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# SYNTHESIS OF 3-*O*-α-L-FUCOPYRANOSYL-L-FUCOSE AND METHYL 3-*O*-β-L-FUCOPYRANOSYL-α-L-FUCOPYRANOSIDE*†

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ABSTRACT

A Koenigs–Knorr reaction of methyl 2,4-di-*O*-benzyl-α-L-fucopyranoside with 2-*O*-benzyl-3,4-di-*O*-*p*-nitrobenzoyl-α-L-fucopyranosyl bromide, followed by catalytic deacylation and hydrogenolysis, led to a stereospecific synthesis of methyl 3-*O*-α-L-fucopyranosyl-α-L-fucopyranoside. Use of 2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl bromide as the halide in the same reaction afforded, in the ratio 2:3, a mixture of the α and β disaccharides from which the pure β-disaccharide could be isolated by crystallization of the intermediate methyl 2,4-di-*O*-benzyl-3-*O*-β-L-fucopyranosyl-α-L-fucopyranoside. The attribution of anomeric configuration and evaluation of optical purity of the products were based on optical rotation and g.l.c. of the per(trimethylsilyl) ethers. Acetolysis of methyl 3-*O*-α-L-fucopyranosyl-α-L-fucopyranoside, followed by catalytic deacetylation, gave 3-*O*-α-L-fucopyranosyl-L-fucose.

## INTRODUCTION

Three disaccharides of L-fucose were isolated[1] from acetolyzates of the seaweed polysaccharide fucoidin and identified as 2-, 3-, and 4-*O*-α-L-fucopyranosyl-L-fucose. 2-*O*-α-L-Fucopyranosyl-L-fucose has been synthesized[2] by reaction of 2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl bromide with a suitable nucleophile, although the apparently stereospecific formation of an α-linked disaccharide was rather unexpected. The synthesis of 2-acetamido-2-deoxy-4-*O*-α-L-fucopyranosyl-D-glucose by means of an acyclic nucleophile has also been reported[3]. Under similar conditions, other nucleophiles reacted with the same halide to produce β-L-linked disaccharides[4–6]. The question may be raised whether the stereochemistry of the reaction was a function of the position of substitution in the L-fucose residue or whether the same bromide would react with a differently located hydroxyl group in a derivative of L-fucose to give a similarly stereospecific formation of α-linked anomer. Since no other fucopyranosyl-L-fucose disaccharide has been synthesized, the 3-*O*-isomer was prepared.

*Dedicated to the memory of Professor W. Z. Hassid.
†Studies on the Koenigs–Knorr reaction. Part VI.

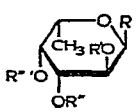
It was also considered of interest to compare the effect of a participating and a non-participating group at C-2 of the bromide on the configuration of the final product.

## RESULTS AND DISCUSSION

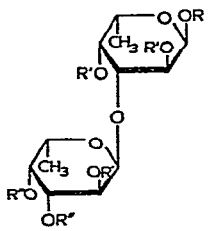
Reaction of methyl 2,4-di-*O*-benzyl-α-L-fucopyranoside[7] (**1**) with 2-*O*-benzyl-3,4-di-*O*-*p*-nitrobenzoyl-α-L-fucopyranosyl bromide[8] (**2**), in the presence of mercuric cyanide, afforded a good yield of methyl 2,4-di-*O*-benzyl-3-*O*-(2-*O*-benzyl-3,4-di-*O*-*p*-nitrobenzoyl-α-L-fucopyranosyl)-α-L-fucopyranoside (**4**) as a strongly levorotatory syrup. Catalytic deacylation of **4** produced crystalline methyl 2,4-di-*O*-benzyl-3-*O*-(2-*O*-benzyl-α-L-fucopyranosyl)-α-L-fucopyranoside (**5**). After catalytic hydrogenolysis of **5**, methyl 3-*O*-α-L-fucopyranosyl-α-L-fucopyranoside (**6**) was isolated and crystallized from ethanol. The stereospecificity of the reaction of **1** with **2** was demonstrated by the homogeneity, on examination by g.l.c. on SE-30 and QF-1 columns, of the per(trimethylsilyl) ether of **6**, prepared from a crude sample of **4** by direct deblocking without any purification of the intermediates **5** and **6**.

