STUDIES ON THE KOENIGS–KNORR REACTION

PART II. SYNTHESIS OF AN α-L-LINKED DISACCHARIDE FROM TRI-*O*-BENZYL-α-L-FUCOPYRANOSYL BROMIDE

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ABSTRACT

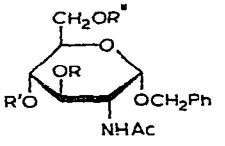
Methyl α-L-fucopyranoside was converted into 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl bromide *via* the intermediates methyl 2,3,4-tri-*O*-benzyl-α-L-fucopyranoside and 2,3,4-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-β-L-fucopyranose. Koenigs–Knorr condensation of the bromide with benzyl 2-acetamido-3,4-di-*O*-acetyl-2-deoxy-α-D-glucopyranoside and removal of protecting groups afforded 2-acetamido-2-deoxy-6-*O*-α,β-L-fucopyranosyl-D-glucose in 65% yield, the product containing a 7:3 ratio of α to β anomers. Optically pure 2-acetamido-2-deoxy-6-*O*-α-L-fucopyranosyl-D-glucose was obtained by hydrogenolysis of the intermediate crystalline benzyl 2-acetamido-2-deoxy-6-*O*-(tri-*O*-benzyl-α-L-fucopyranosyl)-α-D-glucopyranoside.

INTRODUCTION

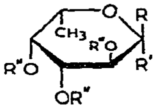
In a previous paper[1], it was reported that the anomeric configuration of the halide employed in the Koenigs–Knorr reaction had no effect on the products obtained by condensation with two different monosaccharides, one of which was a reactive, primary alcohol and the other was a less reactive, secondary alcohol. Glycosyl halides having non-participating groups at C-2 have been employed in the syntheses of α-1,2-*cis*-linked disaccharides[2], and a number of reactions have been performed with those in which all the substituent groups in the halide could be regarded as non-participating, to yield mainly α-linked disaccharides or glycosides[3–6]. In other words, there was a marked degree of stereoselectivity of reaction under the conditions employed. The configuration of the product was largely independent of that of the glycosyl halide, and this fact was adduced as support for the premise that the latter had dissociated into an ion-pair during the course of the reaction. However, a particular configuration of such an ion-pair would be required to favour the formation of one particular anomer. Any explanation for the stereospecificity observed requires the involvement of some process or group to stabilize a chosen configuration at C-1 of the halide so as to direct the incoming nucleophile. In any program for preparation of α-1,2-*cis*-linked disaccharides, it is of importance to elucidate the factors involved in this stereochemical direction.

α-L-Fucosyl disaccharides are of considerable interest biologically and have been isolated from a number of natural products[7–9]. Syntheses of two of these compounds from tri-*O*-acetyl-α-L-fucopyranosyl bromide have been described[10,11], but attempts to extend the reaction led to formation of the β-L anomer[12]. We are at present investigating the effect of different positions of substitution (in the hexopyranosyl ring) of potentially participating groups on the stereochemistry of the product of the reaction of glycosyl halides with carbohydrates. This paper will describe the preparation and behaviour in the Koenigs–Knorr reaction of tri-*O*-benzyl-α-L-fucopyranosyl bromide. Later papers will show the effect on the configuration of the products by the nature and position of substituents in the fucopyranosyl ring.

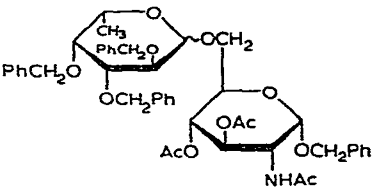
The aglycon employed, benzyl 2-acetamido-3,4-di-*O*-acetyl-2-deoxy-α-D-glucopyranoside (**1**), was selected as an example of a relatively reactive nucleophile. The disaccharide synthesized, 2-acetamido-2-deoxy-6-*O*-α-L-fucopyranosyl-D-glucose (**11**), has been isolated from the partial, acid hydrolyzate of blood-group glycoprotein[13].



