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III. 3 Synthesis of 2-Deoxy-2-fluoro-D-galactopyranose: Reaction of D-Galactal with Acetyl Hypofluorite

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Many papers on the synthesis of fluorinated D-glucopyranose have been published[1-5], and fluorine-18 ($t_{1/2}$ 110 min) labelled hexopyranoses have recently found important application in medical research using positron emission tomography.[6]

In a previous paper[7], we reported that 2-deoxy-2-[^{18}F]-fluoro-D-galactose has been prepared by the reaction of triacetyl-O-D-galactal (1) with [^{18}F]-fluorine gas followed by acidic hydrolysis, and is not only an excellent diagnostic liver-imaging agent but also a tool of great promise for studies of metabolism in healthy or diseased liver in human. Adam has recently reported that 1,3,4,6-tetra-O-acetyl-2-deoxy-2-fluoro-α-D-galactopyranose (2), m.p. 102 °C, is prepared by the reaction of (1) with acetyl hypofluorite and de-O-acetylation of (2) is not performed.[2] As part of the research of medical uses of positron emitting fluorinated carbohydrates, present paper describes the synthesis of 2-deoxy-2-fluoro-D-galactopyranose (3) using acetyl hypofluorite, and a comparison of synthetic methods of (3).

Fluorine gas (1.8%) diluted with N_2 was passed into a suspension of AcONa in $CFCl_3$-AcOH at -78 °C[8] with mechanical stirring to give acetyl hypofluorite (4.6 mmol). A solution of (1) (1.36 g, 5 mmol) in $CFCl_3$ was added to the resulting mixture. After 5 min the mixture was poured into AcOEt. The AcOEt solution was washed with aqueous $Na_2S_2O_3$ and water, dried, and concentrated to give (2) in 90% isolated yield based on acetyl hypofluorite; m.p. 125-126 °C (from i-propyl ether), $[\alpha]_D^{20}$ +155° (c=1, $CHCl_3$). Satisfactory elemental analyses and mass spectral data were obtained. N.m.r. analysis of (2) at 300 MHz gives δ($CDCl_3$) 2.04 (3H, s, CH_3CO), 2.06 (3H, s, CH_3CO), 2.15 (3H, s, CH_3CO), 2.19 (3H, s, CH_3CO), 4.09 (2H, octet, H-6), 4.34 (1H, t, $J_{5,6}$ 6.6 Hz, H-5), 4.91 (1H, octet, $J_{2,F}$ 49.1, $J_{2,3}$ 10.3 Hz, H-2), 5.39 (1H, sextet, $J_{3,F}$ 10.7, $J_{3,4}$ 3.3 Hz, H-3), 5.52 (1H, t, $J_{4,F}$ ca. 3 Hz, H-4), and 6.46 (1H, d, $J_{1,2}$ 4.0 Hz, H-1). For the spectrum, tetramethylsilane was employed as the internal standard. The data are consistent with the structure (2).

A mixture of (2) (1 g) and 14% HCl was refluxed and concentrated to dryness under a reduced pressure. The residue was dissolved in water and then purified with an ion retardation resin column (AG 11-A8) to afford 2-deoxy-2-fluoro-D-galactopyranose (3)[7,9] (400 mg; 77%).

This reaction using acetyl hypofluorite is the best way to prepare (3), 77% overall yield from (1), compared with the reaction with fluorine gas (16% overall yield).[7] In addition, crystalline (2), obtained just after concentration of the reaction mixture, was pure enough for further reaction.

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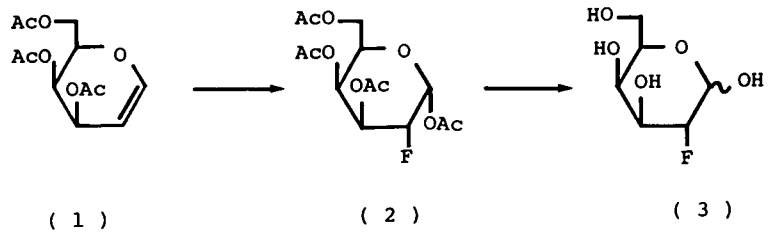

(1) (2) (3)

Fig. 1. Synthesis of 2-deoxy-2-fluoro-D-galactopyranose