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Note

An efficient synthesis of L-fucose and L-(4-^{2}H)fucose

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L-Fucose (**4**), a sugar widespread in Nature[1], has lately acquired special significance as a constituent of several families of blood-group antigens[2]. L-Fucose is either the immunodominant sugar of complex carbohydrate antigens, or its presence may increase the strength of the antigenic response. Its preparation by acid hydrolysis of the *Fucus* species of seaweed[3] is cumbersome, and a synthetic method appears to be preferable. D-Fucose is readily synthesized from D-galactose[1], but the same methods are not practical for L-fucose, because L-galactose is not readily available. Several syntheses from common sugars have recently been published[4–7], but they all involve numerous steps, and the overall yields are low (1–24%). We now describe a synthesis, from the readily available methyl α-L-rhamnopyranoside[8], that requires five steps, all except the last of which proceed in yields of >90%. The last step, the conversion of 6-deoxy-L-talose into L-fucose, is a reaction leading to an equilibrium mixture; the proportion of L-fucose therein is 84%, and the unchanged 6-deoxy-L-talose can be recovered and recycled. In this synthesis, there is no need to purify any of the intermediate products.

6-Deoxy-L-talose (**3**) was prepared by the method described by Collins and Overend[9], but the yield and the convenience of handling in each step have been improved by the use of recently described procedures. Methyl α-L-rhamnopyranoside[8] was converted, in 30 min, into its 2,3-*O*-isopropylidene derivative (**1**) according to Lipták *et al.*[10]. Oxidation of the free hydroxyl group on C-4 was performed with pyridinium dichromate[11] in the presence of molecular sieves in dichloromethane solution[12], to yield methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hexopyranosid-4-ulose (**2**). Collins and Overend used chromium trioxide in pyridine for this oxidation[9]. Borohydride reduction of this hexulose should be

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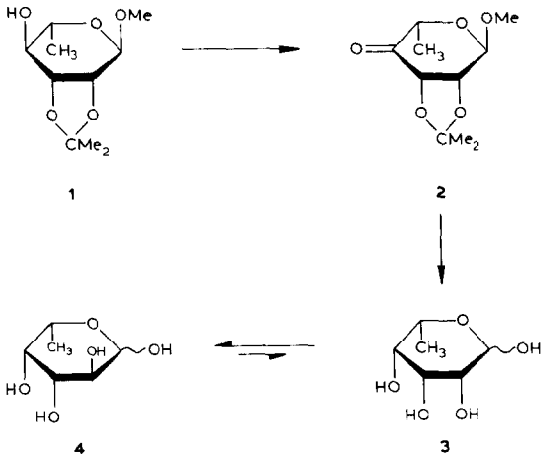
highly stereoselective, because the neighboring substituents are on the "upper" face of the pyranoid ring; in fact, only the *talo* isomer was obtained. Collins and Overend reduced the hexulose by catalytic hydrogenation, and found that 98% of the product was the *talo* isomer[9]. When the reaction was conducted with sodium borodeuteride, methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-(4-^{2}H)talopyranoside was obtained. Acid hydrolysis of these glycoside acetals gave 6-deoxy-L-talose (**3**) and 6-deoxy-L-(4-^{2}H)talose, respectively.

The remarkable epimerization of aldoses at C-2 in the presence of molybdic acid, discovered by Bílik[13], had been used for the synthesis of D-talose from D-galactose[14]. Although the equilibrium between these sugars is 5:1 in favor of D-galactose, this one-step reaction is the best method for preparing D-talose, because the two sugars can readily be separated on a column of a cation-exchange resin in the calcium or barium form[15].



In the present instance, the reaction is effected in the opposite direction, and therefore the equilibrium is very favorable: the reaction mixture produced from 6-deoxy-L-talose contains 84% of L-fucose. Because L-fucose (**4**), in contrast to 6-deoxy-L-talose, forms only a weak complex with cations, it is eluted first from the column, and can thus be obtained rapidly. Its overall yield from methyl α-L-rhamnopyranoside is 72%. Similarly, 6-deoxy-L-(4-^{2}H)talose gives L-(4-^{2}H)fucose. L-Fucose labelled by deuterium on C-3 had already been synthesized from D-mannose[7].

