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Note

Synthesis of 2-acetamido-2-deoxy-3-*O*-α-L-fucopyranosyl-D-glucose

KHUSHI LALL MATTA, EDWARD A. Z. JOHNSON, AND JOSEPH J. BARLOW
Department of Gynecology, Roswell Park Memorial Institute, Buffalo, New York 14203 (U. S. A.)
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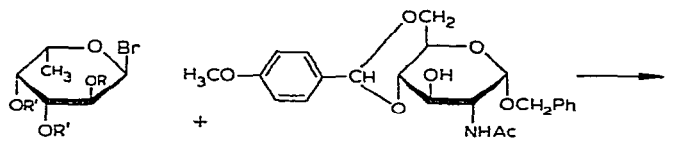
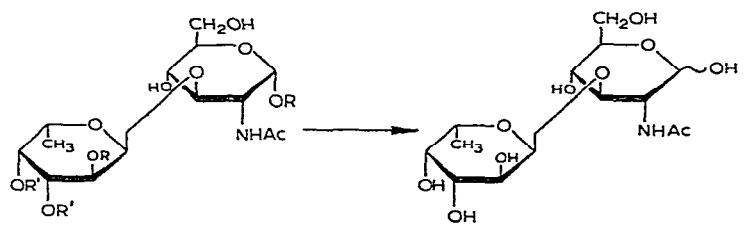
Oligosaccharides containing an α-L-fucopyranosyl moiety linked to a 2-acetamido-2-deoxy-D-glucopyranosyl residue have been isolated from various biological sources[1–4]. Hakomori and Jeanloz[5] have reported a glycolipid pentasaccharide from cancer tissues that also contains a 2-acetamido-2-deoxy-*O*-α-L-fucopyranosyl-D-glucose residue[5].

Our continued interest in disaccharides containing an *O*-α-L-fucopyranosyl group[6], in connection with work on the isolation and characterization of highly



1 { R = CH_2Ph ; R' = $C(=O)-C_6H_4-NO_2$ (*p*) }



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3 { R = CH_2Ph ; R' = $C(=O)-C_6H_4-NO_2$ (*p*) }

4 { R = CH_2Ph ; R' = H }

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specific α-L-fucosidases[7], has led to a facile synthesis of 2-acetamido-2-deoxy-3-*O*-α-L-fucopyranosyl-D-glucose.

Benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside[8], on condensation with *p*-methoxybenzaldehyde in the presence of anhydrous zinc chloride[9], provided the 4,6-acetal **2** in 65% yield. As the *O*-*p*-methoxybenzylidene group can be removed by 80% aqueous acetic acid at room temperature[9], the use of compound **2** was preferred over the known benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside, for which a higher temperature is required for removal of the acetal group. Compound **2** was treated with 2-*O*-benzyl-3,4-di-*O*-*p*-nitrobenzoyl-α-L-fucopyranosyl bromide[10] (**1**) in the presence of mercuric cyanide in 1:1 benzene–nitromethane. After deacetylation of the condensation product, the partially protected disaccharide **3** was isolated by column chromatography in 65% yield. Treatment of compound **3** with a catalytic amount of sodium methoxide in methanol afforded crystalline benzyl 2-acetamido-3-*O*-(2-*O*-benzyl-α-L-fucopyranosyl)-2-deoxy-α-D-glucopyranoside (**4**), which was hydrogenolyzed to give the desired disaccharide **5** as an amorphous material in high yield. The optical rotation of the synthetic disaccharide supported the α-L-configuration, and the purity of the compound was confirmed by t.l.c. and paper chromatography.

EXPERIMENTAL

Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Paper chromatograms were sprayed with sodium metaperiodate followed by ammoniacal silver nitrate[11]. Other experimental techniques have been previously described[6].

*Benzyl 2-acetamido-2-deoxy-4,6-*O*-(p-methoxybenzylidene)-α-D-glucopyranoside* (**2**). — A mixture of benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside (3.1 g), *p*-methoxybenzaldehyde (25 ml), and anhydrous zinc chloride (2 g) was shaken for 3 days at room temperature. The mixture was extracted with ether (3 × 150 ml) to remove excess *p*-methoxybenzaldehyde, and the residue was stirred with cold water (200 ml), filtered, washed with water, and air dried. Crystallization and recrystallization of the material from abs. methanol gave pure compound **2** (2.8 g, 65%); m.p. 265–268°, $[\alpha]_D^{25}$ +82.5° (*c* 1, pyridine); t.l.c. in 4:1 benzene–methanol, R_{FT} 0.49 (R_{FT} refers to mobility relative to 1,2,3,4-tetra-*O*-acetyl-α-L-fucose); ν_{max} 3400 (OH), 3290 (NH), 1660, 1550 (CONH), 1600, 1500, 740, and 694 cm^{-1} (aromatic).

Anal. Calc. for $C_{23}H_{27}NO_7$: C, 64.32; H, 6.34; N, 3.26. Found: C, 64.22; H, 6.60; N, 3.16.

*Benzyl 2-acetamido-3-*O*-(2-*O*-benzyl-3,4-di-*O*-p-nitrobenzoyl-α-L-fucopyranosyl)-2-deoxy-α-D-glucopyranoside* (**3**). — Compound **2** (0.86 g) in 1:1 nitromethane–benzene (200 ml) was boiled until approximately 50 ml of solvent mixture had distilled off and the mixture was then maintained at 50–54°. Mercuric cyanide (0.51 g) and bromide **1** (1.28 g) were introduced, and the mixture was stirred for 48 h. Further amounts of mercuric cyanide (0.25 g) and bromide **1** (0.64 g) were added, and the

mixture was stirred for another 48 h at the same temperature. The mixture was cooled and diluted with benzene (200 ml), washed successively with a cold, saturated solution of sodium hydrogen carbonate (3 × 50 ml), and water until neutral, dried (sodium sulfate), and evaporated to give a syrup (2.7 g).

