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Note

Synthesis of 4-*O*-α-L-fucopyranosyl-L-fucose and methyl 4-*O*-β-L-fucopyranosyl-α-L-fucopyranoside*

MARTA DEJTER-JUSZYNSKI AND HAROLD M FLOWERS
Department of Biophysics, The Weizmann Institute of Science, Rehovoth (Israel)
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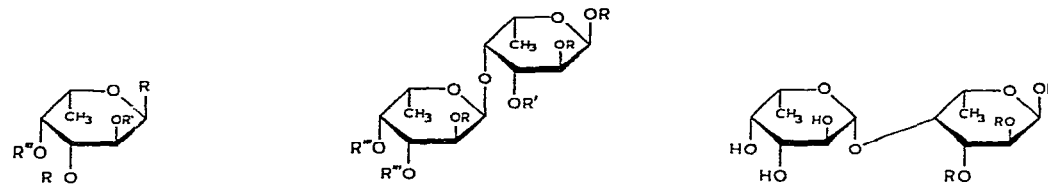
The disaccharide 4-*O*-α-L-fucopyranosyl-L-fucose (**6**) was first identified as a product of acetolysis of fucoidin[1] 4-*O*-L-Fucopyranosyl-L-fucose, with no, as yet, clearly defined anomeric configuration, also forms part of the carbohydrate chain of a number of bacterial polysaccharides[2,3] The chemical synthesis of 4-*O*-glycosyl-hexopyranosides has generally been considered to be difficult, owing to the relatively low reactivity of the 4-hydroxyl group on the hexopyranoside ring, especially when axially oriented, and special approaches have often been developed to overcome this problem[4] The low reactivity of the 4-hydroxyl group in galactopyranosides and fucopyranosides with a number of electrophiles has been well-documented[5–7] However, we have recently shown the relatively high reactivity of this group towards benzylation in derivatives of methyl α-L-fucopyranoside[8] This unexpected finding encouraged us to utilize the partially benzylated products of this reaction and to ascertain their reactivity as nucleophiles in the Koenigs–Knorr reaction Preparation of the disaccharide 3-*O*-α-L-fucopyranosyl-L-fucose, in good yield[9], from methyl 2,4-di-*O*-benzyl-α-L-fucopyranoside has recently been described The present Note describes the synthesis of **6** from methyl 2,3-di-*O*-benzyl-α-L-fucopyranoside

RESULTS AND DISCUSSION

Reaction of methyl 2,3-di-*O*-benzyl-α-L-fucopyranoside (**1**) with 2-*O*-benzyl-3,4-di-*O*-*p*-nitrobenzoyl-α-L-fucopyranosyl bromide (**2**), followed by chromatographic purification, afforded an excellent yield of a syrup showing an n m r spectrum consistent with the structure methyl 2,3-di-*O*-benzyl-4-*O*-(2-*O*-benzyl-3,4-di-*O*-*p*-nitrobenzoyl-α-L-fucopyranosyl)-α-L-fucopyranoside Deacylation of this product, followed by catalytic hydrogenolysis, afforded, in 77% yield from **1**, methyl 4-*O*-α-L-fucopyranosyl-α-L-fucopyranoside (**4**) Compound **4** was a strongly levorotatory, crystalline solid, and its per(trimethylsilyl) ether showed a single peak on g l c Condensation of **1** with 2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl bromide[10], and catalytic deacylation of the product, gave a mixture of disaccharides, in over 50% yield, in the

*Studies on the Koenigs–Knorr reaction, Part VII

ratio of 3.1, which were clearly separated on t l c and isolated on column chromatography. The minor product was a crystalline solid (**7**) and was converted into **4** on catalytic hydrogenolysis Similar treatment of the major product (**8**) gave a different, much less levorotatory, disaccharide, the per(trimethylsilyl) ether of which also showed



