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Note

A new synthesis of 2-*O*-α-L-fucopyranosyl-3-*O*-α-D-galactopyranosyl-D-galactose

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The title trisaccharide (**8**) constitutes an important portion of the antigenic determinant of the blood-group B specific substances[1,2] and syntheses have been reported[3–5]. The new synthesis now reported starts from 2-*O*-allyl-1,6-anhydro-β-D-galactopyranose[6] (**1**) and gives **8** in 10% overall yield. Since the structures of the intermediate disaccharide derivatives (**2–4**) have been inferred from spectroscopic data and these products used in the next step without further characterisation, the structure of trisaccharide **6** has been established unequivocally by homonuclear, two-dimensional *J* (2D-*J*)[7] and 2D-correlation (COSY)[8–10] ^{1}H-n.m.r. spectroscopy.

The reaction of **1** with 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl bromide[11], using the common-ion method[12], gave a mixture of products, the main one (56% yield after chromatography) being the disaccharide **2** whose ^{13}C-n.m.r. spectrum contained signals at 100.0 (C-1) and 98.9 (C-1′) p.p.m. The allyl group of **2** was isomerised to the 1-propenyl group with tris(triphenylphosphine)rhodium(I) chloride[13,14] to give **3** (80%), and the propenyl group was then removed by treatment with mercuric chloride–mercuric oxide in aqueous acetone[15] to afford the selectively protected disaccharide **4**. Reaction of **4** with 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl bromide[16], under common-ion conditions[12], gave a trisaccharide (^{13}C-n.m.r. signals for C-1, C-1′, and C-1″ at 100.6, 98.0, and 98.8 p.p.m., respectively) in 95% yield. Debenzylation followed by acetylation gave crystalline **6**, the structure of which was established by homonuclear 2D-*J* and 2D-correlation ^{1}H-n.m.r. spectroscopy. Standard experimental methods were used to obtain the 2D-*J*[17–19] and COSY[8–10] ^{1}H-n.m.r. spectra. The projection of the 2D-*J* spectrum on the ω_2 frequency axis and the cross sections parallel to the ω_1 axis yielded the multiplet of individual resonances. The connectivity information could be obtained by direct inspection of the COSY spectrum. The ^{1}H chemical shifts and coupling constants obtained for **6** are given in Table I. Acetolysis of **6** gave a crystalline 1.5:1 α,β-mixture of deca-acetates (**7**). Deacetylation of **7** gave the amorphous title trisaccharide **8**, the ^{1}H-n.m.r. spectrum of which was as expected; the $[\alpha]_D$ value accorded with the literature data.

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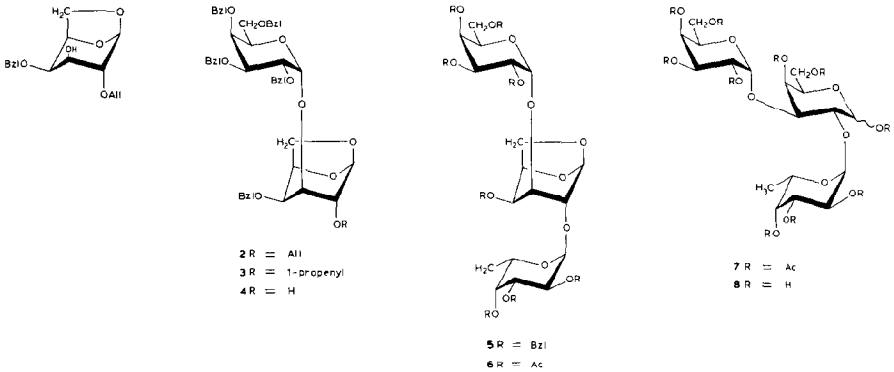

TABLE I

^{1}H-N.M.R. DATA (δ SCALE; J, IN HZ) FOR TRISACCHARIDE **6**, AS OBTAINED BY TWO-DIMENSIONAL SPECTROSCOPY

1,6-Anhydro-β-D-Gal		*α-L-Fuc*		*α-D-Gal*	
H-1	5.41	H-1′	5.21	H-1″	5.06
H-2	3.85	H-2′	5.40	H-2″	5.09
H-3	4.00	H-3′	5.30	H-3″	5.31
H-4	5.00	H-4′	5.29	H-4″	5.45
H-5	4.41	H-5′	4.25	H-5″	4.33
H-6endo	4.37			H-6″a	4.09
H-6exo	3.69			H-6″b	4.00
$J_{1,2}$	2.0	$J_{1',2'}$	3.8	$J_{1'',2''}$	3.8
$J_{2,3}$	1.5	$J_{2',3'}$	10.8	$J_{2'',3''}$	10.0
$J_{3,4}$	5.2	$J_{3',4'}$	3.2	$J_{3'',4''}$	3.4
$J_{4,5}$	3.7	$J_{4',5'}$	1.2	$J_{4'',5''}$	1.4
$J_{5,6endo}$	1.2			$J_{5'',6''}$	6.2
$J_{5,6exo}$	5.0			$J_{5'',6''b}$	6.8
$J_{6endo,6exo}$	7.2			$J_{6''a,6''b}$	11.4

