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AN ALTERNATIVE SYNTHESIS OF 4-DEOXY-4-FLUORO-D-GLUCOSE AND ITS TRANSPORT IN THE HUMAN ERYTHROCYTE*

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ABSTRACT

Treatment of methyl 4-*O*-mesyl-α-D-galactopyranoside with benzyl bromide in *N,N*-dimethylformamide in the presence of silver oxide yielded methyl 2,3,6-tri-*O*-benzyl-4-*O*-mesyl-α-D-galactopyranoside which with *tert*-butylammonium fluoride at reflux underwent nucleophilic displacement to give methyl 2,3,6-tri-*O*-benzyl-4-deoxy-4-fluoro-α-D-glucopyranoside. This compound on hydrogenolysis provided crystalline methyl 4-deoxy-4-fluoro-α-D-glucopyranoside (**9**). The structure of **9** was established by its conversion to the 2,3,6-tri-*O*-acetyl derivative and by n.m.r. and m.s. analysis. Acid hydrolysis of **9** gave 4-deoxy-4-fluoro-D-glucose (**1**). A modification of an established synthesis of 4-deoxy-D-*xylo*-hexose (**2**) from methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside is described. A systematic comparison was made of the transport parameters (K_x and V_{max}) of D-glucose, **2**, and **1** in human erythrocytes The K_x values observed for the above sugars are: 4.0mM, 4.5mM, and 4.6mM, respectively. These results indicate that O-4 in β-D-glucopyranose is not involved in hydrogen bonding to the carrier protein associated with the transport of D-glucose in the erythrocyte.

INTRODUCTION

The synthesis of 4-deoxy-4-fluoro-D-glucose (**1**) by treatment of 1,6:3,4-dianhydro-β-D-galactopyranose with potassium hydrogen fluoride has been reported[2]. Although this synthesis represents an improvement on those previously reported[3], the method has a number of disadvantages: (a) The availability of the starting material is dependent on a photochemical reaction at low concentration (0.3%) of the precursor, 1,6:3,4-dianhydro-2-*O*-tosyl-β-D-galactopyranose, and so the amounts of starting material obtained are restricted by this step. (b) The method of synthesis does not readily permit the introduction of ^{14}C or ^{3}H into **1**. This latter point is of particular importance since 4-deoxy-4-fluoro-D-glucose is now known to have a number of effects on the metabolism of carbohydrates[4,5], which might be understood in more detail if a radio-labelled deoxyfluoro sugar were available.

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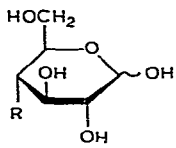
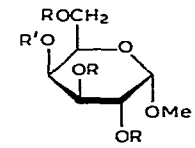
In this paper, therefore, we wish to report (a) an improved alternative synthesis of 4-deoxy-4-fluoro-D-glucose (**1**), which is amenable to the introduction of ^{14}C, and a modified preparation of 4-deoxy-D-*xylo*-hexose[6-8] (**2**); (b) the transport parameters (K_x and V_{max}) obtained for **1**, **2**, and D-glucose in the human erythrocyte.

RESULTS AND DISCUSSION

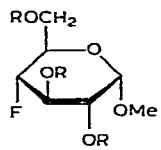
The conformation and mechanistic requirements[9] necessary for a nucleophilic displacement of a sulphonyloxyl group by fluoride anion at C-4 in a hexose dictated the choice of methyl 2,3,6-tri-*O*-benzyl-4-*O*-mesyl-α-D-galactopyranoside (**7**) as a suitable precursor for such an exchange reaction. Methyl 4-*O*-mesyl-α-D-galactopyranoside (**6**) was prepared in good yield by an established sequence[10] (**3**→**4**→**5**→**6**) and converted into **7** in 72% yield by treatment with benzyl bromide in *N*,*N*-dimethylformamide and the presence of silver oxide. Although a direct selective benzoylation



