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Preliminary communication

Carbohydrate synthesis for nuclear medicine: a new, rapid, and stereospecific route to 2-deoxy-2-fluoro-D-glucose

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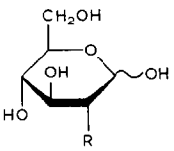
Considerable effort has been devoted[1] to improving the synthesis of 2-deoxy-2-[^{18}F]fluoro-D-glucose (**1a**). This compound has been used[2] in nuclear medicine for quantitative studies of cerebral D-glucose metabolism. The major synthesis problem is related to the short half-life (110 min) of the positron emitter ^{18}F. An efficient synthesis of **1a** requires rapid and stereospecific introduction of the radioactive label to give an intermediate that can be simply and very rapidly transformed into **1a**.



1a R = ^{18}F
1b R = ^{19}F

We now report a new route to 2-deoxy-2-fluoro-D-glucose (**1b**), which is compatible with the properties of ^{18}F and which is readily adaptable for the preparation of **1a**. The route takes advantage of the relative susceptibility of the β-D-mannopyranoside system to nucleophilic 2-substitution reactions[3].

The dibutylstannylene complex of 3,4,6-tri-*O*-benzyl-D-mannose[4] (**2**) was regiospecifically converted by an improved procedure[5], using a benzene solution and 1.1 equiv. each of benzyl bromide and tetrabutylammonium iodide, into syrupy benzyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside (**3**, 70%), $[\alpha]_D^{22}$ −43° (*c* 1.3, chloroform). Treatment of **3** in pyridine solution at −15° in a nitrogen atmosphere with 2 equiv. of trifluoromethanesulphonic anhydride, and then for a further 90 min at 0°, gave 96% of the syrupy triflate **4**, $[\alpha]_D^{22}$ −61° (*c* 1, chloroform). A solution of **4** in *N*,*N*-dimethylformamide in a nitrogen

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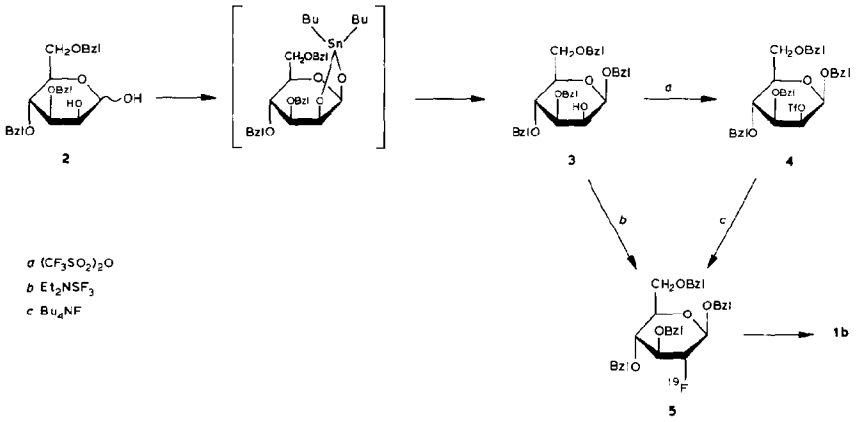
atmosphere was treated with 2 equiv. of tetrabutylammonium fluoride at 60° or with 3.5 equiv. of caesium fluoride at 130°. The nucleophilic displacement was monitored by t.l.c. on silica gel 60 PF_{254} (Merck). After ~30 min, benzyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-fluoro-β-D-glucopyranoside (**5**), $[\alpha]_D^{22}$ −13° (*c* 0.85, chloroform), was isolated by rapid t.l.c. with hexane–ethyl acetate (7:3). The yield of **5** in several experiments was in the range 45–50% for either nucleophile.



In subsequent experiments, the preparation of **5** was considerably improved. A solution of **3** in dry dichloromethane in a nitrogen atmosphere was treated with 2 equiv. of diethylaminosulfur trifluoride[6] at 40°. After 5 min, **5** was isolated by rapid t.l.c. in 80% yield.

O-Debenzylation of a solution of **5** in methanol–ethyl acetate (1:1) was almost instantaneous and quantitative under a pressure of hydrogen of 20 kg and in the presence[7] of 20% $Pd(OH)_2/C$. The weight of the catalyst was twice that of **5**. The resulting 2-deoxy-2-fluoro-D-glucose (**1b**) was purified by rapid filtration of an aqueous solution through a short column of alumina (Merck), and characterised by its ^{13}C-n.m.r. spectrum[8] as well as by its α-tetraacetate[1], m.p. 77°; $[\alpha]_D^{22}$ +143° (*c* 1, chloroform). From the moment of the use of diethylaminosulfur trifluoride, the total time required for the completion of the synthesis is close to 20 min.

Analogues of **5** in which the benzyl groups were replaced by allyl or methyl groups were also prepared. However, the removal of these protecting groups, using potassium *tert*-butoxide in dry dimethyl sulphoxide followed by treatment of the resulting prop-1-enyl derivative with boiling 0.1M hydrochloric acid in the case of the allyl groups[9], and using boron tribromide in the case of the methyl groups[10], was not as rapid as the debenzylation of **5**.

The spectroscopic properties of all of the compounds described were in agreement with the proposed structures.

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