The syrup was dissolved in glacial acetic acid (80 ml), which was then diluted with water (20 ml). The clear solution was stirred for 15 h at room temperature and then evaporated under diminished pressure. The last traces of acetic acid were expelled by evaporation of 1:1 toluene–ethanol from the residue. The residue was taken up in benzene (30 ml) and chromatographed on a column (55 × 2.5 cm) of silica gel. Elution was effected with benzene–ether (1:1, 400 ml) followed by 14:14:1 benzene–ether–methanol. Fractions having R_{FT} 0.64 were combined and evaporated to give a syrup (1.3 g), which was dissolved in chloroform (10–15 ml). The solution was diluted with anhydrous ether to incipient turbidity, and air was passed through until a few crystals appeared. Crystallization was allowed to proceed overnight at 0° to give compound **3** (1.1 g, 65%); m.p. 116–117°, $[\alpha]_D^{22}$ −100° (*c* 1, chloroform); R_{FT} 0.64 in 14:14:1 benzene–ether–methanol, 0.83 in 4:1 benzene–methanol; ν_{max} 3320–3420 (broad OH, NH), 1730 (ester), 1655, 1530 (amide), 1570, 1350 (nitro), 1600, 720, and 700 cm^{-1} (aromatic); n.m.r. data: τ 1.7–2.1 (multiplet, 8 H, *p*-nitrobenzoate groups), 2.65–2.80 (10 H, 2 C_6H_5), 8.1 (3 H, NAc) and 8.8 (doublet, 3 H, CH–CH_3, *J* 6.5 Hz).

Anal. Calc. for: $C_{42}H_{43}N_3O_{16}$: C, 59.64; H, 5.12; N, 4.97. Found: C, 59.37; H, 5.25; N, 4.93.

*Benzyl 2-acetamido 3-*O*-(2-*O*-benzyl*α*-*L*-fucopyranosyl)-2-deoxy-*α*-*D*-glucopyranoside* (**4**). — Compound **3** (0.5 g) was dissolved in abs. methanol (50 ml) containing a catalytic amount of sodium methoxide. The solution was kept for 24 h at 4°, neutralized with aqueous acetic acid, and evaporated to dryness. The solid residue was stirred for 2 h with water (150 ml) and ether (70 ml). The clear aqueous solution was separated and again extracted with ether to remove *p*-nitrobenzoic acid. It was stirred with Dowex 50W-X8 (H^+) for 30 min and then filtered and evaporated. The white, solid material (0.25 g) was crystallized from abs. ethanol (30 ml) to give compound **4** (0.2 g, 62%); m.p. 222–223°; $[\alpha]_D^{22}$ +36.9° (*c* 1, 50% aqueous ethanol). T.l.c. in (*a*) 3:2 benzene–methanol, R_{Fucose} 1.73; (*b*) in 13:6:1 chloroform–methanol–water, R_{Fucose} 2.2; (*c*) in 7:5:2 1-propanol–ethyl acetate–water, R_{Fucose} 1.51; ν_{max} 3400 (OH), 3300 (NH), 1650, 1540 (amide), 1495, 735, and 695 cm^{-1} (aromatic).

Anal. Calc. for $C_{28}H_{37}NO_{10}$: C, 61.41; H, 6.81; N, 2.56. Found: C, 61.19; H, 6.84; N, 2.51.

*2-Acetamido-2-deoxy-3-*O*-α-L-fucopyranosyl-*D*-glucopyranose* (**5**). — A portion of compound **4** (0.18 g) was dissolved in 92% ethanol (220 ml) and hydrogenolyzed in the presence of 10% palladium-on-charcoal (80 mg) at 50 $lb.in^{-2}$ for 72 h. The catalyst was removed by filtration through a Celite pad and the filtrate was evaporated. The residue was dissolved in 13:6:1 chloroform–methanol–water and chromatographed on a column (12 × 2.2 cm) of silica gel. The column was eluted with the same solvent, and 5-ml fractions were collected. Fractions 14–26 contained incompletely

hydrogenolyzed material. Fractions 42–70 (150 ml) gave on evaporation the desired compound **5** as an amorphous material (0.1 g, 79%), $[\alpha]_D^{22}$ −66.6° (*c* 1, water) [Rachaman and Jeanloz[12] reported $[\alpha]_E^{20}$ +11° (*c* 0.9, 60% methanol) for a 2-acetamido-2-deoxy-3-*O*-β-L-fucopyranosyl-D-glucopyranose]; ν_{max} 3320 (broad NH and OH), and 1630, 1535 cm^{-1} (amide).

Anal. Calc. for $C_{14}H_{25}NO_{10}\cdot H_2O$: C, 43.63; H, 7.06; N, 3.63. Found: C, 43.40; H, 6.90; N, 3.61.

The synthetic disaccharide was found to be homogeneous and distinguishable from 2-acetamido-2-deoxy-6-*O*-α-L-fucopyranosyl-D-glucose on t.l.c. in the aforementioned solvents *a–c* and on paper chromatography in *d* 6:4:3 butanol–pyridine–water and *e* 10:4:3 ethyl acetate–pyridine–water. The mobilities of the disaccharides relative to fucose (R_{Fucose}) are as follows.

Compound	*Chromatographic solvent*				
	a	*b*	*c*	*d*	*e*
2-acetamido-2-deoxy-3-*O*-α-L-fucopyranosyl-D-glucose	0.62	0.53	0.61	0.76	0.79
2-Acetamido-2-deoxy-6-*O*-α-L-fucopyranosyl-D-glucose	0.53	0.47	0.59	0.67	0.65

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