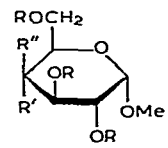
1 R = F
2 R = H



3 R = R′ = H
4 R = Bz, R′ = H
5 R = Bz, R′ = Ms
6 R = H, R′ = Ms
7 R = Bzl, R′ = Ms

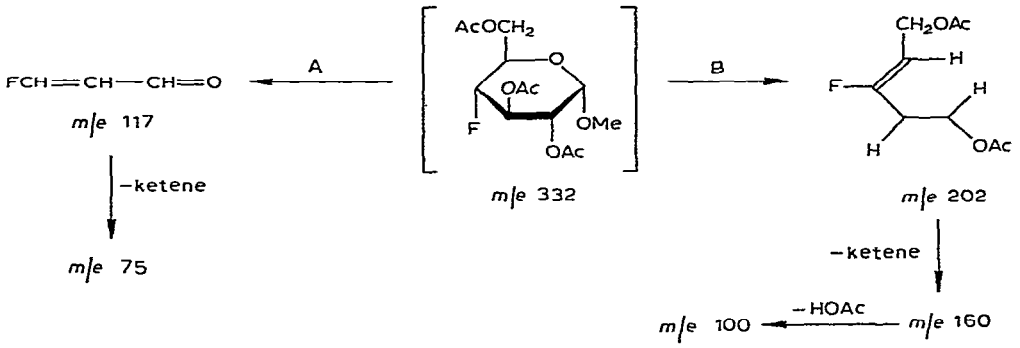


8 R = Bzl
9 R = H
10 R = OAc



11 R = Bz, R′ = H, R″ = I
12 R = Bz, R′ = I, R″ = H
13 R = Bz, R′ = R″ = H
14 R = H, R′ = R″ = H

of **3** at O-2, O-3, and O-6 occurred to yield **4**, all attempts to benzylate **3** selectively in a similar manner with benzyl bromide under a variety of conditions yielded a complex mixture of products. Hence, the more indirect preparation of **7** was undertaken. The n.m.r. spectrum partially fulfilled the structure assigned to **7** with H-1 showing as a doublet (J 2.5 Hz). The other sugar ring-protons, however, showed as a complex multiplet (δ 4.1–3.5), and an interpretation was not possible. Heating **7** with freshly prepared *tert*-butylammonium fluoride[11] in acetonitrile for three days under reflux gave the expected methyl 2,3,6-tri-*O*-benzyl-4-deoxy-4-fluoro-α-D-glucopyranoside (**8**) in 73% yield. The n.m.r. spectrum of **8** did not permit an unambiguous assignment of the structure. Thus, depending on the configuration, the n.m.r. signal for H-4 was expected to be a widely spaced triplet (or quartet), but this could not be distinguished from the superimposed complex multiplet derived from the remaining sugar ring protons. A long-range coupling between the fluorine atom and H-1 has been observed by other workers[3]. The anticipated signal for this proton, however, was shifted upfield (δ 5) and was superimposed over the benzylic ($-CH_2-C_6H_5$) protons. The structure of **8** was subsequently assigned by the hydrogenolysis of **8** to give crystalline methyl 4-deoxy-4-fluoro-α-D-glucopyranoside (**9**), which was converted into the 2,3,6-tri-*O*-acetyl derivative **10**. The n.m.r. spectrum of **10**, in benzene-d_6, showed H-1 as a triplet owing to long-range coupling between



Scheme 1. Part of the mass-spectral fragmentation pattern of methyl 2,3,6-tri-*O*-acetyl-4-deoxy-4-fluoro-α-D-glucopyranoside (**10**) (see Experimental section).

F–H-1 and H-1–H-2. Three pairs of doublets were observed for H-4 and, based on previous work[2,3], they were interpreted as $J_{4,3} = J_{4,5} = 9.5$ Hz and $J_{4,F}$ 3.75 Hz. The large value for $J_{4,3}$ and $J_{4,5}$ was attributed to the D-*gluco* configuration of **10** since H-4, H-3, and H-5 would be all-*trans* and diaxial. Further support for the structure of **10** was provided by the mass spectrum, which gave a fragmentation pattern similar to those proposed for other 4-fluoro-substituted hexopyranoses[3]. Thus, the presence of the fluorine atom at C-4 in **10** makes the cleavage of C-4–C-5 and C-4–C-3 bonds an unfavourable process[13] resulting, in this case, with the observed small peaks at *m/e* 117 and *m/e* 75 (Scheme 1, pathway **A**). The large peaks observed at *m/e* 160, *m/e* 100, and *m/e* 202 (Scheme 1, pathway **B**) are consistent with those reported for other 4-fluoro-substituted hexose derivatives[3,12,13].