1 $R = R' = Ac; R'' = H$
2 $R = R' = Ac; R'' = Tr$
3 $R = Ac$ $R' = R'' = H$
4 $R = R'' = Ac; R' = H$



5 $R = OMe; R' = H; R'' = CH_2Ph$
6 $R = OH; R' = H; R'' = CH_2Ph$
7 $R = H; R' = O_2CC_6H_4NO_2; R'' = CH_2Ph$
8 $R = Br; R' = H; R'' = CH_2Ph$



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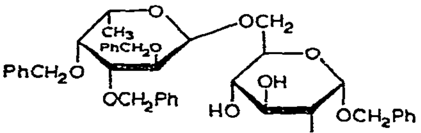

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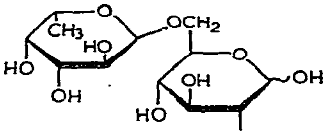

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ERSULTS AND DISCUSSION

Benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside[14] was converted into benzyl 2-acetamido-3,4-di-*O*-acetyl-2-deoxy-6-*O*-trityl-α-D-glucopyranoside (**2**) by selective triphenylmethylation, followed by acetylation without isolation of the intermediate trityl ether. The purified product showed the expected n.m.r. spectrum, the chemical shift of the 4-*O*-acetyl protons being affected markedly by the neighboring trityl group[15]. Detritylation, achieved by means of a solution of hydrogen bromide in acetic acid, gave benzyl 2-acetamido-3,4-di-*O*-acetyl-2-deoxy-α-D-glucopyranoside (**1**). Reconversion of a portion of **1** into **3** under mild conditions showed that the hydroxyl group at C-6 in **1** was indeed unsubstituted. Furthermore, benzyl 2-acetamido-3-*O*-

acetyl-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside[16], prepared by acetylation of benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside[14], was hydrolyzed selectively to afford benzyl 2-acetamido-3-*O*-acetyl-2-deoxy-α-D-glucopyranoside[17] (**3**). Selective acetylation of **3** yielded a crystalline solid which was different from **1** and to which was assigned the structure of benzyl 2-acetamido-3,6-di-*O*-acetyl-2-deoxy-α-D-glucopyranoside (**4**) on the basis of its elemental analysis, n.m.r. spectrum, and the known preferential reactivity of the hydroxyl group at C-6 in hexopyranosides[18].

Methyl 2,3,4-tri-*O*-benzyl-α-L-fucopyranoside (**5**) was prepared in almost quantitative yield by benzylation of methyl α-L-fucopyranoside[19]. Compound **5** could be obtained from L-fucose in an overall yield of 70% without isolation of the intermediate methyl α-L-fucopyranoside. After mild acid hydrolysis, it gave 2,3,4-tri-*O*-benzyl-α-L-fucose (**6**) in excellent yield. Esterification of **6** with *p*-nitrobenzoyl chloride in pyridine afforded 2,3,4-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-β-L-fucopyranose (**7**), the anomeric configuration of the product being assigned on the basis of its optical rotation and n.m.r. spectrum. Brief treatment of **7** with a solution of hydrogen bromide in dichloromethane converted it into tri-*O*-benzyl-α-L-fucopyranosyl bromide (**8**) which was isolated as a syrup. The product was not completely pure as shown by t.l.c., and it was assigned the α-L-configuration on the basis of its optical rotation and n.m.r. spectrum.

The Koenigs–Knorr reaction of **8** with the aglycon **1** in the presence of mercuric cyanide in 1:1 nitromethane–benzene solution afforded a good yield of benzyl 2-acetamido-3,4-di-*O*-acetyl-2-deoxy-6-*O*-(tri-*O*-benzyl-L-fucopyranosyl)-α-D-glucopyranoside (**9**). The anomeric configuration of **9** was not clear from its 60 MHz n.m.r. spectrum, and the optical rotation of the crystalline product was intermediate between that expected for an α-L- and that for a β-L-fucopyranoside. Compound **9** represented the only disaccharide produced in the reaction. After catalytic deacylation, crystallization from methanol gave, in low yield, pure benzyl 2-acetamido-2-deoxy-6-*O*-(tri-*O*-benzyl-α-L-fucopyranosyl)-α-D-glucopyranoside (**10**). The major part of the product remaining in the mother liquor was a mixture of the α- and β-L-fucopyranosides (see next paragraph). Pure **10** was hydrogenolyzed catalytically, and the product separated chromatographically from incompletely hydrogenolyzed material. 2-Acetamido-2-deoxy-6-*O*-α-L-fucopyranosyl-D-glucose (**11**) was isolated as an amorphous solid with a strongly negative optical rotation. A sample of crude **10**, before crystallization, was also hydrogenolyzed, and the resulting disaccharide could not be distinguished from **11** on t.l.c. and paper chromatography. However, the optical rotations of the two products were clearly different. On reduction with sodium borohydride in water, pure **11** and the corresponding mixture afforded sugar alcohols which were converted into their per(trimethylsilyl) ethers and analyzed by g.l.c. The ether obtained from pure **11** showed a single, sharp peak (T_S 1.96), whereas that from the material which had not been crystallized showed two peaks, T_S 1.96 (70%, α) and T_S 2.4 (30%, β).

