Direct Displacement with Anhydrous Fluoride of the C-2 Trifluoromethanesulphonate of Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-2-*O*-trifluoromethylsulphonyl-β-D-mannopyranoside

Shlomo Levy,*[a] Eli Livni,[a] David Elmaleh,[a] and William Curatolo[b]

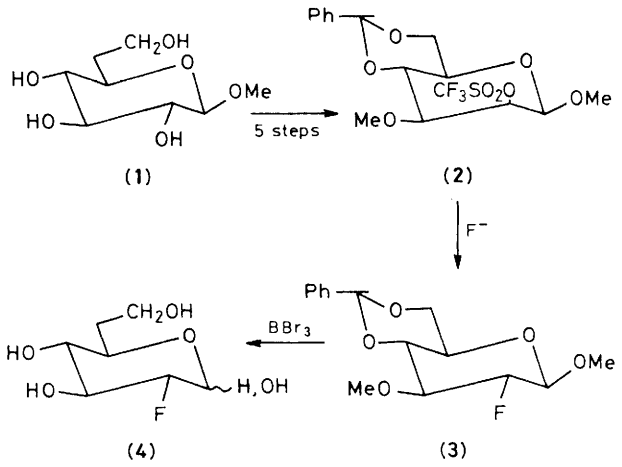
[a] *Massachusetts General Hospital Boston MA 02114 U.S.A.*
[b] *Francis Bitter National Magnet Laboratory, Massachusetts Institute of Technology, Cambridge, MA 02139, U.S.A.*

A displacement reaction with ^{18}F-caesium fluoride (anhydrous) was employed to label 2-deoxy-2-fluoro-D-glucose.

Recent developments in nuclear medicine and radiopharmaceutical chemistry have brought renewed interest in the fluorinated deoxy-carbohydrates. These sugar analogues when labelled with ^{18}F, a positron emitter, ($t_{\frac{1}{2}}$ 110 min)[1] have been proposed as probes for studying energy metabolism in the healthy[2] and diseased brain.[3] Since it enters the metabolic cycle in a way similar to glucose but does not complete the cycle,[4] 2-deoxy-2-fluoro-D-glucose (**4**) has proved to be the most useful among the sugars tested for studying various disorders.[3] Several synthetic routes for its preparation have been previously reported.[5]

The inertness towards replacement of the C-2 hydroxy-group in the glycoside series has been observed in the replacement of the 2-sulphonic ester groups of methyl 4,6-*O*-benzylidene-2-*O*-mesyl-3-*O*-methyl-α-D-mannopyranoside.[6] However, the β-anomer of the mannopyranoside seems to be more reactive for nucleophilic displacement reactions.[6] In this work we describe the first example of such a displacement on methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-trifluoromethylsulphonyl-β-D-mannopyranoside (**2**) by a fluoride ion. Our choice of the β-anomer derivative instead of the more readily available α-anomer is justified by the characteristics of the six-membered ring containing a sulphonyloxy-group.[7]

The triflate (**2**) was prepared by the slow addition of the triflic anhydride (1.15 mmol in 2 ml of dichloromethane) to a cooled solution (−15 °C) of (**1**) (1.09 mmol in 10 ml of CH_2Cl_2 and 0.5 ml of pyridine).[11,13] After the addition was complete the mixture was left for 90 min at room temp., washed with 10% sodium hydrogen carbonate solution then with brine, dried, evaporated, and crystallized (60% diethyl ether in hexane) to yield (**2**) (380 mg, 89%); m.p. 113 °C, *m/z* 428 (M^+). The ^{1}H n.m.r. spectrum and elemental analysis were satisfactory and consistent with the structure assigned.



Scheme 1. Synthesis of 2-deoxy-2-[^{18}F]fluoro-D-glucose.

To the triflate (**2**) (0.46 mmole) in dimethylformamide (5 ml, distilled from CaH_2), anhydrous caesium fluoride (1.7 mmol) was added. The mixture was heated at 130 °C for 30 min. The solvent was evaporated and the residue was separated on preparative plates (eluant, 30% acetone in hexane). Methyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-3-*O*-methyl-β-D-glucopyranoside (**3**) (Scheme 1) was isolated in 41.6% yield, and crystallized from 60% diethyl ether in hexane, m.p. 108 °C, *m/z* 298 (M^+). The values for $J_{1,2}$ and $J_{2,3}$ of 7.6 and 8.0 Hz, respectively, indicate that 1-H, 2-H, and 3-H are axial, and thus in a gluco- rather than manno-pyranoside configuration. Protons 1-H and 2-H are split further by F-2 [*J*1-H, F-2

4.0 Hz, J2-H, F-2 50 Hz]. ^{19}F-Decoupling resulted in collapse of the heteronuclear coupling with 1-H and 2-H and verified their assignment. The determined and calculated elemental analyses were in good agreement. The displacement reaction was carried out in hexamethylphosphoric triamide (30 min, 30% yield) and toluene (20 h, 20% yield). The use of KHF_2 as a nucleophile did not improve the yield.

2-Deoxy-2-fluoro-D-glucose (**4**) was prepared by subsequent hydrolysis of the fluorinated intermediate which required relatively drastic conditions. Clearly the electronegative influence of the fluorine atom at C-2 affects the electron density of the neighbouring atoms by decreasing the ease of protonation of the oxygen at C-3. The most promising process to remove the protecting groups was using boron tribromide in methylene chloride (5 ml of 2M solution) for 30 min at room temp. (90% yield). 2-Deoxy-2-fluoro-D-glucose (**4**) was compared with an authentic sample by t.l.c. and h.p.l.c.

This displacement reaction was employed for labelling 2-deoxy-2-fluoro-D-glucose (**4**) using [^{18}F]-caesium fluoride[9] as the anhydrous fluoride. The product was characterized by h.p.l.c. and by its biodistribution in mice.[10]

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