Hydrolysis of **9** with 2M sulphuric acid gave, in 71% yield, crystalline 4-deoxy-4-fluoro-D-glucose (**1**), which was shown to be identical to that prepared by the previously reported method[2] (mixed m.p., t.l.c., i.r., and optical rotation). The yields in the conversion of **3** to **1** are uniformly high, and the synthesis provides a less tedious access to the final product than by those methods previously reported. Moreover, the route provides a method for the preparation of U-^{14}C-labelled **1**, since D-[U-^{14}C]-galactose is available.

4-Deoxy-D-*xylo*-hexose (**2**) has been made previously *via* a sodium iodide exchange reaction from methyl 2,3,6-tri-*O*-benzoyl-4-*O*-mesyl-α-D-glucopyranoside[6]. We have modified this procedure by starting with the more readily accessible D-galactopyranoside derivative **5**. Thus, treatment of **5** with sodium iodide in *N,N*-dimethylformamide yielded an 11:1 mixture of 4-deoxy-4-iodo-α-D-gluco- and -D-galacto-pyranoside (**11** and **12**) that could be separated by column chromatography. Hydrogenolysis of **11** and **12** gave only the expected methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-α-D-*xylo*-hexopyranoside (**13**) which after alkaline hydrolysis afforded methyl 4-deoxy-α-D-*xylo*-hexopyranoside (**14**). Acid hydrolysis of **14** gave **2**, identical to that previously reported[6–8].

The systematic comparison of the transport parameters (K_x, K_i, and V_{max}) of monodeoxyfluoro- and monodeoxy-monosaccharides has been used in order to

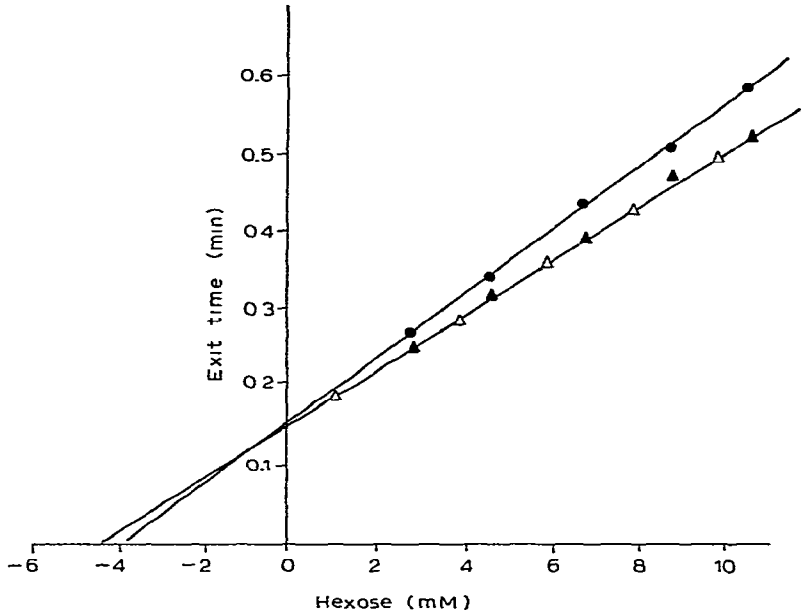


Fig. 1. Exit of D-glucose (●), 4-deoxy-4 fluoro-D-glucose (**1**) (△), and 4-deoxy-D-*xylo*-hexose (**2**) (▲) from the human erythrocyte at 37°.

TABLE I

K_x AND V_{max} VALUES OF D-GLUCOSE, 4-DEOXY-4-FLUORO-D-GLUCOSE (**1**), AND 4-DEOXY-D-*xylo*-HEXOSE (**2**) AT 37°

Compound	K_x (*mM*)	V_{max} (*mmol litre^{-1} min^{-1}*)
D-Glucose	4 0	645
1	4 6	645
2	4 5	645

probe the specificity of hydrogen-bonding sites between D-glucose and the carrier protein(s) known to be present in human erythrocyte[14,15] and the hamster intestine[16]. In the case of the erythrocyte membrane, these and other studies[17] have led to the proposal that hydrogen bonding occurs between O-1, O-3, and the ring oxygen O-5 of the $^1C_4$ (D) conformation of β-D-glucopyranose and at least three receptor sites[18] on the carrier protein. This model is also consistent with the proposed mode of cytochalasin *B* inhibition of D-glucose transport[19]. Recently, the carrier protein in erythrocyte membrane has been located and identified[20].

