STUDIES ON THE KOENIGS–KNORR REACTION

PART III. A STEREOSELECTIVE SYNTHESIS OF 2-ACETAMIDO-2-DEOXY-6-*O*-α-L-FUCOPYRANOSYL-D-GLUCOSE

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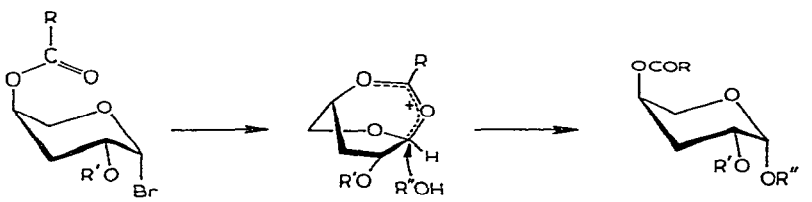
ABSTRACT

Crystalline 2-*O*-benzyl-α-L-fucose was prepared by hydrolysis of methyl 2-*O*-benzyl-3,4-*O*-isopropylidene-α-L-fucopyranoside and converted into 2-*O*-benzyl-3,4-di-*O*-*p*-nitrobenzoyl-α-L-fucopyranosyl bromide *via* the crystalline tri-*p*-nitrobenzoate. Koenigs–Knorr reaction of the bromide with benzyl 2-acetamido-3,4-di-*O*-acetyl-2-deoxy-α-D-glucopyranoside gave an almost stereospecific condensation. The disaccharide produced was almost pure α-L-fucoside, as shown by removal of protecting groups, reduction of the product to the corresponding disaccharide alcohol, and analysis of its per(trimethylsilyl) ether by gas–liquid chromatography. Catalytic deacylation of the product of the Koenigs–Knorr reaction afforded crystalline, optically pure benzyl 2-acetamido-2-deoxy-6-*O*-(2-*O*-benzyl-α-L-fucopyranosyl)-α-D-glucopyranoside, which was converted into 2-acetamido-2-deoxy-6-*O*-α-L-fucopyranosyl-D-glucose by catalytic hydrogenolysis.

INTRODUCTION

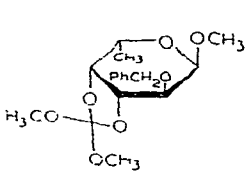
In previous publications[1,2] it has been shown that α-linked disaccharides can be prepared by reaction of aglycons with bromides bearing a non-participating group at C-2. A mechanism of the Koenigs–Knorr reaction involving an intermediate carbonium ion would be expected to predict the formation of equimolecular amounts of α and β anomers if no additional stereochemical-directing effects were involved. Participation of the substituent at C-2 would lead to "*trans*" (β-L-)-glycosides from substituted L-fucopyranosyl bromides, whereas "*cis*" (α-L)-fucopyranosides would result from processes involving direction of the incoming nucleophile to a glycosyl



SCHEME 1

carbonium ion which has been stabilized by participation of a substituent on the β-side of the molecule (Scheme I). In this way, participation of a 4-*O*-acyl group in a substituted fucopyranosyl carbonium ion could facilitate the formation of α-L-fucopyranosides.

Since 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl bromide undergoes a Koenigs–Knorr type reaction with a low degree of stereoselectivity[2], it was of interest to examine the effect of potentially participating groups at C-4 of the halide. As a first approach, we examined the combined effects of acyl substituents at C-3 and C-4 in the glycosyl halide.



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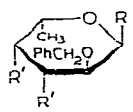
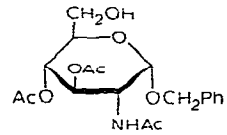


2 R = R′ = OH
3 R = R′ = *p*-O_2N-C_6H_4-CO_2
4 R = Br, R′ = *p*-O_2N-C_6H_4-CO_2



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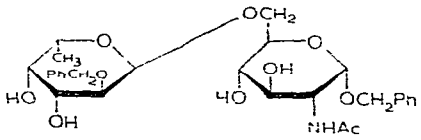

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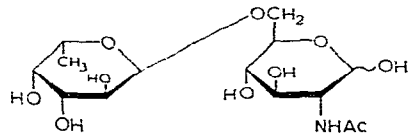

