Carbohydrate Research, 34 (1974) 174–179
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Note

Synthesis of 4-*O*-α-L-rhamnopyranosyl-L-rhamnopyranose

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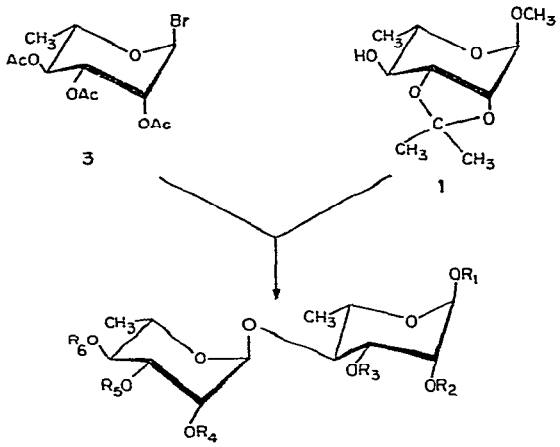
(Received October 26th, 1973; accepted December 10th, 1973)

The identification of rhamnobioses in Nature is a problem of considerable interest. Due to the lack of authentic standards, it is often not possible to characterize them fully[1] or to identify them correctly[2]. Current structural work on *Klebsiella* capsular polysaccharides has revealed the presence therein of many rhamnobiose units[3–5] for which authentic standards and their physical constants would be most



	R_1	R_2	R_3	R_4	R_5	R_6
		C				
4	Me	Me	Me	Ac	Ac	Ac
5	Me	H	H	Ac	Ac	Ac
6	Me	Ac	Ac	Ac	Ac	Ac
7	Me	H	H	H	H	H
8	Me	Me	Me	Me	Me	Me
9	Ac	Ac	Ac	Ac	Ac	Ac
10	H	H	H	H	H	H

useful. For these reasons, we here report the synthesis of 4-*O*-α-L-rhamnopyranosyl-L-rhamnopyranose in an overall yield of 60%.

The condensation of the two monomer units was carried out with mercuric cyanide and acetonitrile (Helferich reaction) as recommended by Kamiya *et al.*[6]. The α-L-linkage predicted by the *trans* rule[7] was confirmed by the p.m.r. chemical shift[8] of the anomeric proton in all the compounds prepared, but particularly in the free disaccharide, where the anomeric proton of the nonreducing moiety is clearly to low field and therefore axially attached. Although it was not possible to assign the signals from the H-6 atoms to the reducing and nonreducing moieties, comparison with analogous systems[9,10] suggested that, in most cases, the high-field signal comes from the reducing sugar.

Details of the individual steps used in the synthesis have been discussed fully in connection with the preparation of the β-D-*gluco* and α-D-*manno* analogs[9,10]. In the present instance, the peracetylated derivatives of the disaccharide methyl glycoside (**6**), the disaccharide (**9**), and the disaccharide alditol (**12**) were obtained crystalline.

EXPERIMENTAL

General methods. — Melting points were obtained for samples between glass slides on a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer model 141 polarimeter at 23 ± 1°. P.m.r. spectra were recorded on a Varian XL-100 instrument, with tetramethylsilane as the internal standard, except as noted. Gas–liquid partition chromatography was conducted with an F and M 720 instrument equipped with dual, thermal-conductivity detectors at a gas flow-rate of 60 ml/min, with the following columns: (*a*) 2 ft × 0.25 in. of 20% of SE-30 (F and M Division, Hewlett Packard, Avondale, Pennsylvania), (*b*) 4 ft × 0.25 in. of 5% of butanediol succinate on Diatoport S (80–100 mesh), and (*c*) 6 ft × 0.25 in. of 15% of OS-138 on Gas Chrom Q (100–120 mesh). Peak areas were determined with an Infotronics CRS-100 electronic integrator. Mass spectra were recorded either with a Micromass 12 gas–liquid chromatography–mass spectrometer, or on an AEI MS 9 instrument. Thin-layer chromatography (t.l.c.) was performed with solvent systems *A* and *B* on silica gel G (from EM Reagents); solvent *A*, 2:1 ethyl ether–toluene; *B*, butanone–water azeotrope. The plates were dried, and components were detected by spraying with 35% ethanolic sulfuric acid and heating for 3–5 min at ~150°. Paper-chromatographic separations were conducted on Whatman No. 1 paper with the upper layer of solvent system *C* (4:1:1 ethyl acetate–pyridine–water), and zones were made visible by using silver nitrate in acetone[11]. Solutions were concentrated below 50° under diminished pressure.

Methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside (**1**). — Compound **1** was prepared as described previously[9], except that the Amberlite IR-120 (H^+) resin was soaked in dry methanol instead of acetone (to avoid formation of acetone polymers).