Although this model for D-glucose binding has been accepted by many, some controversy[14,17] exists as to whether or not OH-4 is involved in hydrogen bonding to the carrier protein. Our results obtained for the exit of D-glucose, **1**, and **2** (Fig. 1 and Table I) from the erythrocyte indicate that O-4 in D-glucose is not involved in

hydrogen bonding. If this were the case, the K_x value for **2** (4.5mM) would be 4- to 5-fold higher[15] (indicating less affinity for the carrier) than the values observed for D-glucose (4.0mM) and **1** (4.6mM).

Since the specificity of the transport system is considered to be asymmetric with an outward- and inward-facing conformation[23], our K_x values for the exit of the sugar analogues relate to the binding specificity of the outward-facing conformation of the carrier.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Thin-layer chromatography was carried out on 20 × 20 cm plastic plates, coated with a 0.2-mm layer of silica gel (Brinkmann). Carbohydrates were detected by spraying with a 50% (v/v) solution of concentrated sulphuric acid in ethanol, followed by heating at 110° for 2–5 min. The following solvent systems (all mixtures v/v) were used: (*A*) ethyl acetate; (*B*) 1:1 ethyl acetate–petroleum ether (b.p. 30–60°); (*C*) 3:2 ether–petroleum ether (b.p. 30–60°); (*D*) 4:1 ethyl acetate–ethyl alcohol; and (*E*) 7:8 ether–petroleum ether (b.p. 30–60°). Chromatography is described in the experimental text. Silica gel used was Grade H (W. R. Grace and Co, Davison Chemical Division, Baltimore, MD 21202 U.S.A.). Optical rotations were determined with a manual Rudolph polarimeter on solution in a 2.0-dm tube. I.r. spectra were recorded over the range 4000–650 cm^{-1} with a Beckman IR-12 spectrophotometer. N.m.r. spectra were recorded with a JEOLCO-C-60HL spectrometer; chemical shifts are expressed in p.p.m. (δ) downfield from the internal standard tetramethylsilane on solutions in chloroform-*d* or benzene-d_6. Electron impact (high resolution) m.s. were recorded with a Varian MAT CH5-DF spectrometer. Microanalyses were determined by A. B. Gygli, Toronto, Ontario, Canada.

Human erythrocyte preparation. — Samples of fresh or recently outdated whole blood (10–25 days old) in acid citrate-dextrose (ACD) was obtained from the Windsor Red Cross Society, Windsor, Ontario. The blood could be stored in this condition for up to 3 weeks at 4°. The cells were separated from 10 ml of blood by centrifugation (3000 r.p.m. for 10 min at 20°), and the plasma and top layer removed. The cells were washed twice and resuspended in saline solution (1%, w/v, sodium chloride–4mM sodium phosphate, pH 7.4). Washed, packed erythrocytes (1 part) were suspended in a solution of 100mM test sugar (19 parts) (D-glucose, **1**, or **2**) and incubated for 30 min at 37° to achieve equilibrium.

Hexose transport (Exit). — A 3-ml cuvette containing 2.5 ml of saline-buffer solution, which was either free of test sugar or contained up to 50% of the preloaded test-sugar concentration in the erythrocyte preparation, was placed in the sample compartment of a Beckman ACTA MVI UV/VIS recording spectrophotometer. The contents of the cuvette were continually stirred with a built-in magnetic stirrer, and the temperature was maintained at 37 ±0.1° by a Forma temperature bath and circulator. A portion (20 μl) of the preloaded erythrocyte suspension was added and

the slit-width control on the spectrophotometer adjusted to bring the E_{700} on the scale to 0–0.1. The absorbance scale was calibrated with the cellular concentration of the sugar by equating the change in absorbance between zero time and at osmotic equilibrium with the known change in the internal cell concentration of test sugar.