Attempts to separate the two anomers of the disaccharide directly by chromatographic methods failed. Fractional crystallization afforded the substituted α-L-fucopyranoside **10**, but the yield was low and most of **10** remained admixed with its β-anomer. The bromide **8** used was thus not a suitable precursor for the preparation of pure α-L- linked disaccharide under the condensation conditions employed. The ratio of anomers produced during the Koenigs–Knorr reaction (70% α: 30% β) was similar to that obtained by other workers using a different acid-acceptor[5,6] and indicated moderate stereospecificity.

EXPERIMENTAL

For General Methods, see Ref. 1.

*Benzyl 2-acetamido-3,4-di-*O*-acetyl-2-deoxy-6-*O*-trityl-α-*D*-glucopyranoside* (**2**). — A stirred solution of benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside[14] (10.0 g) in dry pyridine (100 ml) was evaporated until *ca.* 20 ml of the solvent had distilled to ensure complete dehydration, and then cooled to room temperature. Chlorotriphenylmethane (10.0 g) was added, and the mixture was kept overnight at room temperature. After dilution with chloroform and successive washings with cold solutions of M hydrochloric acid and saturated sodium hydrogen carbonate, and finally with water, the organic layer was dried with calcium chloride and concentrated *in vacuo*. Pyridine (50 ml) and acetic anhydride (50 ml) were added to the dry residue, and the mixture was kept overnight at room temperature. Methanol was added with cooling, and the solution was concentrated *in vacuo*. The residue was dissolved in benzene and the solution was passed through a column of silica gel. After elution of non-carbohydrate-containing impurities with benzene, 14:14:1 benzene–ether–methanol eluted a homogeneous fraction (t.l.c.), which was crystallized from acetone–ether to give 11.0 g (55%), m.p. 145–147°, $[\alpha]_D^{25}$ +100° (*c* 1.05, chloroform); n.m.r. data: τ 2.46–2.71 (20 H, 4 Ph), 8.02 (3 H, 3-OAc), 8.11 (3 H, NAc), and 8.28 (3 H, 4-OAc)[15].

Anal. Calc. for $C_{38}H_{39}NO_8$: C, 71.57; H, 6.16. Found: C, 72.02; H, 6.16.

*Benzyl 2-acetamido-3,4-di-*O*-acetyl-2-deoxy-α-*D*-glucopyranoside* (**1**). — A solution of **2** (10.0 g) in glacial acetic acid (100 ml) was cooled to 15° and a 45% solution of hydrogen bromide in glacial acetic acid (4.5 ml) was added. The mixture was shaken for 90 sec and quickly filtered into ice–water, and the precipitate was washed with glacial acetic acid (10 ml). The filtrate and washings were extracted thrice with chloroform, the combined extracts were washed thrice with water and the solvent removed by evaporation *in vacuo*. The dry residue was crystallized from acetone–ether to give 4.5 g (72%), m.p. 165–167°, $[\alpha]_D^{26}$ +125° (*c* 1.07, chloroform); n.m.r. data: τ 2.61 (5 H, Ph), 7.92 and 7.96 (6 H, 3 and 4-OAc), and 8.10 (3 H, NAc).

Anal. Calc. for $C_{19}H_{25}NO_8$: C, 57.71; H, 6.37. Found: C, 57.80; H, 6.32. Triphenylmethylation of a portion of this product with chlorotriphenylmethane in pyridine during 24 h at room temperature afforded a material identical with **2** on t.l.c.; m.p. 145–147° after purification by chromatography and crystallization from acetone–ether.

