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Note

A short synthesis of 2-deoxy-2-fluoro-D-glucose

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The title compound (**4**) is a proven[1] D-glucose analog and the renewed interest in this substance lies primarily in the use of 2-deoxy-2-[^{18}F]fluoro-D-glucose as an imaging agent in studies of D-glucose metabolism by positron-emission tomography. Several new syntheses[2–7] of **4** have been recently described.

In principle, a fluorine atom can be introduced at C-2 of the D-glucose molecule either by electrophilic addition of a fluorinated residue to D-glucal or its derivatives or by an S_N2 fluoride-ion displacement reaction of suitably protected derivatives of D-mannose (**1**). Of the approaches that belong to the second category, the synthesis by Dessinges *et al.*[2] is unique in that it does not require the isolation of an activated derivative of the alcohol, *e.g.*, a corresponding *O*-sulfonyl derivative. Unfortunately, the preparation of benzyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside, the starting material in the synthesis[2], is a tedious, multistep process. In search for a more readily available starting material having the same stereoconfiguration, we turned our attention to 1,3,4,6-tetra-*O*-acetyl-β-D-mannopyranose (**2**), which can be obtained[8] from **1** in a one-pot operation, and investigated its reaction with diethylaminosulfur trifluoride (Et_2NSF_3). The reaction was performed in dichloromethane, toluene, Diglyme, dimethoxyethane, or acetonitrile and with Et_2NSF_3 alone (≤4 molar proportions). At temperatures up to 70°, only traces of the desired product **2** were formed (t.l.c.). The addition of pyridine[9,10] to the reaction mixture did not affect the desired conversion markedly, but caused partial 1-*O*→2-*O*-acetyl group migration, resulting in the formation of by-products. However, when **2** was treated with Et_2NSF_3 (3 molar proportions) in Diglyme at 100°, a rapid reaction occurred and, after a reaction time of 7 min, crystalline **3** was obtained in 77% yield, following isolation by column chromatography on silica gel. Simple deacetylation (Zemplén) of **3** yielded **4**, the ^{13}C-n.m.r. data of which were in accord with those reported[3,11]. Small differences in the observed chemical shifts and $J_{C,F}$ coupling constants were attributed to different conditions of measurements. The preparation of **4** described herein constitutes the shortest way, reported to date, of obtaining this important fluoro sugar.

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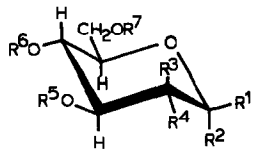

	R^1	R^2	R^3	R^4	R^5	R^6	R^7
1	HOH		OH	H	H	H	H
2	OAc	H	OH	H	Ac	Ac	Ac
3	OAc	H	H	F	Ac	Ac	Ac
4	HOH		H	F	H	H	H

EXPERIMENTAL

General methods. — Melting points were determined with a Büchi melting-point apparatus. Preparative chromatography was performed by gradient elution from slurry-packed columns of Silica gel 60 (Merck, Cat. No. 9385) with 12:1→8:1 toluene–acetone. ^{13}C- (25 MHz) and ^1H-n.m.r. (220 MHz) spectra were recorded at 25° for solutions in $CDCl_3$ (internal standard Me_4Si) and D_2O (internal standard MeOH, δ_{MeOH} *vs.* δ_{Me_4Si} 49.0 p.p.m.). Ammonia c.i. mass spectra were recorded with a Finnigan 10150 spectrometer at a source pressure and temperature of 133 Pa and 100°, respectively. Diglyme (Aldrich) was dried over molecular sieves 4A and Et_2NSF_3 (Aldrich) was distilled under reduced pressure.