Kinetics of hexose transport (Exit). — The rate of exit of hexoses can be followed spectrophotometrically, by the method of Sen and Widdas[21], by use of the simplified rate equation of Miller *et al.*[22] $\Delta t \propto 1/v = [X_0]/V_{max} \cdot K_x + 1/V_{max}$, where v is the initial rate of sugar exit, V_{max} is the maximum rate of transfer, $[X_0]$ is the external concentration of hexose, and K_x is the half-saturation constant of the sugar-carrier complex, and is a parameter considered to reflect the affinity of the sugar for the carrier system. Thus, a linear plot of $1/v$ against $[X_0]$ should give $1/V_{max}$ as the intercept on the y axis and $-K_x$ as the intercept on the x axis (See Fig. 2).

4-Deoxy-4-fluoro-D-glucose. — This compound was prepared by the method of Barford *et al.*[2], m.p. 189–190°, $[\alpha]_D^{23}$ +26.5→ + 50° (*c*, 1.0 water); R_F (*D*) 0.17.

Anal. Calc. for $C_6H_{11}FO_5$: C, 39.56; H, 6.04; F, 10.43. Found: C, 39.40; H, 6.12; F, 10.32.

Methyl 2,3,6-tri-O-benzyl-4-O-mesyl-α-D-galactopyranoside (**7**). — To a solution of methyl 4-*O*-mesyl-α-D-galactopyranoside (**6**, 15 g) in anhydrous *N,N*-dimethylformamide (130 ml) was added silver oxide (39 g) and benzyl bromide (36 ml). The reaction mixture was protected from moisture and stirred magnetically for 3 days at room temperature. Then, it was filtered and the solid washed with chloroform (3 × 25 ml). The filtrate was diluted with chloroform (250 ml), filtered, and washed with water (3 × 200 ml). Pyridine (30 ml) was added to the chloroform layer, and the solution was washed successively with water (2 × 250 ml), 2M hydrochloric acid (3 × 100 ml), saturated sodium hydrogencarbonate (100 ml), and finally with water (2 × 200 ml). The chloroform extract was dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The resulting residue (32 g) was divided into two parts and chromatographed on a column of aluminium oxide (Brinkmann, activity II, 450 g). Elution with 5:1 (v/v) petroleum ether (b.p. 30–60°)–ether (600 ml) removed dibenzyl ether (6 g); elution with ether (500 ml) yielded **7** as a colourless syrup (21.5 g, 72%), $[\alpha]_D^{23}$ +43° (*c* 2.03, chloroform); R_F (*B*) 0.47; $\nu_{max}^{CHCl_3}$ 3090, 3070, 3040 (m, C_6H_5), 2000–1600 (w, C_6H_5), 1500, 1450 (m, C_6H_5), 1175 (s, SO_3), and 790–710 cm^{-1} (m, C_6H_5); n.m.r.: δ 7.25 (s, 15 H, C_6H_5), 5.25 (d, 1 H, *J* 2.5 Hz, H-1), 4.75–4.46 (m, 6 H, CH_2-C_6H_5), 4.1–3.5 (m, 6 H, H-2,-3,-4,-5, and H_2-6), 3.35 (s, 3 H, OCH_3), and 2.9 (s, 3 H, SO_3CH_3).

Anal. Calc. for $C_{29}H_{34}O_8S$: C, 64.20; H, 6.30; S, 5.90. Found: C, 64.10; H, 6.40; S, 5.80.

Methyl 2,3,6-tri-O-benzyl-4-deoxy-4-fluoro-α-D-glucopyranoside (**8**). — Tetrabutylammonium fluoride[11] was prepared by titration of 40% aqueous tetrabutylammonium hydroxide (60 ml) with 50% aqueous hydrofluoric acid to pH 7.0. The solution was concentrated under reduced pressure, and the resulting syrup was dried and stored overnight in the presence of phosphorus pentaoxide at 0.1 mm. A mixture of **7** (7.9 g), tetrabutylammonium fluoride (freshly prepared), and anhydrous aceto-