*Benzyl 2-acetamido-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-α-*D*-glucopyranoside*[16] — A solution of benzyl 2-acetamido-4,6-*O*-benzylidene-α-D-glucopyranoside[14] (4.0 g) in 1:1 acetic anhydride–pyridine (50 ml) was kept overnight at room temperature. The mixture was poured onto crushed ice, and the crystalline precipitate which formed after a few minutes was separated by filtration, washed with water, dried, and recrystallized from ethyl acetate, 4.0 g (90%), m.p. 208–210°, $[\alpha]_D^{25}$ +90.0° (*c* 2.00, methanol); lit.[16]: m.p. 198–200°, $[\alpha]_D^{25}$ +82° (*c* 1.0, pyridine).

Anal. Calc. for $C_{24}H_{27}NO_7$: C, 65.29; H, 6.17; N, 3.17. Found: C, 65.10; H, 6.13; N, 2.80.

Benzyl 2-acetamido-3-O-acetyl-2-deoxy-α-D-glucopyranoside[17] (3). — A mixture of the compound described in the preceding paragraph (2.0 g) and 60% acetic acid (20 ml) was kept for 30 min. at 95–100°. The resulting clear solution was diluted with water (50 ml) and concentrated to a few ml *in vacuo*. A further portion of water was added, and the solution concentrated *in vacuo* to a syrup which was essentially homogeneous (t.l.c.). It crystallized from acetone–ether, 1.4 g (87%), m.p. 118–119°, $[\alpha]_D^{27}$ +116.7° (*c* 0.96, chloroform); lit.[17]: m.p. 119–121°, $[\alpha]_D^{25}$ +132° (pyridine).

Anal. Calc. for $C_{17}H_{23}NO_7$: C, 57.77; H, 6.56; N, 3.99. Found: C, 57.47; H, 6.80; N, 4.12.

Benzyl 2-acetamido-3,6-di-O-acetyl-2-deoxy-α-D-glucopyranoside (4). — A solution of 3 (1.4 g, 4 mmoles) in pyridine (4 ml) was cooled to 0°, and acetic anhydride (0.40 g, 4 mmoles) was added to the stirred solution. After 2 h at room temperature, the solution was cooled and methanol (5 ml) added cautiously. T.l.c. in 9:1 benzene–methanol showed that most of the original 3 had been converted into a material having R_3 2.0. A weak spot also appeared which migrated faster. The solvent was removed *in vacuo*, and the residue was dissolved in benzene and purified by chromatography on silica gel. Benzene–ether (4:1) eluted a small amount of material (60 mg, 5%) which was shown to be benzyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranoside[16] by comparison of the m.p., optical rotation, elemental analysis, and n.m.r. spectrum. Ether–ethyl acetate (9:1) eluted 1.32 g (84%) as a syrup which crystallized spontaneously. Recrystallization from acetone–ether afforded needles, m.p. 90–100°, $[\alpha]_D^{26}$ +81° (*c* 1.6, chloroform).

Anal. Calc. for $C_{19}H_{25}NO_8$: C, 57.71; H, 6.37 ;N, 3.54. Found: C, 57.50; H, 6.32; N, 3.58.

Methyl 2,3,4-tri-O-benzyl-α-L-fucopyranoside (5). — A mixture of methyl α-L-fucopyranoside[19] (5.0 g), benzyl chloride (40 ml), toluene (60 ml), and powdered potassium hydroxide (15 g) was stirred for 5 h at 100°. After dilution with toluene, the mixture was washed several times with water, the organic layer was concentrated *in vacuo*, and residual benzyl chloride and dibenzyl ether were removed by repeated addition and evaporation of large amounts of water. Finally, the product was dried by addition and evaporation of toluene and dissolved in benzene, and the solution was passed through a column of silica gel. Benzene–ether (4:1) eluted a homogeneous material (t.l.c., R_F 0.7) which could not be crystallized, 10 g (80%), $[\alpha]_D^{28}$ −20° (*c* 1.02, chloroform); n.m.r. data: τ 2.71 (15 H, 3 Ph), 6.68 (3 H, OMe), and 8.88 (doublet, *J* 6.5 Hz, 3 H, CH–Me).

