A New, High Yield Synthesis of 2-Deoxy-2-fluoro-D-glucose

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The reaction of 1,6-anhydro-3,4-di-*O*-benzyl-2-*O*-(trifluoromethanesulphonyl)-β-D-mannopyranose (**4**) with tetra-alkylammonium fluorides provides a rapid, high yield synthetic route to 2-deoxy-2-fluoro-D-glucose.

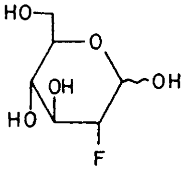
Considerable success has recently been achieved in the synthesis of 2-deoxy-2-fluoro-D-glucose (FDG), based on the fluoride ion displacement of suitably protected 2-*O*-(trifluoromethanesulphonyl)-β-D-mannopyranosides,[1—3] which, in radiosynthesis with ^{18}F, has in principle the advantage of utilizing all the available fluorine. However, a common side reaction is elimination of the sulphonyloxy group by reaction with the favourably disposed C-3 hydrogen. A higher yield procedure for the synthesis of FDG is still desirable. We have found that the side-reaction can be avoided by the use of the C-2 trifluoromethanesulphonate of 1,6-anhydro-β-D-mannopyranose as a substrate, which has a *trans*-diequatorial arrangement of the leaving group and the vicinal hydrogen.[†]

1,6-Anhydro-3,4-di-*O*-benzyl-2-*O*-(trifluoromethanesulphonyl)-β-D-mannopyranose (**4**), chosen as the most suitable precursor for a fluoride displacement, was prepared by the following sequence of reactions. Benzylation of 1,6-anhydro-2-*O*-(*p*-toluenesulphonyl)-β-D-mannopyranose (**1**)[5] with benzyl bromide and silver oxide gave the 3,4-di-*O*-benzyl derivative (**2**), which was desulphonated with potassium hydroxide to (**3**). Conventional sulphonation of (**3**) with trifluoromethanesulphonic anhydride in pyridine gave the required (**4**).[‡]

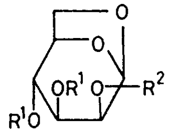
The trifluoromethanesulphonate (**4**) was treated with tetra-n-butyl- and/or tetramethyl-ammonium fluoride in dry acetonitrile, acetone, or tetrahydrofuran (THF). The reactions were complete in 20 min at reflux temperature or even at room temperature, giving 1,6-anhydro-3,4-di-*O*-benzyl-2-deoxy-2-fluoro-β-D-glucopyranose (**6**) {syrup, $[\alpha]_D$ −28°}, after column chromatography on silica gel, in excellent yield as shown in Table 1; no elimination product was obtained. The use of the combination of caesium fluoride in *N,N*-dimethyl formamide (DMF) at higher temperature led to the extensive decomposition of (**4**). The structure of (**6**) was confirmed by elemental analysis and by mass and ^{1}H n.m.r. spectra.[‡] Similar treatment of the trifluoromethanesulphonate (**5**) protected as its 3,4-di-*O*-methyl ether gave the corresponding (**7**) in excellent yield.

[†] The 1,6-anhydro-β-D-hexopyranoses exist in the $^1C_4$(D) conformation of the pyranose with the $E_a{}^2$ (E_0) conformation of the 1,3-dioxolane ring, see ref. 4.

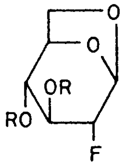
[‡] ^{1}H N.m.r. data: (**4**) ($CDCl_3$) δ 3.51 (1H, t, $J_{3,4}$, $J_{4,5}$ 1.7 Hz, 4-H), 3.78 (1H, dd, $J_{5,6exo}$ 5.9, $J_{6endo,6exo}$ 7.5 Hz, 6-H*exo*), 3.95—4.05 (1H, m, 3-H), 4.25 (1H, dd, $J_{5,6endo}$ 1.2 Hz, 6-H*endo*), 4.32—4.77 (5H, m, 5-H, $PhCH_2O$), 4.88 (1H, dd, $J_{1,2}$ 1.9, $J_{2,3}$ 5.5 Hz, 2-H), 5.53 (1H, br. s, 1-H), 7.19—7.43 (10H, m, aromatic). (**6**) ($CDCl_3$) δ 3.35 (1H, t, $J_{3,4}$, $J_{4,5}$ 1.4 Hz, 4-H), 3.62—3.86 (2H, m, 3-H, 6-H*exo*), 3.91 (1H, dd, $J_{5,6endo}$ 1.2, $J_{6endo,6exo}$ 7.3 Hz, 6-H*endo*), 4.35 (1H, mult. of d, $J_{2,F}$ 45 Hz, 2-H), 4.44—4.72 (5H, m, 5-H, $PhCH_2O$), 5.53 (1H, br. d, $J_{1,F}$ 4.9 Hz, 1-H), 7.18—7.46 (10H, m, aromatic).