Acetolysis of **6** gave 1,2,4,2′,3′,4′-hexa-*O*-acetyl-3-*O*-α-L-fucopyranosyl-L-fucose (**7**) which crystallized from ethanol as a mixture of the anomeric C-1 acetates. Careful catalytic deacetylation of **7** afforded crystalline 3-*O*-α-L-fucopyranosyl-L-fucose (**8**) having the same m.p. and optical rotation as those described by Côté[1].

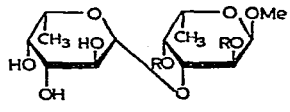
Treatment of the nucleophile **1** with 2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl bromide[2] (**3**), followed by catalytic deacetylation, afforded a syrup in good yield; crystallization of this syrup in absolute ethanol enabled the isolation of methyl



**1** R = OMe; R′ = R‴ = $OH_2Ph$; R″ = H
**2** R = Br; R′ = $CH_2Ph$; R″ = R‴ = *p*-$(NO_2)C_6H_4CO$
**3** R = Br; R′ = R″ = R‴ = Ac



**4** R = Me; R′ = $CH_2Ph$; R″ = *p*-$(NO_2)C_6H_4CO$
**5** R = Me; R′ = $CH_2Ph$; R″ = H
**6** R = Me; R′ = R″ = H
**7** R = R′ = R″ = Ac
**8** R = R′ = R″ = H



**9** R = $CH_2Ph$
**10** R = H

2,4-di-*O*-benzyl-3-*O*-β-L-fucopyranosyl-α-L-fucopyranoside (**9**). Catalytic hydrogenolysis of **9** gave an amorphous solid, to which the structure of methyl 3-*O*-β-L-fucopyranosyl-α-L-fucopyranoside (**10**) was assigned. The β-configuration of the interglycosidic linkage in **9** and **10** was established on the basis of: (a) the higher value of the optical rotation of **10** than **6**; and (b) the separation by g.l.c. of the per(trimethylsilyl) ethers of **10** and **6**, each of which gave a single, sharp peak. A crude sample of **10**, prepared directly from the reaction mixture of **1** with **3**, without crystallization of

intermediates, was shown, by g.l.c. of the per(trimethylsilyl) ether, to contain ~60% of β- and 40% of α-linked disaccharide.

The present report extends the usefulness of the bromide **2**, with a non-participating group at C-2, for the preparation of α-linked disaccharides of L-fucose. Furthermore, in contrast to the synthesis[2] of 2-*O*-α-L-fucopyranosyl-L-fucose, bromide **3** gave, in this case, a product enriched in β-linked disaccharide, from which the pure β-anomer could be isolated by crystallization of the intermediate **9**.

## EXPERIMENTAL

For general methods, see Ref. 9.

*Methyl 2,4-di-*O*-benzyl-3-*O*-(2-*O*-benzyl-3,4-di-*O*-p-nitrobenzoyl-α-L-fucopyranosyl)-α-L-fucopyranoside* (**4**). — A solution of methyl 2,4-di-*O*-benzyl-α-L-fucopyranoside[7] (**1**, 2.0 g, 5.5 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 (1.4 g, 5.5 mmoles) and 2-*O*-benzyl-3,4-di-*O*-*p*-nitrobenzoyl-α-L-fucopyranosyl bromide[8] (**2**, 3.5 g, 5.5 mmoles) were added, and the reaction mixture was stirred for 24 h, a further addition of **2** (1.7 g, 2.7 mmoles) being made after 12 h. The mixture was diluted with benzene, washed successively with a saturated sodium hydrogen carbonate solution and water, dried with calcium chloride, and evaporated *in vacuo*. The residue was dissolved in benzene and chromatographed on a column of silica gel. A homogeneous fraction (t.l.c.), eluted with 4:1 (v/v) benzene–ether, was collected. Evaporation of the solvent *in vacuo* afforded a syrup (**4**, 3.5 g, 70%), $[\alpha]_D^{25}$ −250° (*c* 1.05, chloroform); n.m.r. data: τ 1.78–2.28 (m, 8 H, 2 *p*-nitrobenzoate groups), 2.65–2.90 (m, 15 H, 3 Ph), 6.65 (3 H, OMe), 8.82, and 9.04 (2 d, 6 H, *J* 6.5 Hz, 2 CH–Me).

*Anal.* Calc. for $C_{48}H_{46}N_2O_{15}$: C, 64.71; H, 5.20. Found: C, 64.60; H, 5.38.