2,3,4-Tri-O-benzyl-α-L-fucopyranose (6). — A solution of 5 (5.0 g) in 80% acetic acid (80 ml) and M hydrochloric acid (25 ml) was kept for 2 h at 95–100°. After cooling, the reaction mixture was extracted with chloroform, and the chloroform solution was washed with a cold saturated solution of sodium hydrogen carbonate and water, dried with calcium chloride, and concentrated *in vacuo*. The product (4.2 g, 88%) was crystallized from ether–hexane, m.p. 102–103°, $[\alpha]_{\mathrm{D}}^{25}$ $-26.5°$ (*c* 1.00, chloroform); n.m.r. data: τ 2.68 (15 H, 3 Ph), 4.73 (doublet, *J* 3 Hz, H-1), and 8.88 (doublet, *J* 6.5 Hz, 3 H, CH–Me).

Anal. Calc. for $C_{28}H_{32}O_5$: C, 74.97; H, 7.19. Found: C, 75.22; H, 6.90.

*2,3,4-Tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-β-L-fucopyranose* (**7**). — Pyridine (5 ml) and *p*-nitrobenzoyl chloride (2.1 g) were added to a cooled solution of **6** (4.0 g) in dichloromethane (100 ml). The reaction mixture was kept overnight at room temperature and washed successively with cold hydrochloric acid, water, a cold saturated solution of sodium hydrogen carbonate, and water, dried with calcium chloride, and concentrated *in vacuo*. The solid product (4.8 g, 92%) was crystallized from methanol, m.p. 120–122°, $[\alpha]_{\mathrm{D}}^{25}$ $+29.4°$ (*c* 1.0, chloroform); n.m.r. data: A doublet at τ 4.16 (*J* 8 Hz, H-1) indicated the β-L configuration at C-1.

Anal. Calc. for $C_{34}H_{33}NO_8$: C, 69.97; H, 5.70. Found: C, 70.21; H, 5.85.

*Tri-*O*-benzyl-α-L-fucopyranosyl bromide* (**8**). — A saturated solution of hydrogen bromide in dichloromethane (14 ml) was added to a solution of **7** (4 g) in dichloromethane (100 ml). After 15 min at room temperature, the precipitated *p*-nitrobenzoic acid was removed by filtration, and the solution was washed with a cold saturated solution of sodium hydrogen carbonate and with cold water until neutral, dried with calcium chloride, and evaporated *in vacuo* to a syrup (3.2 g, 92%). Examination of this product by t.l.c. (4:1 benzene–ether) showed that the compound was contaminated with a little unchanged **7**, $[\alpha]_{\mathrm{D}}^{26}$ $-120°$ (*c* 1.00, chloroform); n.m.r. data: the spectrum showed the α-L configuration with no indication of the presence of β-L configuration (τ 3.44, *J* 2.5 Hz, H-1).

*Benzyl 2-acetamido-3,4-di-*O*-acetyl-2-deoxy-6-*O*-(tri-*O*-benzyl-L-fucopyranosyl)-α-D-glucopyranoside* (**9**). — A stirred solution of **1** (1.5 g, 3.8 mmoles) in 1:1 nitromethane–benzene (60 ml) was boiled until *ca.* 20 ml of the solvent mixture had distilled to ensure complete dehydration, and then cooled to room temperature. Mercuric cyanide (1.0 g, 3.8 mmoles) and the bromide **8** (1.9 g, 3.8 mmoles) were added, and the reaction mixture was kept for 48 h at room temperature, a further addition of the bromide (0.9 g) being made after 24 h. The mixture was diluted with benzene (50 ml), and washed with a cold, saturated solution of sodium hydrogen carbonate and with water, dried, and concentrated *in vacuo*. The residue was dissolved in benzene and chromatographed on silica gel. Fractions that were eluted with 1:1 benzene–ether and were identical and homogeneous on t.l.c. were combined to give a syrup, 1.97 g (65%). A portion was crystallized from ether, m.p. 114–118°, $[\alpha]_{\mathrm{D}}{}^{6}$ $+44.2°$ (*c* 1.00, chloroform); the mother liquor showed $[\alpha]_{\mathrm{D}}^{26}$ $+42°$ (*c* 1.03, chloroform); n.m.r. data: τ 2.7 (20 H, 4 Ph), 8.0 (6 H, 2 OAc), 8.12 (3 H, NAc), and 8.88 (doublet, *J* 6.5 Hz, 3 H, CH–Me).

