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Preliminary communication

A facile synthesis of benzyl 2-acetamido-6-*O*-acetyl-4-*O*-(6-*O*-acetyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-2-deoxy-β-D-glucopyranoside, a key intermediate for the synthesis of *O*-α-L-fucopyranosyl-(1→2)-*O*-β-D-galactopyranosyl-(1→4)-*O*-[α-L-fucopyranosyl-(1→3)]-2-acetamido-2-deoxy-D-glucopyranose*

SURJIT S. RANA and KHUSHI L. MATTA**

Department of Gynecologic Oncology, Roswell Park Memorial Institute, New York State Department of Health, Buffalo, New York 14263 (U.S.A.)

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Convenient and practical syntheses of complex saccharides having well defined structures that are generally a part of the carbohydrate moiety of glycoconjugates have been a challenge to carbohydrate chemists. Interest in the chemical synthesis of these molecules has greatly increased, as these synthetic oligosaccharides can be effectively employed in the study of glycosidases, glycosyltransferases, and lectins. Moreover, they can play an important role as synthetic antigens. In recent years, a battery of new catalysts along with different glycosylating agents[2] have proved to be effective in the chemical synthesis of various oligosaccharides.

For sequential synthesis of oligosaccharides, certain glycosylating agents having temporary and persistent protecting-groups have now become available. For rapid synthesis of saccharides, it is also important to develop facile methods for the preparation of appropriately protected sugar alcohols that are to be further glycosylated. In our laboratory, we have developed a practical and convenient methodology for the synthesis of *O*-α-L-fucopyranosyl-(1→2)-*O*-β-D-galactopyranosyl-(1→3)-*O*-[α-L-fucopyranosyl-(1→4)]-2-acetamido-2-deoxy-D-glucopyranose[3], the Lewis b blood-group antigenic determinant, from the readily accessible benzyl 2-acetamido-2-deoxy-3-*O*-β-D-galactopyranosyl-β-D-glucopyranoside[3]. In the present studies, we describe a facile procedure for preparation of the title compound, a key intermediate for a synthesis of *O*-α-L-fucopyranosyl-(1→2)-*O*-β-D-galactopyranosyl-(1→4)-*O*-[α-L-fucopyranosyl-(1→3)]-2-acetamido-2-deoxy-D-glucopyranose[4,5], which has been found to occur as part of the carbohydrate moiety of blood-group substances.

Alais and Veyrières[6] have now described a practical technique for the preparation of 2-acetamido-2-deoxy-4-*O*-β-D-galactopyranosyl-D-glucopyranose (*N*-acetyllactosamine) from the commercially available 3-*O*-β-D-galactopyranosyl-D-arabinose. The

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**To whom correspondence should be directed.

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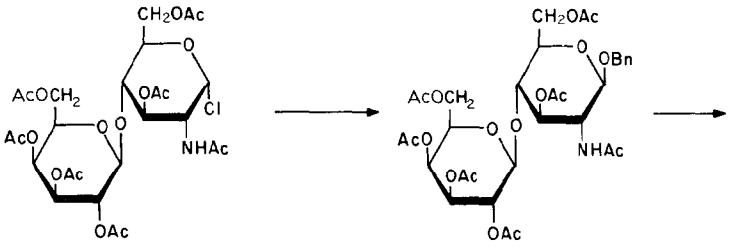
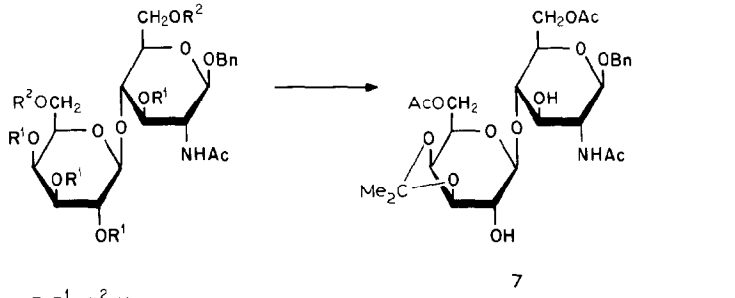
purified *N*-acetyllactosamine was conveniently converted into the acetylated sugar halide 1, as described by Kaifu and Osawa[7]. Treatment of halide **1** (5 g, 7.64 mmol) in benzene (20 mL) with benzyl alcohol (3.5 mL), in the presence of mercuric cyanide (3 g), afforded benzyl 2-acetamido-3,6-di-*O*-acetyl-2-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**2**) in 74% yield (4.1 g); amorphous; $[\alpha]_D$ −34.1° (*c* 1, chloroform); ^{1}H-n.m.r. data ($CDCl_3$): δ 1.90 (s, 3 H, NAc), 1.93, 2.03 and 2.10 (s each, 18 H, 6 OAc), and 7.25 (m, 5 H, aromatic). On *O*-deacetylation, compound **2** (3.5 g) gave benzyl 2-acetamido-2-deoxy-4-*O*-β-D-galactopyranosyl-β-D-glucopyranoside (**3**) in 83% yield (1.9 g); m.p. 265–266° (from methanol), $[\alpha]_D$ −23.2° (*c* 1.6, Me_2SO).

Anal. Calc. for $C_{21}H_{31}NO_{11}$: C, 53.27; H, 6.60; N, 2.96. Found: C, 53.24; H, 6.45; N, 2.76.