1,2,3,4-Tetra-O-acetyl-α-L-rhamnopyranose (**2**). — L-Rhamnose monohydrate (1 g) was acetylated with pyridine (25 ml) and acetic anhydride (25 ml) for 5 h at room

temperature. This is essentially the procedure of Fischer *et al.*[12], except that the excess reagents were removed by successive evaporations with ethanol and then with water, yielding the syrupy product (1.8 g, 98%); $[\alpha]_D$ −63° (*c* 2.3, chloroform) {lit.[7] $[\alpha]_D^{25}$ −61.7° (*c* 2.7, chloroform)}; R_F 0.58 (solvent *A*); p.m.r. data ($CDCl_3$): τ 3.98 (1-proton doublet, $J_{1,2}$ 1.4 Hz, H-1), 7.85, 7.86, 7.95, 8.01 (3-proton singlets, 4 OAc), and 8.77 (3-proton doublet, $J_{5,6}$ 6 Hz, CH_3).

*2,3,4-Tri-*O*-acetyl-*α*-*L*-rhamnopyranosyl bromide* (**3**). — Compound **2** (6 g) was stirred with glacial acetic acid (6 ml), chloroform (6 ml), and 30–32% hydrogen bromide in acetic acid (12 ml) for 3 h at 0°, essentially as described by Fischer *et al.*[12]. The mixture was diluted with chloroform (100 ml), successively washed with ice–water (2 × 75 ml), saturated sodium hydrogen carbonate solution (75 ml), and ice–water (75 ml), dried, and evaporated to a syrup that crystallized from ethyl ether (anhydrous, 6 ml) and petroleum ether (b.p. 65–70°, 6 ml) at −10° to give 5.1 g of **3** (80%), m.p. 64.5–65.5°, $[\alpha]_D$ −173.5° (*c* 2.4, chloroform) {lit.[12] m.p. 71–72°, $[\alpha]_D$ −169.0° (*c* 12.3, tetrachloroethane)}; R_F 0.65 (solvent *A*); p.m.r. ($CDCl_3$): τ 3.70 (1-proton doublet, $J_{1,2}$ 1.6 Hz, H-1), 7.86, 7.94, 8.02 (3-proton singlets, 3 OAc), and 8.73 (3-proton doublet, $J_{5,6}$ 6 Hz, CH_3).

*Methyl 2,3-*O*-isopropylidene-4-*O*-(2,3,4-tri-*O*-acetyl-*α*-*L*-rhamnopyranosyl)-*α*-*L*-rhamnopyranoside* (**4**). — To a stirred solution of compound **1** (1.0 g, 4.6 mmoles) and dry mercuric cyanide (1.0 g) in acetonitrile (2 ml, distilled over calcium hydride, CaH_2) was added bromide **3** (2.5 g), in portions, during 3 h. At 4 h, the acetonitrile was evaporated under diminished pressure, and the resulting syrup was dissolved in chloroform (100 ml). The solution was successively washed with 1M potassium bromide (2 × 100 ml), water (100 ml), saturated sodium hydrogen carbonate solution (100 ml), and water (2 × 100 ml), and evaporated under diminished pressure to an impure, amorphous material (3.0 g) which showed a major component (~80%) on t.l.c. with solvent *A* (R_F 0.62). For analytical purposes, a small amount was purified by preparative t.l.c.[13]; $[\alpha]_D$ −74° (*c* 2.0, chloroform); p.m.r. ($CDCl_3$): τ 4.66 (1-proton doublet, $J_{1',2'}$ 1.9 Hz, H-1'), 5.12 (1-proton singlet, H-1), 6.60 (3-proton singlet, OCH_3), 7.83, 7.94, 8.01 (3-proton singlets, 3 OAc), 8.45, 8.65 (3-proton singlets, CMe_2), 8.66 (3-proton doublet, $J_{5,6}$ 6 Hz, CH_3), and 8.75 (3-proton doublet, $J_{5,6}$ 6 Hz, CH_3).

*Methyl 4-*O*-(2,3,4-tri-*O*-acetyl-*α*-*L*-rhamnopyranosyl)-*α*-*L*-rhamnopyranoside* (**5**). — A solution of impure, amorphous compound **4** (3.0 g) in chloroform (135 ml) was treated for 1 h at room temperature with trifluoroacetic acid containing 1% of water (15 ml). The mixture was then concentrated, and remaining trifluoroacetic acid was removed by addition and distillation of toluene. The resulting syrup (2.7 g) showed mainly one spot on t.l.c., R_F 0.13 (solvent *A*) and 0.78 (solvent *B*); p.m.r. ($CDCl_3$): τ 6.63 (3-proton singlet, OCH_3), 7.86, 7.95, 8.01 (3-proton singlets, 3 OAc), 8.66 (3-proton doublet, $J_{5,6}$ 6 Hz, CH_3), and 8.77 (3-proton doublet, $J_{5,6}$ 6 Hz, CH_3).