*Methyl 2,4-di-*O*-benzyl-3-*O*-(2-*O*-benzyl-α-L-fucopyranosyl)-α-L-fucopyranoside* (**5**). — A portion of **4** (2.5 g) was dissolved in 1:1 chloroform–methanol (200 ml) containing a catalytic amount of sodium methoxide, and the solution was kept overnight at room temperature, neutralized with acetic acid, and evaporated *in vacuo*. The material was dissolved in benzene and purified by column chromatography on silica gel. Benzene–ether (1:1) eluted fractions which were homogeneous on t.l.c. Evaporation of the solvent *in vacuo* afforded a syrup (1.46 g, 88%), a portion of which (100 mg) was crystallized from ether to give **5** (80 mg), m.p. 114–116°; $[\alpha]_D^{25}$ −134° (*c* 1.00, chloroform); n.m.r. data: τ 2.76 (15 H, 3 Ph), 6.68 (3 H, OMe), and 8.80 (d, *J* 6.5 Hz, 6 H, 2 CH–Me).

*Anal.* Calc. for $C_{34}H_{42}O_9$: C, 68.67; H, 7.12. Found: C, 68.73; H, 7.17.

*Methyl 3-*O*-α-L-fucopyranosyl-α-L-fucopyranoside* (**6**). — A portion of crude **5** (1.0 g) was dissolved in 90% ethanol, and 10% palladium-on-charcoal (100 mg) was added. The mixture was shaken with hydrogen at 3.5 atm for 24 h at room temperature, the catalyst was removed by filtration, and the solvent evaporated *in vacuo*. The residue was dissolved in 65:15:2 (v/v) chloroform–methanol–water, and the solution

was chromatographed on silica gel. Fractions that were eluted with the same solvent mixture and were identical and homogeneous on t.l.c. were combined to give a solid (0.49 g, 90%). Crystallization from absolute ethanol afforded **6**, m.p. 103–106°; $[\alpha]_D^{25}$ −272° (*c* 0.90, absolute ethanol); n.m.r. data (deuterium oxide): $\tau$ 6.78 (3 H, OMe), 8.88, and 8.95 (2 d, 6 H, *J* 6.5 Hz, 2 CH–Me).

*Anal.* Calc. for $C_{13}H_{24}O_9$: C, 48.14; H, 7.46. Found: C, 47.84; H, 7.62.

A portion of **6**, before crystallization, was converted into the per(trimethylsilyl) ether and analyzed by g.l.c. One sharp peak was observed either on a column of 3% SE-30 (A) at 200° ($T_{sucrose}$ 0.30), or of 2% QF-1 (B) at 170° ($T_{sucrose}$ 0.39).

*1,2,4,2',3',4'-Hexa-*O*-acetyl-3-*O*-α-*L*-fucopyranosyl-*L*-fucose* (**7**). — To a cooled solution of **6** (0.25 g) in a mixture of acetic anhydride (7.5 ml) and glacial acetic acid (1.5 ml) was added a cooled solution of 10:1 (v/v) glacial acetic acid–sulfuric acid (0.57 ml). After 20 h at 4°, the reaction mixture was diluted with water and stirred with an excess of sodium carbonate for 2 h. Chloroform was added, and the chloroform layer was washed with water until neutral, dried (calcium chloride), and evaporated *in vacuo* to a solid (0.22 g, 56%). Crystallization from absolute ethanol afforded **7** (190 mg, 48%), m.p. 183–185°; $[\alpha]_D^{25}$ −160° (*c* 0.90, chloroform); n.m.r. data: $\tau$ 3.5 (d, 0.6 H, *J* 3 Hz, H-1 of α-anomer), 4.25 (d, 0.4 H, *J* 8 Hz, H-1 of β-anomer), 7.78, 7.82, 7.95, 8.02 (18 H, 6 OAc), and 8.84 (d, 6 H, *J* 6.5 Hz, CH–Me).

*Anal.* Calc. for $C_{24}H_{34}O_{15}$: C, 51.24; H, 6.09. Found: C, 51.38; H, 6.15.

*3-*O*-α-*L*-Fucopyranosyl-*L*-fucose* (**8**). — To a solution of **7** (200 mg) in methanol (10 ml), cooled in an ice–salt mixture, was added barium methoxide (2 ml of a 0.03M solution). The reaction mixture was kept for 24 h at 5°, the barium salts were removed by stirring with Amberlite IR-120 ($H^+$), and the solution was filtered and evaporated *in vacuo*. The material was purified by column chromatography on silica gel. Fractions that were eluted with 65:25:2 (v/v) chloroform–methanol–water were combined to give a solid (125 mg, 65%), which was homogeneous on t.l.c. in 65:25:2 (v/v) and 13:6:1 (v/v) chloroform–methanol–water, and 3:3:1 (v/v) ethyl acetate–2-propanol–water, and on paper chromatography in 3:3:1 (v/v) pyridine–1-butanol–water. Crystallization from absolute alcohol–chloroform gave **8** (100 mg, 53%), m.p. 200–202°; $[\alpha]_D^{25}$ −190° (*c* 0.90, water); lit.[1]: m.p. 198–200°; $[\alpha]_D$ −200 → −191° (*c* 1.0).