1 R = OMe, R' = R'' = Bzl R''' = H
2 R = Br, R = Bzl, R'' = R''' = $COC_6H_4NO_2$ (*p*)
3 R = Me R = R'' = Bzl R''' = $COC_6H_4NO_2$ (*p*)
4 R = Me, R = R'' = R''' = H
5 R = Me R = R'' = R''' = Ac
6 R = R' = R'' = R''' = H
7 R = Me, R = Bzl, R'' = R''' = H
8 R = Bzl
9 R = H

a single peak on g l c , but with a $T_{Sucrose}$ value different from that of the ether prepared from **4** This second disaccharide, formulated as methyl 4-*O*-β-L-fucopyranosyl-α-L-fucopyranoside (**9**), was also a crystalline solid Acetylation of **4** afforded the crystalline pentaacetate **5** Acetolysis of **5** with a mixture of cooled acetic acid, acetic anhydride, and sulfuric acid, followed by careful catalytic deacetylation and passage through a column of Sephadex G-25, gave a hygroscopic syrup This was shown to be identical with an authentic specimen of 4-*O*-α-L-fucopyranosyl-L-fucose (**6**), kindly provided by Dr. Côté, on t l c and paper chromatography, each in two separate systems that clearly differentiated **6** from 3-*O*-α-L-fucopyranosyl-L-fucose The synthetic and natural specimens of **6** had identical optical rotations

Reaction of **1** with bromide **2** resulted in a stereospecific synthesis of the α-L-linked disaccharide **6** However, 2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl bromide gave a mixture of disaccharides enriched in the β-L anomer. The high reactivity of the 4-hydroxyl group in **1**, which was certainly no lower than that of the 3-hydroxyl group in the 2,4-di-*O*-benzyl isomer towards the same reagents[9], would indicate that the 4_{ax}-hydroxyl group in hexopyranosides is not necessarily unreactive Much of our information on the selective reactivity of hydroxyl groups in sugars has been obtained from esters (acetates or benzoates) In these protected sugars, the neighboring acyl group may afford the possibility of cyclization with the free hydroxyl group or exert electronic influences specifically lowering the reactivity Such hindrances would not necessarily be encountered with vicinal benzyl ethers Use of partially benzylated sugars as protected intermediates for syntheses requiring reaction with these otherwise less reactive hydroxyl groups could then be advantageous

EXPERIMENTAL

For general methods, see Ref. 11, except for microanalyses of **4** and **5**, which were performed by Sandoz Ltd , Microanalytical Laboratories, Basel, Switzerland

Methyl 4-O-α-L-fucopyranosyl-α-L-fucopyranoside (**4**) — A solution of methyl 2,3-di-*O*-benzyl-α-L-fucopyranoside[8] (**1**, 1 0 g, 2 8 mmol) in 1 1 (v/v) 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 9 g, 3 5 mmol) and 2-*O*-benzyl-3,4-di-*O*-*p*-nitrobenzoyl-α-L-fucopyranosyl bromide[1,2] (**2**, 1 8 g, 2 8 mmol) were added, and the reaction mixture was stirred for 24 h, further additions of **2** being made after 6 and 12 h (2 8 mmol each time) The mixture was diluted with benzene, washed successively with a saturated solution of sodium hydrogencarbonate and water, dried (calcium chloride) and evaporated *in vacuo* The residue was dissolved in benzene and chromatographed on silica gel A homogeneous fraction (t l c) eluted with 9 1 (v/v) benzene–ether was collected and, after evaporation of the solvent *in vacuo*, a syrup was obtained (**3**, 2 1 g, 85%), $[\alpha]_D^{25}$ −226° (*c* 1 17, chloroform), n m r data τ 1 82–2 36 (m, 8 H, 2 *p*-nitrobenzoate groups), 2 72–2 92 (m, 15 H, 3 Ph), 6 68 (3 H, OMe), 8 70, and 9 20 (2 d, 6 H, *J* 6 5 Hz, 2 CH–Me)