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RESULTS AND DISCUSSION

Hydrolysis of syrupy methyl 2-*O*-benzyl-3,4-*O*-isopropylidene-α-L-fucopyranoside (**1**), prepared from methyl 3,4-*O*-isopropylidene-α-L-fucopyranoside[3], gave crystalline 2-*O*-benzyl-L-fucose (**2**). This product showed a m.p. and a numerical value of optical rotation very similar to those described for 2-*O*-benzyl-α-D-fucose[4] and thus, was, probably the α-L anomer. The tri-*p*-nitrobenzoate was shown to be an anomeric mixture from which the pure α-L anomer (**3**) could be isolated by careful recrystallization from ethyl acetate. The anomeric mixture was converted into 2-*O*-benzyl-3,4-di-*O*-*p*-nitrobenzoyl-α-L-fucopyranosyl bromide (**4**) by treatment with hydrogen bromide in methylene chloride[2].

The bromide **4**, slightly contaminated, could not be obtained in crystalline form, but its highly negative optical rotation was indicative of the α-L-anomeric configuration, and no peak due to the β-L anomer could be detected in the n.m.r. spectrum. Reaction of **4** with benzyl 2-acetamido-3,4-di-*O*-acetyl-2-deoxy-α-D-glucopyranoside[2] (**5**) in nitromethane–benzene solution in the presence of mercuric cyanide, followed by removal of the protecting groups, gave in good yield, the disaccharide 2-acetamido-2-deoxy-6-*O*-L-fucopyranosyl-D-glucose. The product was

reduced with sodium borohydride to the sugar alcohol which was converted into its per(trimethylsilyl) ether and analyzed by g.l.c. The peaks due to α- and β-linked disaccharides were clearly separated and the ratio of the anomers in the originally synthesized disaccharide could be calculated (α to β 19:1), showing the high stereoselectivity of reaction.

Pure benzyl 2-acetamido-2-deoxy-6-*O*-(2-benzyl-α-L-fucopyranosyl)-α-D-glucopyranoside (**6**) was obtained in 40% yield after catalytic deacylation of the Koenigs–Knorr condensation product and recrystallisation from methanol. It afforded the optically pure disaccharide, 2-acetamido-2-deoxy-6-*O*-α-L-fucopyranosyl-D-glucose (**7**), on catalytic hydrogenolysis.

The overall yield (36%) of pure α-linked disaccharide from **5** was good, and the separation from the contaminating β-anomer was much more convenient than that previously described[2] involving 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl bromide. The high stereoselectivity of the Koenigs–Knorr reaction of bromide **4** resulting in the marked formation of the α-linked anomer (*cis* to the substituent at C-2) would support the hypothesis that the substituent at C-4 does participate in this reaction to stabilize the intermediate carbonium ion and direct the attacking nucleophile to the opposite side of the molecule, as illustrated in Scheme 1.

In order to separate the possible effects of C-3 and C-4 substituents, it will be necessary to synthesize bromides selectively substituted at these positions and to determine the configuration of the disaccharides obtained from them.

EXPERIMENTAL

General. — The methods have been previously reported[1]. The solvents used for t.l.c. were 4:1 benzene–ethyl acetate, 1:1 benzene–ether, and 14:14:1 benzene–ether–methanol.

2-O-Benzyl-L-fucose (**2**). — A mixture of methyl 3,4-*O*-isopropylidene-α-L-fucopyranoside[3] (9.0 g), benzyl chloride (30 ml), toluene (10 ml), and powdered potassium hydroxide (18.0 g) was stirred for 2–3 h at 100°. After addition of toluene to the cooled mixture, the organic layer was washed several times with water and then evaporated in *vacuo*, and several large amounts of water were added to the residue and evaporated. The crude, residual oil was dissolved in benzene and the solution was chromatographed on silica gel. Benzene–ethyl acetate (4:1) eluted methyl 2-*O*-benzyl-3,4-*O*-isopropylidene-α-L-fucopyranoside (**1**) which showed only one spot on t.l.c. but could not be crystallized; (9.1 g, 70%), $[\alpha]_D^{25}$ −98.5° (*c* 1,16, chloroform) ; n.m.r. data: τ 2.74 (5H, C_6H_5) 6.72 (3H, OMe) 8.65, 8.74, 8.83 (9H, C–Me_2 and CH–Me).