EXPERIMENTAL

General methods. — Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. T.l.c. was performed on silica gel GF_{254} (Merck) with detection by charring with sulfuric acid. Column chromatography was performed on Merck silica gel (70–230 mesh). ^{1}H-N.m.r. spectra were recorded with a Varian 390 (90 MHz), Varian XL-100 (100 MHz), or Bruker WP-360 (360 MHz) spectrometer. ^{13}C-N.m.r. spectra were recorded with a Varian XL-100 (25.2 MHz) or Bruker WP-360 (90.5 MHz) spectrometer. The two-dimensional J spectrum was recorded with a Bruker AM-400 spectrometer at 27°. The data matrix was 128 × 4K, and the spectral widths were ω_1 ±25 and ω_2 800 Hz. The recycle delay was 4 s, and

$\Delta t_1/2$ was 10 ms. The COSY spectrum was recorded with a Varian XL-300 spectrometer. The two-dimensional map was composed of 256–512 data-point spectra, each incremented by 1.7 ms. A delay of 4 s was allowed between each pulse sequence. The data were acquired with quadrature phase detection in both dimensions, and the final data were symmetrised. Optical rotations were determined with a Perkin–Elmer 141 polarimeter.

4-O-Acetyl-1,6-anhydro-3-O-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)-2-O-(2,3,4-tri-O-acetyl-α-L-fucopyranosyl)-β-D-galactopyranose (**6**). — A mixture of 2-*O*-allyl-1,6-anhydro-4-*O*-benzyl-β-D-galactopyranose[6] (**1**; 2 g, 6.8 mmol), tetraethylammonium bromide (1.5 g, 6.8 mmol), 4 Å molecular sieves (14 g), and dichloromethane (40 mL) was treated with a solution of 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl bromide (9.7 g, 15 mmol) in dichloromethane (20 mL) and *N,N*-dimethylformamide (1.8 mL). After being stirred in the dark at room temperature for 72 h, the mixture was filtered, diluted with dichloromethane and methanol (10 mL), stirred for 1 h, washed with cold M hydrochloric acid, saturated aqueous sodium hydrogencarbonate, and water, dried, and concentrated, to give a syrup (10 g) that was subjected to column chromatography. Elution with 4:1 hexane–ethyl acetate removed the fast-moving impurities, and the main product was then eluted with 7:3 hexane–ethyl acetate. After further purification by column chromatography (19:1 benzene–ethyl acetate), the pure, main product **2** (0.55 g, 56%) was obtained. N.m.r. data ($CDCl_3$): ^1H (100 MHz), δ 7.30 (m, 25 H, 5 Ph), 5.80 (m, 1 H, =CH), and 5.20–3.20 (m, 28 H); ^{13}C (25.2 MHz), δ 134.2 (=CH), 117.2 ($=CH_2$), 100.0 (C-1), and 98.9 (C-1′).

A solution of **2** (1 g, 1.23 mmol), tris(triphenylphosphine)rhodium(I) chloride (80 mg, 0.09 mmol) and diazabicyclo[2.2.2]octane (30 mg, 0.28 mmol) in aqueous 90% ethanol (50 mL) was heated under reflux for 3 h, cooled, poured into water, and extracted with chloroform. The dried extract was concentrated to give a syrup that was purified by preparative t.l.c. (6:4 hexane–ethyl acetate), to afford pure **3** (0.80 g, 80%). ^1H-N.m.r. data (90 MHz, $CDCl_3$): δ 7.35 (m, 25 H, 5 Ph), 5.40–3.40 (m, 26 H), and 1.50 (m, 3 H, Me).

A mixture of **3** (0.80 g, 1 mmol) and yellow mercuric oxide (0.90 g, 4.1 mmol) in 10:1 acetone–water (30 mL) was treated with a solution of mercuric chloride (0.90 g, 3.3 mmol) in 10:1 acetone–water (10 mL). After 10 min, the mixture was filtered through Celite and concentrated, and a solution of the residue in chloroform was washed with aqueous potassium iodide, dried, and concentrated to give a syrup that was purified by preparative t.l.c. (7:3 hexane–ethyl acetate), to give pure **4** (0.60 g, 72%). N.m.r. data ($CDCl_3$): ^1H (100 MHz), δ 7.30 (m, 25 H, 5 Ph), and 5.30–3.60 (m, 24 H); ^{13}C (25.2 MHz), δ 100.1 (C-1), and 99.0 (C-1′).