*Methyl 2,3-di-*O*-acetyl-4-*O*-(2,3,4-tri-*O*-acetyl-*α*-*L*-rhamnopyranosyl)-*α*-*L*-rhamnopyranoside* (**6**). — Crude compound **5** (2.7 g) was acetylated with pyridine (25 ml) and acetic anhydride (25 ml) for 5 h at room temperature. The excess reagents were

removed by successive evaporation with ethanol and then with water. The resulting syrup crystallized from ethanol (13 ml) when nucleated with a crystal obtained from a t.l.c. separation[13]; yield 1.6 g (3.0 mmoles; 65%, based on **1**). Recrystallization from ethanol gave pure **6**, m.p. 182–183°, $[\alpha]_D$ −51.7° (*c* 2.3, chloroform); R_F 0.51 (solvent *A*); p.m.r. ($CDCl_3$): τ 5.02 (1-proton doublet, $J_{1',2'}$ 1.4 Hz, H-1'), 5.42 (1-proton doublet, $J_{1,2}$ 1.2 Hz, H-1), 6.62 (3-proton singlet, OCH_3), 7.88–8.03 (15-protons, 5 OAc), 8.63 (3-proton doublet, $J_{5,6}$ 6 Hz, CH_3), and 8.78 (3-proton doublet, $J_{5,6}$ 6 Hz, CH_3).

Anal. Calc. for $C_{23}H_{34}O_{14}$: C, 51.68; H, 6.41. Found: C, 51.78; H, 6.52.

Methyl 4-O-α-L-rhamnopyranosyl-α-L-rhamnopyranoside (**7**). — Compound **6** (1.3 g) was deacetylated with sodium methoxide (0.2M, 35 ml) for 1 h at room temperature. Sodium ions were removed from the chilled solution with Amberlite IR-120 (H^+) resin, and remaining traces of acid were removed with Duolite A-4 (OH^-) resin. The syrup obtained on evaporation showed one spot in t.l.c., R_F 0.19 (solvent *B*); yield 0.73 g (97%); $[\alpha]_D$ −109° (*c* 2.5, water); R_{Glc} 4.0 (solvent *C*); p.m.r. (D_2O, external tetramethylsilane): τ 4.81 (1-proton doublet, $J_{1',2'}$ 1.8 Hz, H-1'), 5.28 (1-proton doublet, $J_{1,2}$ 1.0 Hz, H-1), 6.58 (3-proton singlet, OCH_3), 8.64 (3-proton doublet, $J_{5,6}$ 6 Hz, CH_3), and 8.68 (3-proton doublet, $J_{5,6}$ 6 Hz, CH_3).

The methyl glycoside **7** was methylated by a method previously described[9], to give the corresponding hexamethyl ether **8**. A small amount was purified by preparative t.l.c.[13] for analytical purposes: R_F 0.29 (solvent *A*); $[\alpha]_D$ −81.5° (*c* 2.1, chloroform); p.m.r. ($CDCl_3$): τ 4.77 (1-proton doublet, $J_{1',2'}$ 1.7 Hz, H-1'), 5.26 (1-proton doublet, $J_{1,2}$ 1.6 Hz, H-1), 6.45–6.63 (18 protons, 6 OCH_3), 8.69 (3-proton doublet, $J_{5,6}$ 6 Hz, CH_3), and 8.74 (3-proton doublet, $J_{5,6}$ 6 Hz, CH_3). Hydrolysis of **8**, followed by reduction and acetylation, gave equimolar amounts of 1,5-di-*O*-acetyl-2,3,4-tri-*O*-methyl-L-rhamnitol and 1,4,5-tri-*O*-acetyl-2,3-di-*O*-methyl-L-rhamnitol, identified by g.l.c. (column *c*, 220°, retention times 14.0 and 23.6 min, respectively) and mass-spectrometric analysis in comparison with authentic standards[14].

Periodate oxidation of **7** by a procedure previously described[9] showed a total consumption of 3.0 moles per mole in 70 h. Subsequent reduction, methanolysis, and acetylation gave 3-deoxy-L-glycerol diacetate and 4-deoxy-L-erythritol triacetate, identified by comparative g.l.c. (column *b*, 60–220°, programmed at 2°.min^{-1}; retention times 9.2 and 35.6 min, respectively) and mass-spectrometric analysis with use of authentic standards.