A suspension of **1** (6.0 g) in 1.5M sulfuric acid (100 ml) was stirred for 2 h at 100°. The cooled mixture was extracted with chloroform to remove unhydrolyzed glycoside, and the aqueous layer was neutralized with an excess of barium carbonate. After filtration, the clear, aqueous solution was evaporated *in vacuo*. The residue gave two spots on t.l.c. in 65:15:2 chloroform–methanol–water, the slower-migrating (minor) spot being apparently L-fucose. The residue was dissolved in the same solvent mixture,

and the solution was chromatographed on silica gel to give a product (2.5 g, 50%) which crystallized from water in needles, m.p. 168–170°; $[\alpha]_D^{25}$ −64.5° (*c* 0.99, water); n.m.r. data [$(CD_3)_2SO$]: τ 2.7 (5H, C_6H_5) and 8.92 (doublet, *J* 6.5 Hz, 3H, CH-Me). A further quantity of **2** (0.8 g, 16%) was obtained by repeating the hydrolysis of the unchanged **1** recovered from the chloroform layer.

Anal. Calc. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.61; H, 6.96. Schmidt and Wernicke[4] reported for 2-*O*-benzyl-α-D-fucose: m.p. 164°; $[\alpha]_D$ +66.3° (water).

2-O-Benzyl-1,3,4-tri-O-p-nitrobenzoyl-α-L-fucopyranose (**3**). — Compound **2** (1.7 g) was dissolved in dry pyridine (50 ml), and *p*-nitrobenzoyl chloride (14 g) was added with stirring to the cooled solution, which was then kept overnight at room temperature. It was diluted with dichloromethane (50 ml) and washed successively with cold hydrochloric acid, water, a cold saturated solution of sodium hydrogen carbonate, and water, dried with calcium chloride, and evaporated *in vacuo*. Crystallization from ethyl acetate–hexane gave 2.7 g (58%) m.p. 163–167°; $[\alpha]_D^{25}$ −189° (*c* 1.06, chloroform); n.m.r. data: τ 3.10 (doublet, *J* 3 Hz, C-1 of α-anomer); 3.82 (doublet, *J* 8 Hz, C-1 of β-anomer); ratio of *p*-nitrobenzoate to phenyl to methyl protons, 12:5:3.

Anal. Calc. for $C_{34}H_{27}N_3O_{14}$: C, 58.20; H, 3.88; N, 5.99. Found: C, 58.22; H. 3.82; N, 5.94.

Recrystallization from ethyl acetate afforded **3**, m.p. 202–204°; $[\alpha]_D^{26}$ −285° (*c* 1.30, chloroform); n.m.r. data: no doublet at τ 3.82; doublet at τ 3.24 (*J* 3 Hz, C-1 of α-anomer, 1 H).

Benzyl 2-acetamido-6-O-(2-O-benzyl-α-L-fucopyranosyl)-2-deoxy-α-D-glucopyranoside (**6**). — A saturated solution of hydrogen bromide in dichloromethane (50 ml) was added to a solution of **3** and its β-anomer (2.4 g) in dichloromethane (50 ml). After 3 h 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 cold water until neutral, dried with calcium chloride, and evaporated *in vacuo* to give syrupy 2-*O*-benzyl-3,4-di-*O*-*p*-nitrobenzoyl-α-L-fucopyranosyl bromide (**4**) (2.0 g, 92%); $[\alpha]_D^{27}$ −272° (*c* 1.0, chloroform); n.m.r. data: τ 1.72–2 (multiplet, 8 H, 2 *p*-nitrobenzoate groups); 2.72 (5 H, C_6H_5); 3.28 (doublet, *J* 3.5 Hz, H-1), 8.71 (doublet, *J* 6.5 Hz, 3 H, CH-Me). Examination of this product on t.l.c. in 9:1 benzene–ether showed a slight contamination with unchanged **3**.