FDG



(1) $R^1 = H$ $R^2 = p\text{-}MeC_6H_4SO_2$
(2) $R^1 = PhCH_2$ $R^2 = p\text{-}MeC_6H_4SO_2$
(3) $R^1 = PhCH_2$ $R^2 = H$
(4) $R^1 = PhCH_2$ $R^2 = CF_3SO_2$
(5) $R^1 = Me$ $R^2 = CF_3SO_2$



(6) $R = PhCH_2$
(7) $R = Me$

Table 1.

Compound	Florinating agent	Solvent	Temperature /°C	Time /min	Product (% Yield)
(**4**)	Me_4NF	MeCN	reflux	20	(**6**) (91)
	Bu_4NF	MeCN	room	20	(**6**) (85)
	Bu_4NF	acetone	reflux	20	(**6**) (80)
	Bu_4NF	THF	reflux	20	(**6**) (82)
	CsF	DMF	120 °C	30	decomp.
(**5**)	Me_4NF	MeCN	reflux	20	(**7**) (87)
	Bu_4NF	MeCN	room	20	(**7**) (90)

The cleavage of the anhydro bridge in 1,6-anhydrohexopyranoses with electronegative groups at C-2 proceeds with great difficulty.[6] However, the direct conversion of (**6**) into FDG was achieved by heating with 50% (v/v) methanesulphonic acid at 120 °C for 30 min (70% yield). The FDG thus obtained had m.p., optical rotation, and ^1H n.m.r. spectral properties as reported.[2,7] Thus FDG was obtained in 64% overall yield from (**4**).

The use of (**4**) as a precursor in the synthesis of FDG leads to a higher yielding and cleaner fluorination under extremely mild conditions than previously published procedures. It is also comparable to a method using the 2,3-cyclic sulphate of methyl 4,6-*O*-benzylidene-β-D-mannopyranoside as a substrate, reported by Tewson.[8] The present method could be also adapted for the preparation of ^{18}F-labelled FDG for medical imaging.

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References

1 S. Levy, E. Livni, D. Elmaleh, and W. Curatolo, *J. Chem. Soc., Chem. Commun.*, 1982, 972; S. Levy, D. R. Elmaleh, and E. Livni, *J. Nucl. Med.*, 1982, **23**, 918.
2 T. Haradahira, M. Maeda, Y. Kai, H. Omae, and M. Kojima, *Chem. Pharm. Bull.*, 1984, **32**, 165.
3 A. Dessinges, A. Olesker, and G. Lukacs, *Carbohydr. Res.*, 1984, **126**, C6.
4 M. Černý and J. Staněk, Jr., *Adv. Carbohydr. Chem. Biochem.*, 1977, **34**, 23.
5 G. O. Aspinall and G. Zweifel, *J. Chem. Soc.*, 1957, 2271.
6 L. J. Carson, *J. Org. Chem.*, 1965, **30**, 3953; J. Pacák, Z. Točík, and M. Černý, *Chem. Commun.*, 1969, 77.
7 J. Adamson, A. B. Foster, L. D. Hall, R. N. Johnson, and R. H. Hesse, *Carbohydr. Res.*, 1970, **15**, 351; L. Phillips and V. Wray, *J. Chem. Soc. B*, 1971, 1618.
8 T. J. Tewson, *J. Org. Chem.*, 1983, **48**, 3507; *J. Nucl. Med.*, 1983, **24**, 718.