The opportunity was taken to determine the tautomeric composition of 6-deoxy-L-talose (**3**) in aqueous solution. Comparison of the ^{13}C-n.m.r. spectrum of the deuterated and the nondeuterated sugar established the position of the C-4 signals, and most of the other signals were readily assigned by comparison with the ^{13}C spectrum of D-talose[16]. Integration of the signals gave the composition as 44%

of α-pyranose, 28% of β-pyranose, 16% of α-furanose, and 11% of β-furanose at 30°, which is similar to that of D-talose[17] (42:29:16:13).

The ^{13}C-n.m.r. spectrum of 6-deoxy-L-talose (**3**) also settled a controversy concerning the spectrum of D-talose. Angyal and Tran[17] recently suggested that the previous assignments[16,18] for the signals of C-3 and C-4 of the α-pyranose form should be reversed. Comparison of the ^{13}C-n.m.r. spectra of galactose and fucose shows that, on removal of the hydroxyl group from C-6, the signal of C-4 moves downfield by ~2.7 p.p.m. but that that of C-3 is not affected. The same relationship was also found valid for the β-pyranose form of talose. The previous authors[16,18] had assigned a signal at 70.6 p.p.m. to C-3, and one at 66.0 p.p.m. to C-4, of the α-pyranose form of talose. The spectra of both the 4-deuterated and the non-deuterated 6-deoxy-L-talose show a signal at 66.1 p.p.m.; this therefore cannot be the signal of C-4. In fact, the C-4 signal of the α-pyranose was found to be at 73.0 p.p.m., consistent with that of talose being at 70.6 p.p.m. The previous assignments, therefore, did need to be reversed.

EXPERIMENTAL

General methods. — Melting points were determined with a heated Leitz microscope, and are corrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. The progress of reactions was monitored, and the purity of the products was checked, by t.l.c. on silica gel (Merck F 254; E. Merck, Darmstadt) with the following eluants: *A*, 3:1 dichloromethane–diethyl ether, and *B*, 2:3:3 water–propanol–ethyl acetate; the components were located by spraying with 10% sulfuric acid, followed by heating under an i.r. lamp. Evaporations were conducted at <45° under diminished pressure. ^{1}H-N.m.r. spectra were recorded at 250 MHz with a Caméca spectrometer (Thomson–C.S.F., Paris) by Mr. H. Reutenauer; the positions of the peaks are expressed in δ units from the signal of internal tetramethylsilane or sodium 2,2,3,3-tetradeuterio-4,4-dimethyl-4-silapentanoate; ^{13}C-n.m.r. spectra were recorded at 25.182 MHz with a Bruker WP-100 instrument by Mrs. M. L. Dheu-Andriès or Mr. C. Gey, acetone (31.07 p.p.m.) being used as the internal standard. Mass spectra were recorded by Mr. C. Bosso or Mr. L. Patron with a M.S.-30 double-focusing spectrometer (A.E.I. Kratos) on electron impact (direct introduction, 2 kV acceleration, 70 eV ionization, a current of 330 μA, and a source temp. of 150–250°); the spectrometer was coupled to a Varian 100-MS computer. L.c. was conducted at 3.5 MPa with a Waters M-6000 instrument coupled to a UK6 high-pressure injector, using an NH_2 column (Waters) with 9:1 acetonitrile–water as the eluant. The compounds were detected by means of a differential refractometer (R-401) connected to a 10-mV Sefram detector. Elemental analyses were performed by the Central Microanalytical Service of C.N.R.S. at Lyon.

Methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside (**1**). — This was prepared according to Lipták *et al.*[10], except that the reaction mixture was stirred for

0.5 h; t.l.c. (system *A*) then showed the presence of only one compound of R_F 0.43. The syrupy product (98%) had $[\alpha]_D^{25}$ −16.3° (*c* 1, chloroform); lit.[10] $[\alpha]_D$ −16.0° (*c* 1.1, acetone); ^{1}H-n.m.r. data ($CDCl_3$): δ 4.85 (s, $J_{1,2}$ <0.5 Hz, H-1), 4.13 (d, $J_{2,3}$ 5.5 Hz, H-2), 4.08 (t, $J_{3,4}$ 6 Hz, H-3), 3.64 (dq, $J_{4,5}$ 9.5, $J_{5,6}$ 6.5 Hz, H-5), 3.39 (dd, H-4), 3.38 (s, OMe), 1.52, 1.35 (s, CMe_2), and 1.30 (d, H-6); ^{13}C-n.m.r. data ($CDCl_3$): δ 107.57 (CMe_2), 96.31 (C-1), 76.75, 73.97, 72.55 (C-2,3,4), 63.83 (C-5), 53.00 (OMe), 26.14, 24.29 (CMe_2), and 15.59 (C-6).

*Methyl 6-deoxy-2,3-*O*-isopropylidene-α-*L*-lyxo-hexopyranosid-4-ulose* (**2**). — To a stirred solution of the rhamnoside **1** (1.30 g, 6 mmol) in dichloromethane (30 mL) were added pyridinium dichromate (4.5 g, 12 mmol) and 4A molecular sieves (8 g), and the progress of the reaction was monitored by t.l.c. (system *A*). After a period varying between 24 and 36 h, the starting material (R_F 0.43) had disappeared, and a single product (R_F 0.82) was present. After the addition of diethyl ether (90 mL), the mixture was passed through silica gel containing 10% of calcium sulfate (Silica Gel G, Merck; 50 g). The silica was washed with diethyl ether (3 × 20 mL), and the combined filtrates were evaporated, to give **2** as a syrup (1.2 g, 93%); $[\alpha]_D^{20}$ −87.1° (*c* 1.1, chloroform); lit.[9] $[\alpha]_D^{20}$ −107° (*c* 3.5, ethanol); ^{1}H-n.m.r. data ($CDCl_3$): δ 4.81 (s, $J_{1,2}$ <0.5 Hz, H-1), 4.41 (s, 2 H, H-2,3), 4.22 (q, $J_{5,6}$ 6.5 Hz, H-5), 3.43 (s, OMe), 1.44, 1.33 (s, CMe_2), and 1.36 (d, H-6); ^{13}C-n.m.r. data ($CDCl_3$): δ 202.29 (C-4), 109.14 (CMe_2), 96.12 (C-1), 76.74, 73.86 (C-2,3), 67.67 (C-5), 53.65 (OMe), 24.63, 23.41 (CMe_2), and 13.84 (C-6).

Anal. Calc. for $C_{10}H_{16}O_5$: C, 55.5; H, 6.9. Found: C, 55.7; H, 7.2.

*Methyl 6-deoxy-2,3-*O*-isopropylidene-α-*L*-talopyranoside.* — To a stirred solution of the hexosidulose **2** (1.2 g, 5.55 mmol) in methanol (100 mL) was added sodium borohydride (200 mg, 5 mmol), and the progress of the reaction was monitored by t.l.c. (system *A*). After 30 min, the starting material was replaced by a single spot, R_F 0.69. After the addition of a few drops of 10% acetic acid, the solution was evaporated, the residue successively dissolved in methanol (3 × 20 mL) and toluene (20 mL), and evaporated each time to dryness. The yield was quantitative. For characterization, the compound in solvent system *A* was passed through a column of aluminum oxide (Woelm, basic, activity grade 1; 120 g); evaporation gave a colorless syrup, $[\alpha]_D^{20}$ −38.3° (*c* 2.73, chloroform); ^{1}H-n.m.r. data ($CDCl_3$): δ 4.92 (s, $J_{1,2}$ <0.5 Hz, H-1), 4.21 (dd, $J_{2,3}$ 6, $J_{3,4}$ 5 Hz, H-3), 4.03 (d, H-2), 3.84 (q, $J_{4,5}$ <0.5, $J_{5,6}$ 6.5 Hz, H-5), 3.56 (d, H-4), 3.39 (s, OMe), 1.52, 1.36 (s, CMe_2), and 1.32 (d, H-6); ^{13}C-n.m.r. data ($CDCl_3$): δ 109.57 (CMe_2), 98.93 (C-1), 73.76 (C-3), 73.58 (C-2), 67.15 (C-4), 63.16 (C-5), 55.30 (OMe), 26.22, 25.66 (CMe_2), and 17.04 (C-6).

