

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

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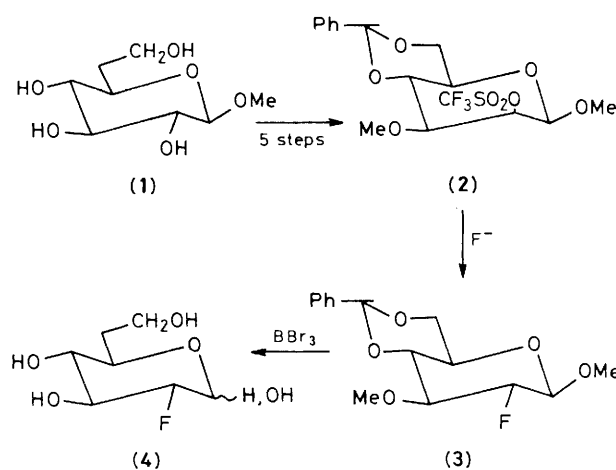
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A displacement reaction with ¹⁸F-caesium fluoride (anhydrous) was employed to label 2-deoxy-2-fluoro-D-glucose.

Recent developments in nuclear medicine and radiopharmaceutical chemistry have brought renewed interest in the fluorinated deoxy-carbohydrates. These sugar analogues when labelled with ¹⁸F, a positron emitter, (*t*_{1/2} 110 min)¹ have been proposed as probes for studying energy metabolism in the healthy² 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 CH₂Cl₂ 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 ¹H n.m.r. spectrum and elemental analysis were satisfactory and consistent with the structure assigned.



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

To the triflate (2) (0.46 mmole) in dimethylformamide (5 ml, distilled from CaH₂), 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-F}, F-2

4.0 Hz, J_{2-H}, F-2 50 Hz]. ¹⁹F-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 KHF₂ 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 electro-negative 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 [¹⁸F]-caesium fluoride⁹ as the anhydrous fluoride. The product was characterized by h.p.l.c. and by its biodistribution in mice.¹⁰

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