SYNTHESIS OF SOME 2-DEOXY-2-FLUORO[^{18}F]HEXOPYRANOSES, POTENTIAL DIAGNOSTIC IMAGING AGENTS

Masao Tada,* Taiju Matsuzawa, Hiroshi Ohrui,† Hiroshi Fukuda, Tatsuo Ido,†† Toshihiro Takahashi,†† Makoto Shinohara,†† and Kumiko Komatsu

Research Institute for Tuberculosis and Cancer, Tohoku University, Seiryo-machi, 4-1, Sendai 980, Japan

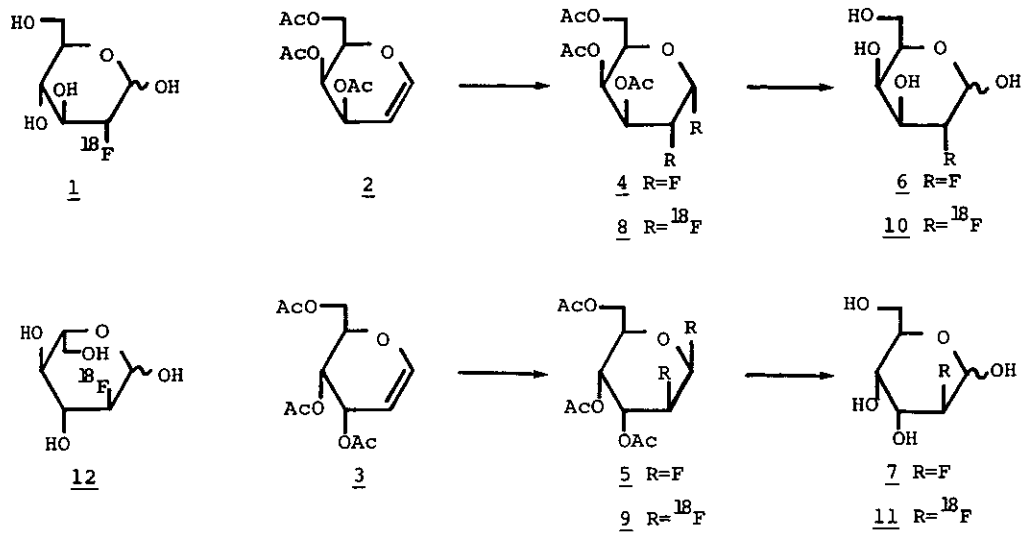
†Faculty of Agriculture, Tohoku University, Tsutsumidoriamamiya-machi, 1-1, Sendai 980, Japan

††Cyclotron and Radioisotope Center, Tohoku University, Aramaki-aza-aoba, Sendai 980, Japan

Abstract— 2-Deoxy-2-fluoro[^{18}F]-D-galacto-, -D-altro-, and -L-gluco-pyranose have been prepared by the reactions of corresponding glycals with fluorine[^{18}F] gas followed by acidic hydrolysis, respectively. The gas was produced by the ^{20}Ne(d, α)^{18}F nuclear reaction using the cyclotron. D-Galactopyranose derivative showed markedly diagnostic liver-imaging activity.

The synthesis of carbohydrates labeled with short-lived radionuclides such as those required for positron emission tomography (e.g. ^{18}F: $t_{1/2}$ 110 min) has recently received much attention because positron emitting carbohydrate derivatives have definite advantages for medical use. 2-Deoxy-2-fluoro[^{18}F]-D-glucopyranose (1)[1~3] has been well used as imaging agent in studies of myocardial and cerebral glucose metabolism[4] and tumor detection.[5,6] As part of the investigation of the synthesis of positron emitting fluorohexopyranoses, this paper describes the preparations of some 2-deoxy-2-fluorohexopyranoses with a fluorine gas.