*Anal.* Calc. for $C_{12}H_{22}O_9 \cdot 0.5H_2O$: C, 45.14; H, 7.26. Found: C, 45.08; H, 7.28.

*Methyl 2,4-di-*O*-benzyl-3-*O*-β-*L*-fucopyranosyl-α-*L*-fucopyranoside* (**9**). — Treatment of **1** (2.0 g, 5.5 mmoles) with 2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl bromide[2] (**3**, 5.2 g, 8.2 mmoles) in the presence of mercuric cyanide (1.4 g, 5.5 mmoles), as described for **4**, afforded a syrup which was dissolved in methanol (50 ml) containing a catalytic amount of sodium methoxide. The solution was kept overnight at room temperature, neutralized with acetic acid, and the solvent evaporated *in vacuo*. The residue was dissolved in chloroform and the chloroform solution washed several times with water, dried (calcium chloride), and evaporated *in vacuo* to a syrup (1.7 g, 61%). This was crystallized from absolute ethanol to give **9** (0.25 g, 16%), m.p. 112–

114°; $[\alpha]_D^{25}$ −40° (*c* 1.02, chloroform); n.m.r. data: τ 2.68 (10 H, 2 Ph), 6.70 (3 H, OMe), 8.84, and 8.96 (2 d, 6 H, *J* 6.5 Hz, 2 CH–Me).

*Anal.* Calc. for $C_{27}H_{36}O_9$: C, 64.27; H, 7.19. Found: C, 64.10; H, 7.25.

*Methyl 3-O-β-L-fucopyranosyl-α-L-fucopyranoside* (**10**). — Compound **9** (200 mg) was hydrogenolyzed as described for **6** and, after the usual processing and column chromatography on silica gel, afforded **10** as an amorphous solid (105 mg, 90%), $[\alpha]_D^{25}$ −123°; n.m.r. data: τ 6.75 (3 H, OMe) and 8.88 (d, 6 H, *J* 6.5 Hz, 2 CH–Me).

*Anal.* Calc. for $C_{13}H_{24}O_9$: C, 48.14; H, 7.46. Found: C, 48.45; H, 7.50.

The per(trimethylsilyl) ether of **10** showed a single peak on g.l.c. either on column A at 200° ($T_{sucrose}$ 0.58) or on column B at 170° ($T_{sucrose}$ 0.85).

Hydrogenolysis of a portion of crude **9** afforded a syrup which was converted into the per(trimethylsilyl) ether and analyzed by g.l.c. Two peaks were observed on both columns A and B, under the conditions previously described, with $T_{sucrose}$ 0.30 and 0.58, and 0.39 and 0.85, respectively; the ratio of α to β anomers was 2:3.

REFERENCES

1 R. H. CÔTÉ, *J. Chem. Soc.*, (1959) 2248–2254.
2 H. M. FLOWERS, A. LEVY, AND N. SHARON, *Carbohyd. Res.*, 4 (1967) 189–195.
3 M. A. SHABAN AND R. W. JEANLOZ, *Carbohyd. Res.*, 20 (1971) 399–405.
4 E. S. RACHAMAN AND R. W. JEANLOZ, *Carbohyd. Res.*, 10 (1969) 429–434.
5 E. S. RACHAMAN AND R. W. JEANLOZ, *Carbohyd. Res.*, 10 (1969) 435–439.
6 M. DEJTER-JUSZYNSKI AND H. M. FLOWERS, *Carbohyd. Res.*, 30 (1973) 287–292.
7 M. DEJTER-JUSZYNSKI AND H. M. FLOWERS, *Carbohyd. Res.*, 28 (1973) 61–74.
8 M. DEJTER-JUSZYNSKI AND H. M. FLOWERS, *Carbohyd. Res.*. 23 (1972) 41–45.
9 H. M. FLOWERS *Carbohyd. Res.*, 18 (1971) 211–218.