Anal. Calc. for $C_{10}H_{18}O_5$: C, 55.00; H, 8.25. Found: C, 55.10; H, 8.15.

When the reduction was performed with sodium borodeuteride, the 4-deuterium-labelled compound was obtained, $[\alpha]_D^{20}$ −34.8° (*c* 1.22, chloroform); in the n.m.r. spectra, the H-4 and the C-4 signals were absent.

6-Deoxy-L-talose (**3**). — The preceding glycoside (1.2 g, 5.5 mmol) was boiled under reflux with 0.5M sulfuric acid (50 mL) for 5 h. The solution was made

neutral with Amberlite IR-45 (OH^-) resin, and evaporated, to yield a chromatographically homogeneous (R_F 0.68 in system *B*) syrup (850 mg, 94%). After addition of ethanol, crystals (450 mg) were obtained, m.p. 119-120°, $[\alpha]_D^{20}$ −17.3° (*c* 1.3, water; equil. after 24 h) [the lit. values[9] for the m.p. range from 116–118° to 126–127°, and for the equil. rotation, from −18.9 to −20.9°]; ^{13}C-n.m.r. data (D_2O): δ 101.52 (*αf*-1), 96.95 (*βf*-1), 95.38 (*αp*-1), 94.69 (*βp*-1), 87.31 (*βf*-4), 86.64 (*αf*-4), 76.24 (*αf*-2), 73.00 (*αp*-4), 71.96 (*βp*-4 + *βp*-2 or 5), 71.84 (*βp*-2 or 5), 71.74 (*βf*-3?), 71.38 (*βf*-2?), 71.28 (*αp*-2), 69.57 (*βp*-3), 69.47 (?), 67.98 (?), 67.59 (*αp*-5), 66.12 (*αp*-3), 19.27 (*βf*-6), 18.91 (*αf*-6), 16.60 (*αp*-6), and 16.42 (*βp*-6).

When the deuterium-labelled glycoside was similarly hydrolyzed, 6-deoxy-L-[4-^{2}H]talose, m.p. 123–124°, $[\alpha]_D^{20}$ −20.3° (*c* 1.3; equil. in water), was obtained. In the ^{13}C-n.m.r. spectrum, signals at δ 87.31, 86.64, and 73.00 were absent.

L-*Fucose* (**4**). — A solution of **3** (450 mg) and molybdic oxide (10 mg) in water (10 mL) was boiled under reflux. The progress of the reaction was monitored by t.l.c. (system *B*; R_F of fucose, 0.59) or by l.c., 6-deoxytalose being eluted before fucose. Equilibrium was reached after 6 h; the mixture was evaporated, and the residue was passed through a column[15] of Dowex-50W X-2 (Ca^{2+}) resin (100 g) in 3:7 (v/v) methanol–water. The first fraction contained L-fucose (379 mg, 84%) as a syrup that crystallized from ethanol and then had m.p. 137–138°, $[\alpha]_D^{20}$ −77° (*c* 1; equil. in water) [lit.[5] m.p. 137–139°, $[\alpha]_D^{23}$ −75°]; methylphenylhydrazone, m.p. 172–174°, $[\alpha]_D^{20}$ +5° (*c* 2, pyridine) {lit.[5] m.p. 180-182°, $[\alpha]_D^{23}$ +6° (*c* 5, pyridine)}. The second fraction contained 6-deoxy-L-talose (53 mg, 12%).

When the reaction was conducted with 6-deoxy-L-(4^2-H)talose (425 mg), L-(4-^{2}H)fucose (350 mg, 83%) was obtained; m.p. (after crystallization from ethanol) 138–140°, $[\alpha]_D^{20}$ −77° (*c* 1; equil. in water); extent of deuterium substitution (by m.s.) >90%.In the ^{13}C-n.m.r. spectrum (D_2O) the signals[19] of C-4 at δ 73.0 (α) and 72.5 (β) were absent.

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