nitrile (70 ml) was heated under reflux at 70–80°, and the reaction was monitored by t.l.c. (*E*). After 3 days, the reaction appeared to be complete, and the mixture was poured into water (50 ml) and extracted with ether (3 × 150 ml). The ether layer was dried ($MgSO_4$) and concentrated under diminished pressure. The syrupy residue was chromatographed on a column of silica gel (grade H, mesh size 60–200, 240 g). Elution with 7:3 (v/v) ether–petroleum ether (b.p. 30–60°) yielded **8** as a colourless syrup (5 g, 73%), $[\alpha]_D^{23}$ +48.8° (*c* 1.23, chloroform); R_F (*C*) 0.63, (*A*) 0.68; $\nu_{max}^{CHCl_3}$ 3090, 3070, 3090 (m, C_6H_5), 2000–1600 (w, C_6H_5), 1500, 1450 (m, C_6H_5), 1050 (s, C-F), and 790–710 cm^{-1} (m, C_6H_5); n.m.r.: δ 7.3 (s, 15 H, C_6H_5), 5.05–3.5 (m, 13 H, H-1,-2,-3,-4,-5,H_2-6, and CH_2-C_6H_5), and 3.4 (s, OCH_3).

Anal. Calc. for $C_{28}H_{31}FO_5$: C, 72 10; H, 6.65; F, 4 07. Found: C, 72.00; H, 6.69; F, 4 16.

Methyl 4-deoxy-4-fluoro-α-D-glucopyranoside (**9**). — A solution of **8** (4.9 g) in ethanol (85 ml) was shaken in the presence of hydrogen and palladium-on-charcoal (5 g, 5%) at room temperature until the hydrogen uptake ceased (24 h). The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The residue was dissolved in the minimum amount of methanol, placed on a column of silica gel (grade H, mesh size 60–200, 70 g), and eluted with ethyl acetate (600 ml). After removal of the solvent under reduced pressure, it crystallised (1.1 g, 53%). Recrystallisation from 1:1 (v/v) ethyl acetate–acetone gave **9** as a colourless compound, m.p. 129–130°, $[\alpha]_D^{23}$ +131° (*c* 0.92, water); R_F (*A*) 0.3, (*C*) 0.44; $\nu_{max}^{CHCl_3}$ 3460, 3380 (s, OH), and 1035 cm^{-1} (s, C-F); n.m.r.: δ 4.8–4.55 (m, 3 H, OH-2,-3, and -6), 4.2–3.5 (m, H-1,-2,-3,-4, and -5), 3.4 (s, 3 H, OCH_3), and 3.15 (s, 2 H, H_2-6).

Anal. Calc. for $C_7H_{13}FO_5$: C, 42.85; H, 6 63; F, 9.69. Found: C, 42.68; H, 6.71; F, 9.43.

4-Deoxy-4-fluoro-D-glucose (**1**). — A solution of **9** (500 mg) in 2M sulphuric acid (50 ml) was heated under reflux for 3 h and the reaction was monitored by t.l.c. (*C*). After neutralisation with solid barium carbonate, the reaction mixture was filtered, and the filtrate concentrated to dryness under reduced pressure. The residue was taken up in absolute ethanol, and the solution was filtered through a bed of Kieselguhr and decolourizing charcoal, and evaporated to dryness. The syrupy residue crystallised on being kept at room temperature. Recrystallisation from ethanol–ethyl acetate gave **1** (330 mg, 71%) as a colourless solid, m.p. 189–190°, $[\alpha]_D^{23}$ +26.5→ +50° (equil. *c* 1.0, water); R_F (*C*) 0.17; i.r. identical with that of an authentic sample[2]; lit.[2] m.p. 187–189°, $[\alpha]_D^{23}$ +26→49° (9 min, *c* 1.0, water); mixed m.p. with authentic sample 188–189°.

Anal. Calc. for $C_6H_{11}FO_5$: C, 39.50; H, 6.00; F, 10.40. Found. C, 39.34; H, 6.12; F, 10.32.