1,2,3-Tri-O-acetyl-4-O-(2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranose (**9**). — Crude compound **5** (2.7 g) in acetic anhydride (15 ml) was shaken with 1% (v/v) concentrated sulfuric acid–acetic anhydride (30 ml) for 2 h at room temperature. The mixture was diluted with chloroform (200 ml), successively washed with water (2 × 200 ml), saturated sodium hydrogen carbonate solution (2 × 200 ml), and water (2 × 200 ml), and remaining acetic anhydride or acetic acid was removed by addition and distillation of ethanol. The resulting syrup crystallized from ethanol (7 ml) when nucleated with a crystal obtained from a t.l.c. separation[13]; yield 1.7 g (3.0 mmoles; 65% based on **1**). Recrystallization from ethanol gave pure **9**, m.p. 162–

163°, $[\alpha]_D$ −63.6° (*c* 2.1, chloroform); R_F 0.51 (solvent *A*); p.m.r. ($CDCl_3$): τ 4.00 (1-proton doublet, $J_{1,2}$ 1.7 Hz, H-1), 4.99 (1-proton doublet, $J_{1',2'}$ 1.9 Hz, H-1'), 7.83–8.02 (18 protons, 6 OAc), 8.62 (3-proton doublet, $J_{5,6}$ 6 Hz, CH_3), and 8.77 (3-proton doublet, $J_{5,6}$ 6 Hz, CH_3).

Anal. Calc. for $C_{24}H_{34}O_{15}$: C, 51.25; H, 6.09. Found: C, 51.27; H, 6.10.

4-O-α-L-Rhamnopyranosyl-L-rhamnopyranose (**10**). — The peracetate **9** (0.8 g) of disaccharide **10** was deacetylated with sodium methoxide (0.2M, 20 ml) for 1 h at room temperature. After the usual processing, the resulting syrup (0.4 g, 91%) had $[\alpha]_D$ −68° (*c* 2.2, water); R_{Glc} 2.2 (solvent *C*); p.m.r. (D_2O, external tetramethylsilane): τ 4.82 (1-proton doublet, $J_{1',2'}$ 1.7 Hz, H-1'), 4.88 (0.64-proton doublet, $J_{1,2}$ 1.3 Hz, H-1, α-L form), 5.14 (0.36-proton doublet, $J_{1,2}$ 1.0 Hz, H-1, β-L form), and 8.67 and 8.68 (3-proton doublets, $J_{5,6}$ 6 Hz, 2 CH_3).

G.l.c. (column *a* at 230°) of the per-*O*-(trimethylsilyl) disaccharide gave one peak (77.5%) at 7.2 min and a second peak at 11.4 min [per-*O*-(trimethylsilyl)sucrose eluted[15] at 19.4 min].

4-O-α-L-Rhamnopyranosyl-L-rhamnitol (**11**). — The free disaccharide **10** (0.2 g) was reduced with sodium borohydride (0.08 g) in water (5 ml) for 6 h. Passage through a column of Amberlite IR-120 (H^+) resin, concentration of the effluent, and distillation with methanol, gave **11**; yield 0.19 g (95%), $[\alpha]_D$ −50° (*c* 2.1, water); R_{Glc} 1.3 (solvent *C*); p.m.r. (D_2O, external tetramethylsilane): τ 5.02 (1-proton doublet, $J_{1',2'}$ 1.7 Hz, H-1') and 8.71 (6-proton doublet, $J_{5,6}$ 6 Hz, 2 CH_3).

G.l.c. of the per-*O*-(trimethylsilyl)alditol on column *a* at 230° gave one peak at 11.6 min [per-*O*-(trimethylsilyl)sucrose[15], 19.8 min].

The alditol **11** (0.19 g) was acetylated with pyridine (4 ml) and acetic anhydride (4 ml) for 5 h at room temperature to give heptaacetate **12** (0.35 g, 95%), crystallized from ethanol (3 ml). Recrystallization from ethanol gave pure **12**, m.p. 138.5–139.5°, $[\alpha]_D$ −67.2° (*c* 2.1, chloroform); R_F 0.42 (solvent *A*); p.m.r. ($CDCl_3$): τ 5.13 (1-proton doublet, $J_{1',2'}$ 1.8 Hz, H-1'), 7.83–7.99 (21 protons, 7 OAc), 8.59 (3-proton doublet, $J_{5,6}$ 6 Hz, CH_3), and 8.75 (3-proton doublet, $J_{5,6}$ 6 Hz, CH_3).

Anal. Calc. for $C_{26}H_{38}O_{16}$: C, 51.48; H, 6.32. Found: C, 51.69; H, 6.18.

G.l.c. of the peracetylated alditol **12** on column *a* at 260° gave one peak at 6.4 min (sucrose octaacetate, 16.2 min).

ACKNOWLEDGMENTS

We are indebted to the National Research Council of Canada for continued financial support, and one of us (G.M.B.) is grateful for the award of N.R.C. and H. R. MacMillan Family Scholarships.

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