To a mixture of **4** (0.36 g, 0.47 mmol), tetraethylammonium bromide (0.10 g, 0.47 mmol), 4 Å molecular sieves (1 g), and dichloromethane (15 mL) was added a solution of 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl bromide[16] (0.35 g, 1 mmol) in dichloromethane (15 mL) and *N,N*-dimethylformamide (15 drops). The mixture was stirred at room temperature in the dark. After 36 h, more fucopyranosyl

bromide (0.05 g, 0.23 mmol) was added and, after 72 h, the mixture was filtered, diluted with dichloromethane, treated with methanol (2 mL), stirred for 1 h, washed with cold M hydrochloric acid, aqueous sodium hydrogencarbonate, and water, dried, and concentrated. P.l.c. (7;3 hexane–ethyl acetate) of the syrupy residue gave pure **5** (0.34 g, 95%). N.m.r. data: ^{1}H (90 MHz), δ 7.30 (m, 40 H, 8 Ph), 5.40–3.30 (m, 36 H), and 1.20 (m, 3 H, Me); ^{13}C (25.2 MHz), δ 100.6 (C-1), 98.8 (C-1″), 98.0 (C-1′), and 16.6 (C-6′).

A mixture of **5** (0.19 g, 0.15 mmol), 10% Pd/C (0.19 g), and acetic acid (10 mL) was stirred under hydrogen for 24 h, filtered, and concentrated. The syrupy residue was treated with acetic anhydride (7 mL) and pyridine (7 mL). After 24 h, the mixture was concentrated to give **6** (0.09 g, 65%), m.p. 239–241° (from ethanol), $[\alpha]_D^{20}$ −14° (*c* 0.45, chloroform). For ^{1}H-n.m.r. data, see Table I. ^{13}C-N.m.r. data (90.5 MHz, $CDCl_3$): δ 100.5 (C-1), 97.5 (C-1″), 96.0 (C-1′), and 15.6 (C-6′).

Anal. Calc. for $C_{34}H_{46}O_{22}$: C, 50.73; H, 5.64. Found: C, 50.61; H, 5.74.

*1,4,6-Tri-*O*-acetyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-α-*D*-galactopyranosyl)-2-*O*-(2,3,4-tri-*O*-acetyl-α-*L*-fucopyranosyl)-*D*-galactopyranose* (**7**). — To a solution of **6** (0.071 g, 0.69 mmol) in 2:3 acetic anhydride–acetic acid (1.2 mL) was added 1:10 conc. sulfuric acid–acetic anhydride (0.22 mL). The mixture was kept at room temperature for 75 min, cooled in an ice bath, neutralised with aqueous 5% sodium hydrogencarbonate at 0°, and extracted with chloroform. The extracts were washed with water, dried, and concentrated to give the $\alpha\beta$-mixture **7** (0.060 g, 75%), m.p. 183–185° (from ethanol), $[\alpha]_D^{20}$ −7° (*c* 0.2, chloroform). N.m.r. data: ^{1}H (360 MHz, $CDCl_3$): δ 6.30 (d, 1 H, H-1α), 5.59 (d, 1 H, H-1β), and 1.03 (d, 3 H, Me); ^{13}C (90.5 MHz), δ 98.4 (C-1′), 93.5 (C-1β), 92.1 (C-1″), 90.3 (C-1α), and 15.1 (C-6′).

Anal. Calc. for $C_{38}H_{52}O_{25}$: C, 50.30; H, 5.47. Found: C, 50.21; H, 5.46.

*2-*O*-α-*L*-Fucopyranosyl-3-*O*-α-*D*-galactopyranosyl-*D*-galactopyranose* (**8**). — A solution of $\alpha\beta$-**7** (0.05 g, 0.06 mmol) in methanol (2.2 mL) was treated with methanolic 0.2M sodium methoxide (0.64 mL). After 30 min at room temperature, the mixture was neutralised with Amberlite IR-120 (H^+) resin, filtered, and concentrated. Treatment of the residue with ethanol gave amorphous **8** (0.026 g), $[\alpha]_D^{20}$ −34° (*c* 1.2, water); lit.[4] $[\alpha]_D$ −35° (*c* 1, water–methanol). ^{1}H-N.m.r. data (360 MHz, D_2O): δ 5.34 (d, 1 H, *J* 3.3 Hz), 5.18 (d, 1 H, *J* 3.2 Hz), 5.07 (d, 1 H, *J* 3.0 Hz), and 1.20 (d, 3 H, C-Me).

Anal. Calc. for $C_{18}H_{32}O_{15}$: C, 44.26; H, 6.61. Found: C, 44.31; H, 6.78.

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