We have studied the reaction of fluorine gas with tri-O-acetyl-D-galactal (2), and also with D-altro-analogue (3). In each case the product (4; 30% or 5; 11%), corresponding to cis-addition of fluorine to the opposite side of an acetoxyl group at C-3, has been isolated. Compounds 4 and 5 were then hydrolyzed with diluted HCl



to give 6 and 7, respectively.[7,8]

The typical reaction procedure is described for the preparation of 6. A solution of 2 (1.36 g; 5 mmol) in $CFCl_3$ (50 ml) was cooled to -78 °C. Fluorine gas (1.8%) diluted with N_2 was passed into the solution for 3 h (flow rate: ca. 50 ml/min). The reaction mixture was allowed to rise to room temperature, passed through a short silica-gel column, and evaporated to dryness under a reduced pressure. The residue was fractionated by a silica-gel column (5 x 25 cm) using a mixture of benzene and ethyl ether (10/1, v/v) to give 4 (465 mg). A mixture of 4 (880 mg) and 7% HCl (20 ml) was refluxed for 1 h 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 6 (270 mg; 52% based on 4).

Fluorine[^{18}F] gas was produced from the deutron bombardment (2 h; 10 μA) of a mixture of neon and fluorine (99.95/0.05, v/v) at a pressure of 25 atm in a nickel target chamber by the $^{20}Ne(d, \alpha)^{18}F$ nuclear reaction using the Tohoku University Cyclotron. The fluorine[^{18}F] gas thereby formed was released from the chamber at a controlled flow rate (ca. 200 ml/min) and then bubbled through a solution of glycal in $CFCl_3$ under -78 °C. The target chamber was swept with a stream of neon gas until all radioactive gas had been displaced.

Through a cooled solution of 2 (67 mg; 250 μmol) in $CFCl_3$ (10 ml), the radioactive gas was carefully bubbled. The reaction mixture was then fractionated by a silica-gel column (0.9 x 10 cm) to give the difluoride, 8. Its suspension in 3% HCl (5 ml) was refluxed for 15 min, cooled, and then chromatographed over a series of columns

(0.9 x 1 cm, 0.9 x 10 cm, and 0.9 x 5 cm), which had been packed with activated charcoal, ion retardation resin (AG 11-A8), and neutral alumina, respectively. From the eluate, 2-deoxy-2-fluoro[^{18}F]-D-galactopyranose (10) was obtained. The reaction of 3 with fluorine[^{18}F] gas followed by acidic hydrolysis in an analogous fashion gave 2-deoxy-2-fluoro[^{18}F]-D-altropyranose (11). Tri-O-acetyl-L-glucal prepared from L-glucopyranose was treated in a similar manner as in the case of D-isomer (1)[1] to afford 2-deoxy-2-fluoro[^{18}F]-L-glucopyranose (12). In each hot experiment, the combined preparation time was complete in ca. 2 h. The sugars (10, 11, and 12) were then applied to high performance liquid chromatography (HPLC). HPLC conditions used are as follows. A column, its size, solvent system, and flow rate are μBondapak carbohydrate (Waters), 30 x 0.4 cm, CH_3CN-H_2O (85:15), and 2 ml/min, respectively. The retention time of 10 is 3.8 min which is the same value in the case of its radioinactive compound (6) under the same HPLC conditions. The HPLC radiochromatogram of 10 is shown in Fig. 1.

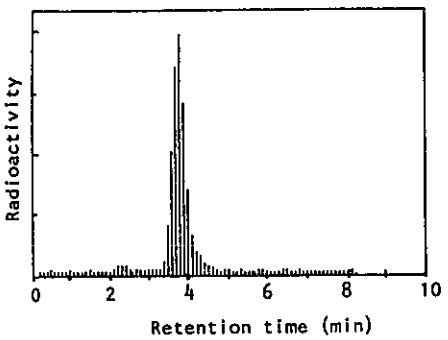


Fig. 1. The chromatogram of 10.

The radiochemical purity of 10, 11, and 12 is 98– 99%. The radiochemical yield, the specific activity, and the retention time of HPLC of these reaction products are shown in Table 1.

Table 1. 2-Deoxy-2-fluoro[^{18}F]hexopyranoses

Compound	Radio-chemical yield (%)	Specific activity (mCi/mg)	HPLC retention time (min)
10	10.0	12	3.8
11	2.0	7	3.1
12	18.5	10	3.6

The positron emitting compounds, 10, 11, and 12, have been submitted to animal testings (biodistribution studies, metabolic studies, positron emission tomography, and autoradiography). The results show that compound 10 is proved to be important for

the assessment of liver function and is a diagnostic liver-imaging agent of great promise.[9]

The synthesis of other fluorinated carbohydrates is currently under investigation.

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