A portion of **3** (2 0 g) was dissolved in 1 1 (v/v) chloroform–methanol (100 ml) containing a catalytic amount of sodium methoxide The solution was kept overnight at room temperature, and then neutralized with acetic acid and evaporated *in vacuo* The residue was dissolved in benzene and chromatographed on silica gel Benzene–ether (1 1, v/v) eluted fractions which were homogeneous on t l c Evaporation of the solvent *in vacuo* afforded a syrup, $[\alpha]_D^{25}$ −137° (*c* 1 21, chloroform); n m r. data τ 2 78 (15 H, 3 Ph), 6 70 (3 H, OMe), 8 78, and 9 08 (2 d, 6 H, *J* 6 5 Hz, 2 CH–Me) The syrup obtained was dissolved in 90% ethanol (100 ml) 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* to give a syrup (0 65 g, 90%) Crystallization from methanol–diisopropyl ether afforded a hygroscopic solid (**4**) (0 52 g), m p 102–104°, $[\alpha]_D^{25}$ −240° (*c* 0 95, water), n m r data (deuterium oxide) τ 5 12 (d, *J* 3 Hz, H-1′), 6 64 (3 H, OMe), 8 68, and 8 84 (2 d, 6 H, *J* 6 5 Hz, 2 CH–Me)

Anal Calc for $C_{13}H_{24}O_9$ $0.5H_2O$ C, 46 9, H, 7 6, O, 45 7. Found C, 47 4, H, 7 2, O, 46 0

Catalytic hydrogenolysis of **7** (200 mg) afforded a syrup (115 mg, 90%) which was identical with **4** on t l c in 9 1 (v/v) acetone–methanol and 65 15 2 (v/v) chloroform–methanol–water, and showed the same optical rotation. A portion of **4**, before crystallization, was converted into the per(trimethylsilyl) ether and analyzed by g l c ; one sharp peak was observed on a column of 3% SE-30 at 200° $T_{Sucrose}$ 0 37

Methyl 2,3-di-O-acetyl-4-O-(2,3,4-tri-O-acetyl-α-L-fucopyranosyl)-α-L-fucopyranoside (**5**) — A portion of **4** (0 50 g) was acetylated with acetic anhydride (10 ml) in pyridine (10 ml) overnight at room temperature Methanol was added with cooling, and the solution was concentrated *in vacuo* Toluene was added, and the solution concentrated again to a syrup which was dissolved in chloroform and extracted with water, dried (calcium chloride), and concentrated *in vacuo* to a syrup (0 79 g, 90%) Crystallization from abs ethanol afforded **5** (0 60 g), m p 90–93°, $[\alpha]_D^{25}$ −212°

(*c* 0 83, chloroform); n m r data τ 6.68 (3 H, OMe), 7 86, 8 00, and 8 08 (15 H, 5 OAc), and 8 72, 8 82, and 8 92 (6 H, CH–Me)

Anal Calc for $C_{23}H_{34}O_{14}$: C, 51 7, H, 6 4 Found C, 51 5; H, 6 4

4-O-α-L-Fucopyranosyl-L-fucose (**6**). — To a cooled solution of **5** (0 40 g) in a mixture of acetic anhydride (8 ml) and glacial acetic acid (1 6 ml) was added a cooled solution of 10 1 (v/v) glacial acetic acid–sulfuric acid (0 61 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 washed with water until neutral, dried (calcium chloride), and concentrated *in vacuo* to a syrup (0 29 g, 70%), n m r data τ 3 60 (d, 0 6 H, *J* 3 Hz, H-1 of α-anomer), 7 86, 7 90 7 93, 7 96, 8 0, 8 08 (18 H, 6 OAc), 8 72, 8 82, and 8 92 (6 H, 2 CH–Me)

To a solution of the syrup (0 25 g) in methanol (12 ml), cooled in an ice–salt mixture, was added 15mM barium methoxide (2 5 ml) The reaction mixture was kept overnight at 4°, the barium salts were removed by stirring with Amberlite IR-120(H^+) ion-exchange resin, and the solution was filtered and evaporated *in vacuo* The residual material was purified by column chromatography on Sephadex G-25 to give a syrup (**6**, 0 10 g, 70%), $[\alpha]_D^{25}$ −171° (*c* 0 85, water), lit [1] $[\alpha]_D$ −170° (*c* 1, water), homogeneous on t l c in 65 25 2 (v/v) and 13 6 1 (v/v) chloroform–methanol–water and on paper chromatography (4 1 5, v/v, butanol–acetic acid–water, R_{Fuc} 0 66, lit [1] 0 62, 3 1 1, v/v, butanol–pyridine–water R_{Fuc} 0 70, lit [1]. 0 64) The syrup was indistinguishable from an authentic sample, provided by Dr Côté, in these chromatographic systems