A solution of benzyl 2-acetamido-3,4-di-*O*-acetyl-2-deoxy-α-D-glucopyranoside[2] (**5**, 0.8 g, 2 mmoles) in 1:1 nitromethane–benzene (60 ml) was evaporated until approximately 20 ml of the solvent mixture had distilled and then cooled to room temperature. Mercuric cyanide (0.51 g, 2 mmoles) and **4** (1.28 g, 2 mmoles) were added, and the reaction mixture was stirred for 48 h, a further addition of **4** (0.64 g, 1 mmole) being made after 24 h. The mixture was diluted with benzene, washed successively with sodium hydrogen carbonate solution and water, dried (calcium chloride), and evaporated *in vacuo*. The residue was dissolved in benzene and chromatographed on a column of Silica gel. A fraction showing only one spot on t.l.c. was eluted by 14:14:1 benzene–ether–methanol. Evaporation of the solvent *in vacuo* afforded a syrup

(1.32 g, 70%); n.m.r. data: τ 1.74–2.14 (multiplet, 8 H, 2 *p*-nitrobenzoate groups), 2.64 and 2.74 (10 H, 2 C_6H_5), 7.94 and 7.99 (6 H, 2 OAc), 8.12 (3H, NAc) and 8.8 (doublet, *J* 6.5 Hz, 3H, CH-Me). No other disaccharide material was obtained. A later fraction was eluted and shown to be unchanged **5** (0.170 g, 22%). The disaccharide was dissolved in methanol (50 ml) containing a catalytic amount of sodium methoxide. The solution was kept overnight at room temperature, neutralized with aqueous acetic acid (25%), and evaporated *in vacuo*. An aqueous solution of the residue was extracted with ether to remove *p*-nitrobenzoic acid, stirred with Amberlite IRC-50 (H^+) for 30 min, and filtered. The filtrate was evaporated *in vacuo* and the residue (0.75 g, 68% overall yield from **5**) was crystallized from abs. ethanol (0.44 g, 40% from **5**), m.p. 198–202°; $[\alpha]_D^{25}$ +28.6° (*c* 0.5, abs. ethanol); n.m.r. data: τ 2.68 (10 H, 2 C_6H_5), 8.13 (3 H, NAc), 8.92 (doublet, *J* 6.5 Hz, 3 H, CH-Me).

Anal. Calc. for $C_{28}H_{37}NO_{10}$: C, 61.41; H, 6.81. Found: C, 61.57; H, 6.60.

*2-Acetamido-2-deoxy-6-*O*-α-L-fucopyranosyl-D-glucose* (**7**). — Crystalline **6** (200 mg) was dissolved in 90% ethanol (100 ml), and 10% palladium-on-charcoal (50 mg) was added. The mixture was shaken with hydrogen at 3.5 atm. for 48 h at room temperature, the catalyst was removed by filtration, and the solvent evaporated *in vacuo*. The residue was dissolved in 13:6:1 chloroform–methanol–water and the solution was chromatographed on silica gel. Earlier fractions contained apparently incompletely hydrogenolyzed material and were not investigated further. Later, combined fractions eluted from the column gave 122 mg (90%) of **7**, showing only one spot on t.l.c. in 3:3:2 2-propanol–ethyl acetate–water and 13:6:1 chloroform–methanol–water. The amorphous product obtained could not be crystallized; $[\alpha]_D^{25}$ −65° (*c* 1.05, water). It was identical with the disaccharide previously described[2] on the basis of t.l.c., paper chromatography, and optical rotation comparisons. The per(trimethylsilyl) ether of the derived sugar alcohol showed a single peak on g.l.c.[2], T_S 1.96.

*2-Acetamido-2-deoxy-6-*O*-α- and β-L-fucopyranosyl-D-glucose.* — A portion of crude **6** was hydrogenolyzed and the disaccharide isolated by chromatography, as just described; $[\alpha]_D^{27}$ −51° (*c* 1.1, water). The per(trimethylsilyl) ether of the derived sugar alcohol showed, on g.l.c., two peaks having T_S 1.96 (95%) and T_S 2.4 (5%).

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