrogenolysed in the presence of 10% palladium-on-carbon (400 mg) for 72 h. The filtered mixture was then concentrated to a syrup (0.8 g), R_F 0.21 (Schleicher–Shüll 2043b paper, 1-butanol–pyridine–water, 6:4:3).

After drying over P_2O_5, the syrup was conventionally acetylated with acetic anhydride (15 ml) and pyridine (15 ml). The product was crystallised from 70% ethanol to give **13** (1.08 g, 63.5%), m.p. 82–85°, $[\alpha]_D$ −32° (*c* 0.7, chloroform), R_F 0.39 (benzene–methanol, 9:1).

Anal. Calc. for $C_{36}H_{50}O_{23}$: C, 50.82; H, 5.92. Found: C, 51.30; H, 6.12.

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