3 $R^1 = R^2 = H$
4 $R^1 = R^2 = SiMe_3$
5 $R^1 = SiMe_3$, $R^2 = Ac$
6 $R^1 = H$, $R^2 = Ac$
Bn = benzyl

A solution of **3** (2 g) in absolute pyridine (60 mL) was treated with hexamethyldisilazane (24 mL), followed by the addition of chlorotrimethylsilane[8] (10 mL). After being stirred for 24 h at 60°, the mixture was processed, to give the completely silylated derivative **4** (3.68 g) in 96% yield; amorphous; $[\alpha]_D$ −17.6° (*c* 2.6, chloroform); the i.r. spectrum showed the absence of hydroxyl group. Compound **4** (4.53 g, 5 mmol) in absolute pyridine (10 mL) and acetic anhydride (7.5 mL) was treated with glacial acetic acid (1.2 g, 20 mmol) at room temperature[9,10]; the course of the reaction was monitored by t.l.c. in 4:1 (v/v) ether–hexane. After 40 h, the mixture was processed, to give

a solid mass that was purified by chromatography on a column of silica gel, with elution with 4:1 (v/v) ether–hexane, to afford amorphous **5** (3.64 g, 86%): $[\alpha]_D$ −13.7° (*c* 2, chloroform). A mixture of compound **5** (4.35 g, 5.14 mmol) in methanol (25 mL) was exposed to the action of 30% acetic acid for 6 h at room temperature[9], to give benzyl 2-acetamido-6-*O*-acetyl-4-*O*-(6-*O*-acetyl-β-D-galactopyranosyl)-2-deoxy-β-D-glucopyranoside (**6**) in 84% yield (2.4 g); amorphous; $[\alpha]_D$ −15° (*c* 1.4, Me_2SO), ^{1}H-n.m.r. data (Me_2SO-d_6): δ 1.80 (s, 3 H, NAc), 1.97 and 2.03 (s each, 2 × 3 H, 2 OAc), 7.3 (m, 5 H, aromatic), and 7.77 (1 H, NH).

Anal. Calc. for $C_{25}H_{35}NO_{13}\cdot H_2O$: C, 52.16; H, 6.48; N, 2.43. Found: C, 51.96, H, 6.24; N, 2.42.

TABLE I

^{13}C-N.M.R. CHEMICAL SHIFTS[a]

Atom	*Compound*		
	3	6	7
C-1	100.38	100.19	98.99
C-2	54.65	54.45	56.58
C-3	72.03	71.74	72.56
C-4	81.27	80.46	80.77
C-5	74.94	72.64	72.99
C-6	60.39	62.98	63.43
CH_2Ph	69.41	69.56	70.65
$NCOCH_3$	22.93	22.82	23.39
$OCOCH_3$		20.37, 20.60	20.62, 20.95
$NHCOCH_3$	168.56	168.72	170.67
$OCOCH_3$		169.90, 170.05	170.92
C-1′	103.83	103.48	102.83
C-2′	70.49	69.83	71.46
C-3′	73.08	71.74	78.95
C-4′	68.06	68.01	72.99
C-5′	75.45	72.29	72.99
C-6′	60.39	63.21	63.18

[a] Solvent was Me_2SO-d_6, except for $CDCl_3$ for 7. Chemical shifts in p.p.m. downfield from Me_4Si (internal) at 25.2 MHz.

Isopropylidenation[11] of compound **6** (2 g, 3.6 mmol) with 2,2-dimethoxypropane (4 mL) in *N*,*N*-dimethylformamide in the presence of *p*-toluenesulfonic acid (30 mg) for 1 h at 60° gave a solid mass which was purified by chromatography on a column of silica gel with elution with 19:1 (v/v) chloroform–methanol, to give amorphous **7** (1.4 g) in 65.3% yield; $[\alpha]_D$ +3.1° (*c* 1.2, chloroform); ^{1}H-n.m.r. data ($CDCl_3$): δ 1.3 and 1.47 (2 s, 2 × 3 H, isopropylidene methyls), 1.93 (s, 3 H, NAc), 2.03 and 2.07 (s each, 2 × 3 H, 2 OAc), 5.70 (d, 1 H, $J_{NH,2}$ 7 Hz, NH), and 7.3 (m, 5 H, aromatic). The ^{13}C-n.m.r. spectrum exhibited resonance for the acetal carbon atom at 110.45 p.p.m.,

and the chemical shifts for the methyl groups (26.21 and 28.01 p.p.m.) were slightly separated, thereby supporting the presence of a five-membered[12], cyclic ring.

Anal. Calc. for $C_{28}H_{39}NO_{13}$: C, 56.27; H, 6.58; N, 2.34. Found: C, 56.06; H, 6.47; N, 2.13.

Starting from benzyl 2-acetamido-3-*O*-allyl-6-*O*-benzyl-2-deoxy-α-D-glucopyranoside as the key intermediate, Jacquinet and Sinaÿ[5] accomplished the synthesis of *O*-α-L-fucopyranosyl-(1→2)-*O*-β-D-galactopyranosyl-(1→4)-*O*-[α-L-fucopyranosyl-(1→3)]-2-acetamido-2-deoxy-α-D-glucopyranose. As this "aglycon", as well as the glycosylating reagent 3,4,6-tri-*O*-benzyl-1,2-*O*-(*tert*-butoxyethylidene)-α-D-galactopyranose employed in their synthetic methodology, involve multisteps for their preparation, we consider that synthetic diol 7 may prove to be a suitable, key intermediate for the facile synthesis of *O*-α-L-fucopyranosyl-(1→2)-*O*-β-D-galactopyranosyl-(1→4)-*O*-[α-L-fucopyranosyl-(1→3)]-2-acetamido-2-deoxy-D-glucopyranose. According to our preliminary investigations, L-fucosylation of 7 with 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl bromide, under catalysis by bromide ion[13], afforded mono-fucosylated product.

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