Anal. Calc. for $C_{46}H_{53}NO_{12}$: C, 68.05; H, 6.58. Found: C, 68.24; H, 6.55.

*Benzyl 2-acetamido-2-deoxy-6-*O*-(tri-*O*-benzyl-α-*L*-fucopyranosyl)-α-*D*-glucopyranoside* (**10**). — A portion of **9** (1.5 g) was dissolved in anhydrous methanol containing a catalytic amount of sodium methoxide, and the reaction mixture was kept for 1 h at 60°, cooled, neutralized with a drop of aqueous acetic acid (25%), and concentrated *in vacuo*. The residue was dissolved in chloroform, and the chloroform solution was extracted several times with water, dried with calcium chloride, and concentrated *in vacuo* to afford 1.25 g (90%) of a solid, $[\alpha]_D^{26}$ +17.3° (*c* 1.02, chloroform). The product was crystallized from methanol; yield 0.13 g (10%), m.p. 165–168°, $[\alpha]_D^{26}$ +7° (*c* 1.00, chloroform); $[\alpha]_D^{26}$ of the mother liquor +30° (*c* 1.05, chloroform); n.m.r. data: τ 2.72 (20 H, 4 Ph), 8.10 (3 H, NAc), and 8.89 (doublet, *J* 6.5 Hz; 3 H, CH-Me).

Anal. Calc. for $C_{42}H_{49}NO_{10}$: C, 69.31; H, 6.79. Found: C, 69.10; H, 6.69.

*2-Acetamido-2-deoxy-6-*O*-α-*L*-fucopyranosyl-*D*-glucose* (**11**). — A portion of crystallized **10** (100 mg) was dissolved in ethanol (90%, v/v, 50 ml) and hydrogenolyzed in the presence of palladium-on-charcoal (10%) for 48 h at 3.3 atm. The catalyst was removed by filtration, and the solvent was evaporated *in vacuo*. The resulting solid was dissolved in 13:6:1 chloroform–methanol–water and chromatographed on silica gel. Earlier fractions contained apparently incompletely hydrogenolyzed material and were not investigated further. Later fractions eluted from the column gave 44 mg (80%) of **11**, homogeneous on t.l.c. in 3:3:2 2-propanol–ethyl acetate–water and 13:6:1 chloroform–methanol–water and on paper chromatography in 8:2:1 ethyl acetate–pyridine–water (R_{fucose} 0.36), 25:25:6 butyl alcohol–acetic acid–water (R_{fucose} 0.59), and 7:1:2 propyl alcohol–ethyl acetate–water (R_{fucose} 0.75). The solid product could not be crystallized, $[\alpha]_D^{25}$ −66° (*c* 1.00, water). Rachaman and Jeanloz[12] reported $[\alpha]_D^{20}$ +31→29° (*c* 0.8, 70% ethanol) for the β-L linked disaccharide.

Anal. Calc. for $C_{14}H_{25}NO_{10}\cdot H_2O$: C, 43.63; H, 7.06. Found: C, 43.74; H, 7.13.

A portion of **11** (10 mg) was reduced to the sugar alcohol by treatment of an aqueous solution with excess sodium borohydride overnight, followed by neutralization of the excess borohydride with glacial acetic acid, treatment with Amberlite IR-120 (H^+), concentration *in vacuo*, and several additions and evaporations of methanol to remove borate ions. The disaccharide alcohol was finally dried and converted into the per(trimethylsilyl) ether. G.l.c. of this derivative showed one sharp peak with T_S 1.96.

*2-Acetamido-2-deoxy-6-*O*-α,β-*L*-fucopyranosyl-*D*-glucose.* — A portion of crude **10** was hydrogenolyzed and the disaccharide isolated, $[\alpha]_D^{25}$ −21.4° (*c* 1.00, water). The per(trimethylsilyl) derivative of the sugar alcohol was analyzed by g.l.c. Two peaks were obtained: T_S 1.96 (70%) and T_S 2.4 (30%).

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