Methyl 2,3,6-tri-O-acetyl-4-deoxy-4-fluoro-α-D-glucopyranoside (**10**). — To a solution of **9** (200 mg) in ice-cold pyridine (5 ml) was added acetic anhydride (0.5 ml). The solution was kept for 24 h at room temperature, and then poured into ice–water (15 ml). The product was extracted with chloroform (3 × 10 ml), and the chloroform extract was washed successively with 2M hydrochloric acid (3 × 10 ml), saturated

sodium hydrogencarbonate (10 ml), and water (10 ml), dried ($MgSO_4$), filtered, and evaporated to dryness, leaving **10** as a colourless viscous syrup, $[\alpha]_D^{23}$ +41.0° (*c* 0.55, chloroform); R_F (*A*) 0.2; $\nu_{max}^{CHCl_3}$ 1730 (s, C=O) and 1320–1275 cm^{-1} (s, C-O-C); n.m.r. (C_6D_6): δ 6.0–5.4 (3 pairs of d, 1 H, $J_{4,5}$ 9.5, $J_{4,3}$ 9.5, $J_{4,F}$ 3.75 Hz, H-4), 4.65 (t, 1 H, H-1), 4.6–4.1 (m, 2 H, H_2-6), 4.1–3.9 (m, 5 H, H-1,-2,-3,-5, and H_2-6), 3.7 (t, *J* 9.0 Hz, H-3), 3.55–3.3 (m, 1 H, H-2), 2.65 (s, 3 H, OCH_3), and 1.45 (d, 9 H, *J* 4.5 Hz, $COCH_3$); e.i.m.s. (*m/e* 160 as base peak): *m/e* 291(5), 249(7), 242(18), 231(20), 204(6), 203(64), 202(23), 194(8), 189(11), 182(8), 169(30), 161(21), 160(100), 159(5), 149(26), 145(19), 144(33), 143(6), 142(17), 141(13), 140(10), 139(22), 131(18), 129(15), 127(5), 122(5), 121(51), 119(13), 118(8), 117(11), 112(13), 108(9), 107(23), 105(54), 103(53), 102(73), 101(41), 100(73), 99(32), 98(15), 97(13), 94(7), 87(11), 85(6), 82(5), 81(10), 79(6), 75(1), 72(23), 71(5), 70(25), 69(13), 61(11), 60(10), 59(14), 57(19), 55(12), 53(5), 51(7), 45(11), 44(42), 43(>100), 42(19), 41(12), 40(5), 39(8), 32(40), 31(5), 29(19), and 28(>100); peaks *m/e* 75, 100, 117, 160, and 202 correspond to Scheme 1.

Anal. Calc. for $C_{13}H_{19}FO_8$: C, 48.44; H, 5.90; F, 5.90. Found: C, 48.40; H, 5.86; F, 5.69.

*Methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-iodo-*α*-*D*-gluco-* (**11**) *and* α-D-*galacto-pyranoside* (**12**). — A mixture of **5** (10 g) and sodium iodide (12.8 g) was heated under reflux for 1 h in anhydrous *N,N*-dimethylformamide (140 ml). The reaction mixture was cooled and diluted with ether (250 ml). The ether solution was washed with water (4 × 200 ml), dried ($MgSO_4$), and evaporated to a thick syrup, which was shown by t.l.c. (*F*) to contain at least two products and some unreacted starting material. The syrup was divided into two parts and chromatographed on a column of silica gel (grade H, 190 g). Elution with 2:5 (v/v) ether–petroleum ether (b.p. 30–60°) yielded 500 mg of a colourless thick syrup, which was identified by n.m.r. as **12**, R_F (*E*) 0.51; $\nu_{max}^{CHCl_3}$ 3050 (w, C_6H_5), 1730 (s, C=O), and 1280 cm^{-1} (s, C-O-C); n.m.r.: δ 8.3–7.2 (m, 15 H, C_6H_5), 6.4–4.9 (m, 7 H, H-i,-2,-3,-4,-5, and H_2-6), and 3.5 (s, 3 H OCH_3).

Elution with 3:5 (v/v) ether–petroleum ether (b.p. 30–60°) gave a colourless light solid, which was redissolved in benzene and evaporated to dryness. Recrystallisation from absolute ethanol gave **11** (5.5 g); m.p. 159°, $[\alpha]_D^{23}$ +110° (*c* 1.55, chloroform); R_F (*E*) 0.46; $\nu_{max}^{CHCl_3}$ (w, C_6H_5), 1730 (s, C=O), and 1280 cm^{-1} (s, C-O-C); n.m.r.: δ 8.3–7.25 (m, 15 H, C_6H_5), 6.2 (t, *J* 9.5 Hz, H-4), 5.3 (s, 1 H), 5.15 (t, 1 H, $J_{2,1}$ 4, $J_{2,3}$ 5 Hz, H-2), 5–4.1 (m, 4 H, H-3,-5, and H_2-6), and 3.5 (s, 3 H, OCH_3).