Methyl 2,3-di-O-benzyl-4-O-α-L-fucopyranosyl-α-L-fucopyranoside (**7**) *and methyl 2,3-di-O-benzyl-4-O-β-L-fucopyranosyl-α-L-fucopyranoside* (**8**) — Reaction of **1** (2 40 g) with 2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl bromide[10] (4 0 g) in the presence of mercuric cyanide (3 3 g) in 1 1 (v/v) nitromethane–benzene overnight at room temperature afforded a mixture which was catalytically deacetylated with sodium methoxide in methanol After being concentrated to a few ml, the solution was diluted with chloroform and washed with water The chloroform layer was evaporated to a syrup, which was dissolved in 1 1 (v/v) benzene–ether and applied to a silica gel column Benzene–ether (1 1, v/v) eluted 0 85 g (35 5%) of unchanged **1** Ethyl acetate–acetone (4 1, v/v) eluted a product (**8**, 1 35 g, 40 0%) followed by a different product (**7**, 0 45 g, 13 3%) Compound **8** was a syrup, $[\alpha]_D^{24}$ −37 7° (*c* 1 34, chloroform), n m r data· τ 2 74 (10 H, 2 Ph), 6 70 (3 H, OMe), 8 72, and 8 80 (2 d, 6 H, *J* 6 5 Hz, 2 CH–Me)

Compound **7** crystallized on removal of the solvent It was recrystallized from acetone, m p 172–174°, $[\alpha]_D^{24}$ −145 2° (*c* 0 90, chloroform), n m r data τ 2 76 (10 H, 2 Ph), 6 72 (3 H, OMe), 8 76, and 9 08 (2 d, 6 H, *J* 6 5 Hz), on t l c in 4 1 (v/v) ethyl acetate–acetone, it gave a single spot R_S 0 83

Anal Calc for $C_{27}H_{36}O_9$ C, 64 27; H, 7 19 Found C, 64 08, H, 7 21

Methyl 4-O-β-L-fucopyranosyl-α-L-fucopyranoside (**9**) — Catalytic hydrogenolysis of **8** (1 30 g) gave a syrup (0 80 g, 96%) which crystallized from methanol–diisopropyl ether in needles, m p 175–177°, $[\alpha]_D^{24}$ −132 5° (*c* 1 05, water), n m r

data· τ 6 58 (3 H, OMe), 8 65, and 8 70 (2 d, J 6 5 Hz, 2 CH–Me) (the anomeric protons could not be distinguished); t l c (65 15 2, v/v, chloroform–methanol–water)· R_4 1 2

Anal Calc for $C_{13}H_{24}O_9$· C, 48 14, H, 7 46 Found C, 47 99, H, 7 35

On g l c, the per(trimethylsilyl) ether of **9** gave one sharp peak $T_{Sucrose}$ 0 33.

REFERENCES

1 R H Côté, *J Chem Soc*, (1959) 2248–2254
2 I W Sutherland, *Biochem J*, 115 (1969) 935–945
3 P J Garegg, B Lindberg, T Onn, and T Holme, *Acta Chem Scand*, 25 (1971) 1185–1194
4 N K Kochetkov, O V Chizhov, and A F Bochkov, in G O Aspinall (Ed), *Carbohydrates*, Butterworth, London, 1973, pp 147–190
5 J M Williams and A C Richardson, *Tetrahedron*, 23 (1967) 1369–1378
6 A C Richardson and J M Williams, *Tetrahedron*, 23 (1967) 1641–1646
7 J G Gardiner and E Percival *J Chem Soc*, (1958) 1414–1418
8 M Dejter-Juszynski and H M Flowers, *Carbohyd Res*, 28 (1973) 61–74
9 M Dejter-Juszynski and H M Flowers, *Carbohyd Res*, 37 (1974) 75–79
10 H M Flowers, A Levy, and N Sharon, *Carbohyd Res*, 4 (1967) 189–195
11 H M Flowers, *Carbohyd Res*, 18 (1971) 211–218
12 M Dejter-Juszynski and H M Flowers, *Carbohyd Res*, 23 (1972) 41–45