A Rapid, Stereospecific Synthesis of 2-Deoxy-2-fluoro-D-glucose using the Fluoride Ion

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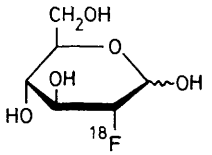
The reaction of KHF_2 with 1,2-anhydro-3,4 : 5,6-di-*O*-isopropylidene-1-*C*-nitro-D-mannitol (**4**) provides a rapid, stereospecific route to 2-deoxy-2-fluoro-D-glucose (**2**), the ^{18}F-labelled analogue of which, (**1**), is an important radiopharmaceutical of use in medical imaging.

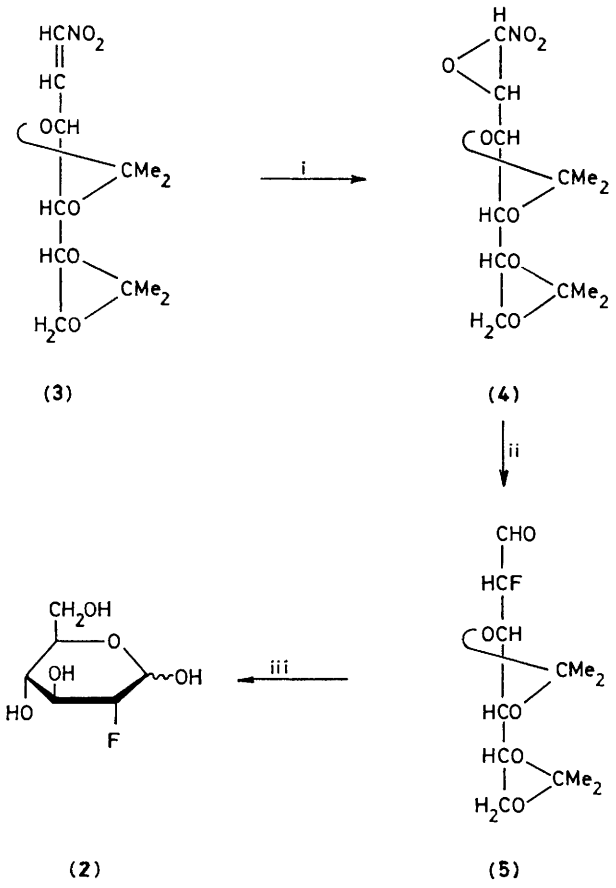
The central importance of 2-deoxy-2-[^{18}F]fluoro-D-glucose (**1**) is in the exploitation of positron emission tomography (p.e.t.),[1] for which it has been a key to the measurement of both myocardial[2] and regional cerebral[3] glucose metabolism. Although several syntheses of 2-deoxy-2-fluoro-D-glucose (**2**) have been published,[4] it has been that of Ido *et al.*[4c] which, almost exclusively, has been used, after suitable adaptation,[5] for the preparation of (**1**). Very recently, brief abstracts indicating the salient features of two alternative syntheses of (**1**) were published;[6]† their radiochemical yields did not exceed 20%. The evident, growing interest in p.e.t.,[7] and the pressing need for the efficient utilization of ^{18}F in the synthesis of (**1**), prompted us to report a new, rapid, stereospecific synthesis of (**2**), in which the fluoride ion is employed. This procedure could be easily adaptable for the preparation of (**1**) for medical imaging.



(**1**)

Compound (**3**) is obtained readily from 1-deoxy-3,4: 5,6-di-*O*-isopropylidene-1-*C*-nitro-D-*manno*- and -*gluco*-hexitol by

† Subsequent to the submission of the present manuscript, another new synthesis of (**2**) was reported: M. J. Adam, *J. Chem. Soc., Chem. Commun.*, 1982, 730.



i, H_2O_2, $NaHCO_3$; ii, KHF_2; iii, BCl_3, CH_2Cl_2.

the method of Funibashi *et al.*[8] Treatment of (**3**) with 30% hydrogen peroxide[9] gave an 87% yield of a mixture of 1,2-anhydro-3,4:5,6-di-*O*-isopropylidene-1-*C*-nitro-D-mannitol (**4**) and -D-glucitol, from which crystalline (**4**) (m.p. 112.5—113 °C) was isolated in 72% yield.

The epoxide ring was opened by heating (**4**) with potassium hydrogen fluoride in ethane-1,2-diol at 110 °C. Within 25 min (**4**) was no longer detectable by thin-layer chromatography on silica gel G, using 1:1 (*v*/*v*) toluene–ethyl acetate (solvent A). Extraction of the reaction solution (after dilution with water) with CH_2Cl_2 afforded (**5**)‡ in 79% yield. Compound (**5**) (R_f 0.37, solvent A) was shown to be homogeneous by ^1H- and ^{19}F-nuclear magnetic resonance spectroscopy. No evidence for the formation of the *manno*-epimer of (**5**) has been obtained, despite a careful search by chromatographic methods.

The deacetalation of (**5**) was accomplished within 5 min by treatment with a dry solution of boron trichloride in CH_2Cl_2 at room temperature. This treatment yielded (**2**) (m.p. 159—165 °C[4b]) in 85% yield [66% overall yield from (**4**)]. The product was further characterized by conversion[4b] into 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-β-D-glucopyranose, the m.p., and ^1H n.m.r. spectrum of which were in agreement with the data of Adamson *et al.*[4b]

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‡ The following data are consistent with the proposed structure of (**5**). ^1H n.m.r.: δ 9.34 (d, 1H, $^3J_{1,F}$ 17.5 Hz, H-1 aldehyde), 6.02 (dd, 1H, $^2J_{2,F}$ 32.9, $^3J_{2,3}$ 8.4 Hz, H-2); this indicates $^3J_{1,2}$ *ca.* 0 Hz.