Anal. Calc. for $C_{28}H_{25}IO_8$: C, 54.56; H, 4.09; I, 20.59. Found: C, 54.80; H, 4.30; I, 20.40.

Elution with ether gave 600 mg of the starting material (comparative t.l.c., i.r., n.m.r., and m.p.).

*Methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-*α*-*D*-xylo-hexopyranoside* (**13**). — A solution of sodium acetate (3 g) in ethanol (3.1 ml of water and 31 ml of absolute ethanol) was added to a mixture of methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-iodo-α-D-gluco- and

-α-D-galacto-pyranoside (**11** and **12**, 4.5 g) in ethyl acetate (62 ml). The mixture was shaken in the presence of hydrogen and palladium-on-charcoal (2 g, 5%) at room temperature until the hydrogen uptake ceased (13 h). The reaction mixture was treated as previously reported[6] to yield a syrup that crystallised. Recrystallisation from absolute ethanol gave colourless, needle-shaped crystals (5.2 g), m.p. 116–117°, $[\alpha]_D^{23}$ +137° (*c* 1.1, chloroform); R_F (*E*) 0.44; n.m.r.: δ 8.2–7.2 (m, 15 H, C_6H_5), 5.8 (sex., 1 H, *J* 4.5 Hz, H-1), 5.4 (d, 1 H, *J* 3 Hz, H-2), 5.2 (d, 1 H, *J* 3 Hz, H-3), 4.6–4.4 (m, 3 H, H-5, H_2-6), 3.5 (s, 3 H, OCH_3), 2.7–2.3 (m, 1 H, H-4_e), and 2.0 (t, 1 H, *J* 10.5 Hz, H-4_a); lit.[6] m.p. 116–117°, $[\alpha]_D^{23}$ +133° (*c* 1.0, chloroform).

Anal. Calc. for $C_{28}H_{26}O_8$: C, 68.56; H, 5.34. Found: C, 68.38; H, 5.21.

Methyl 4-deoxy-α-D-glucopyranoside (**14**). — A suspension of **13** (2.0 g) in anhydrous methanol (40 ml) was cooled to 4°, and an ice-cold solution of sodium methoxide (75 mg of sodium in 1.5 ml of anhydrous methanol) was added. The reaction mixture was stirred for 20 h at 4°, neutralized with Amberlite LR-120 (H^+) ion-exchange resin (20 ml), and filtered. The filtrate was evaporated *in vacuo*. The residue was dissolved in the minimum amount of methanol and chromatographed on a column of silica gel (grade H, 40 g). Elution with 9:1 (v/v) ethyl acetate–ethanol gave a chromatographically pure compound. Recrystallisation from ethyl acetate gave 560 mg (76%) of **14**, m.p. 90–91°, $[\alpha]_D^{23}$ +176° (*c* 1.2, methanol); R_F (*D*) 0.32; lit.[6] m.p. 90–91°, $[\alpha]_D^{23}$ +175° (*c* 1.0, methanol).

4-Deoxy-D-xylo-hexopyranose (**2**). — A solution of methyl 4-deoxy-α-D-*xylo*-hexopyranoside (**14**, 500 mg) in water (30 ml) was heated under reflux with Amberlite IR-120 (H^+) ion-exchange resin (20 ml) for 8 h and the reaction was monitored by t.l.c. (*D*). The reaction mixture was filtered and the filtrate evaporated to a thick syrup. This was dissolved in absolute ethanol (20 ml), the solution filtered through a bed of decolourising charcoal and evaporated to dryness to yield a syrup that crystallised after 12 h. Recrystallisation from ethyl acetate–methanol gave 280 mg (60%) of **2**, m.p. 139–141°, $[\alpha]_D^{23}$ +38→ +60° (equil. *c* 1.2, water); R_F (*D*) 0.24; lit.[6]: $[\alpha]_D$ +29→ +55.5°, +44→ +60°, +36→58° (equil., water).

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