*1,3,4,6-Tetra-*O*-acetyl-β-*D*-mannopyranose* (**2**). — This compound was prepared with a slight modification of the procedure described by Deferrari *et al.*[8] as we found that the amount of PBr_3 used in the original procedure (0.65 mL/g of the starting material **1**) was insufficient to generate the amount of HBr necessary to convert the intermediate 1,2,3,4,6-penta-*O*-acetyl-D-mannopyranose into the corresponding glycosyl bromide. Starting with 6.6 g of D-mannose[8] and using 5.3 mL of PBr_3, the reaction gave consistently 2.2–2.4 g (~18%)* of crystalline **2**. The crystalline material was sufficiently pure (t.l.c., ^1H-n.m.r.) and was used without recrystallization for the next step. An analytical sample of **2**, recrystallized from ethanol, exhibited m.p. 165–167°; lit.[8] m.p. 164–165°; ^1H-n.m.r. ($CDCl_3$): δ 5.78 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 5.38 (1 H, $J_{4,5}$ 10 Hz, H-4), 5.07 (dd, 1 H, $J_{2,3}$ 3, $J_{3,4}$ 10 Hz, H-3), 4.30 (dd, 1 H, $J_{5,6a}$ 5, $J_{6a,6b}$ 12 Hz, H-6a), 4.19 (bt, 1 H, $J_{2,3}$ 3 Hz, H-2), 4.11 (dd, 1 H, $J_{5,6b}$ 2.2 Hz, H-6b), 3.78 (ddd, 1 H, $J_{4,5}$ 9.5 Hz, H-5), 2.54 (d, 1 H, $J_{2,OH}$ 3 Hz, OH, disappears on deuteration), 2.17, 2.11, 2.08, and 2.05 (4 × s, 4 × 3 H, 4 × OAc).

*1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-fluoro-β-*D*-glucopyranose* (**3**). — To a suspension of **2** (0.7 g, 2 mmol) in Diglyme (5 mL) was added Et_2NSF_3 (0.72 mL, 6 mmol). The mixture was stirred at 100–110° (bath) for 7 min, cooled to 0°, and methanol (1 mL) was added. After partitioning between dichloromethane and aqueous $NaHCO_3$ solution, the organic phase was dried (Na_2SO_4) and evaporated,

*On the same scale of the reaction, the yield of 1.8 g is erroneously reported[8] as 29%.

and the residue was chromatographed to give the fastest-moving product. Crystallization from ether–2-propyl ether gave pure **3** (0.54 g, 77%), m.p. 95–96°; lit.[12] m.p. 91–92°; ^{1}H-n.m.r. ($CDCl_3$): δ 5.80 (dd, 1 H, $J_{1,2}$ 8, $J_{1,F}$ 3.2 Hz, H-1), 5.39 (dt, 1 H, $J_{3,4}$ 9.5, $J_{3,F}$ 14 Hz, H-3), 5.08 (t, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 4.45 (ddd, 1 H, $J_{2,3}$ 9.3, $J_{2,F}$ 51 Hz, H-2), 4.31 (dd, 1 H, $J_{6a,6b}$ 12 Hz, H-6a), 4.10 (dd, 1 H, H-6b), 3.88 (ddd, 1 H, $J_{5,6a}$ 4.5, $J_{5,6b}$ 2.2 Hz, H-5), 2.19, 2.10, 2.09, and 2.04 (4 × s, 4 × 3 H, 4 × OAc).

*2-Deoxy-2-fluoro-*D*-glucose* (**4**). — A solution of **3** (155 mg) in methanol (5 mL) was treated with M methanolic sodium methoxide (1 mL) and kept overnight at room temperature. After neutralization with Amberlite IR-120 (H^+) cation-exchange resin, the solution was concentrated and the residue crystallized from methanol–ethyl acetate to give **4** (72 mg, 90%), m.p. 180–181°; lit.[13] m.p. 170–176° and 177–179° for two independently prepared samples of **4**; lit.[12] m.p. 160–165°; ^{13}C-n.m.r. (D_2O): δ 93.7 (d, $J_{C,F}$ 22.7 Hz, C-1β), 93.0 (d, $J_{C,F}$ 183.2 Hz, C-2β), 90.4 (d, $J_{C,F}$ ~188 Hz, C-2α), 89.8 (d, $J_{C,F}$ 21.3 Hz, C-1α), 76.1 (s, C-5β), 74.2 (d, $J_{C,F}$ 16.9 Hz, C-3α), 71.3 (s, C-5α), 71.3 (d, $J_{C,F}$ 17.3 Hz, C-3α), 69.4 (d, $J_{C,F}$ 8.1 Hz, C-4β), 69.3 (d, $J_{C,F}$ 8.1 Hz, C-4α), 60.7 (s, C-6β), and 60.5 (s, C-6α).

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