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A RAPID AND EFFICIENT SYNTHESIS OF 2-DEOXY-2-[^{18}F]FLUORO-ACETAMIDO-D-MANNOPYRANOSE AND -D-GALACTOPYRANOSE

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SUMMARY

Rapid and efficient syntheses of 2-deoxy-2-[^{18}F]fluoro-acetamido-D-mannopyranose (1) and -D-galactopyranose (2), respectively, starting from [^{18}F]fluoride and ethyl bromo-acetate are described. [^{18}F]Fluoride was produced by the ^{18}O (p, n) ^{18}F nuclear reaction using the cyclotron. The total times required for synthesis of (1) and (2) are ca. 80 min. The radiochemical yield and purity of (1) are an 18% and >98%, respectively. Compound (2) is also synthesized with the same radiochemical yield and purity.

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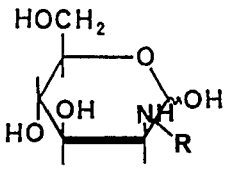
INTRODUCTION

In previous papers (1,2), we reported an efficient, one-pot synthesis of 2-deoxy-2-[^{18}F]fluoroacetamido-D-glucopyranose, a potential diagnostic imaging agent, and some of its biological characteristics. It is well known that 2-amino-2-deoxy-D-glucopyranose is the most abundant aminosugar widely occurring as its N-acetylated derivative in polysaccharides, glycoproteins and proteoglycans. 2-Acetamido-2-deoxy-D-mannopyranose and -D-galactopyranose also occur in glycoproteins (3). Our interest in fluorine substitution for hydrogen in these sugars has stemmed from the physicochemical characteristics of fluorine atom, e.g. fluorine atom mimics hydrogen atom with respect to steric requirements at enzyme receptor sites (4).

As a part of the synthetic study of aminosugars labelled with positron emitting radionuclides for medical use, the rapid and efficient syntheses of 2-deoxy-2-[^{18}F]fluoroacetamido-D-mannopyranose (1) and -D-galactopyranose (2) as potential diagnostic imaging agents will be reported here.

RESULTS AND DISCUSSION

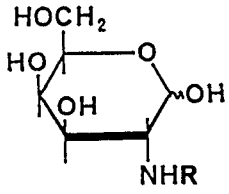
The methods for the syntheses of unlabelled 2-deoxy-2-fluoroacetamido-D-mannopyranose (3) and -D-galactopyranose (4) from 2-amino-2-deoxy-D-mannopyranose (5) and tetra-O-acetyl derivative of 2-amino-2-deoxy-D-galactopyranose (6), respectively, with fluoroacetic acid have been described by Fondy et al. (5,6). These methods are not suitable for the syntheses of sugars labelled with fluorine-18 because of the half-life



(5): R=H

(3): R=$COCH_2F$

(1): R=$COCH_2{}^{18}F$



(6): R=H

(4): R=$COCH_2F$

(2): R=$COCH_2{}^{18}F$

constraint (^{18}F: $t_{1/2}$ 109.8 min).

We established the one-pot synthetic method of 2-deoxy-2-[^{18}F]fluoroacetamido-D-glucopyranose (ca. 9.1% radiochemical yield) starting from [^{18}F]fluoride and ethyl bromoacetate (1). The method is a combination of halogen exchange, alkaline hydrolysis, and condensation. One reason for the low yield of the labelled fluoroacetamido-D-glucopyranose is suggested to be incomplete alkaline hydrolysis of ethyl [^{18}F]fluoroacetate (7), due to insufficiency in an amount of alkali and reaction time. By examination of reaction conditions, a 5-minute hydrolysis with 1 N aqueous potassium hydroxide at 82°C was found to be optimal. High performance liquid chromatographic (HPLC) demonstration of dependence of the hydrolysis of ethyl [^{18}F]fluoroacetate on reaction time is shown in Fig. 1. This partially improved method was then applied to the syntheses of the tittled sugars (1 and 2).

[^{18}F]Fluoride was produced via the ^{18}O (p, n) ^{18}F nuclear reaction with a circulating 20% enriched [^{18}O]water target using the Tohoku University Cyclotron (8). The ^{18}F nuclide thereby formed was converted into potassium [^{18}F]fluoride with potassium carbonate. After addition of 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosan (Kryptofix 222), the resulting mixture was submitted to the improved one-pot

synthesis to afford the desired sugar (1) from (5). The total synthesis time and radiochemical yield and purity of (1) were ca. 80 min, 18% (decay-corrected, based on [^{18}F]fluoride), and >98%, respectively.

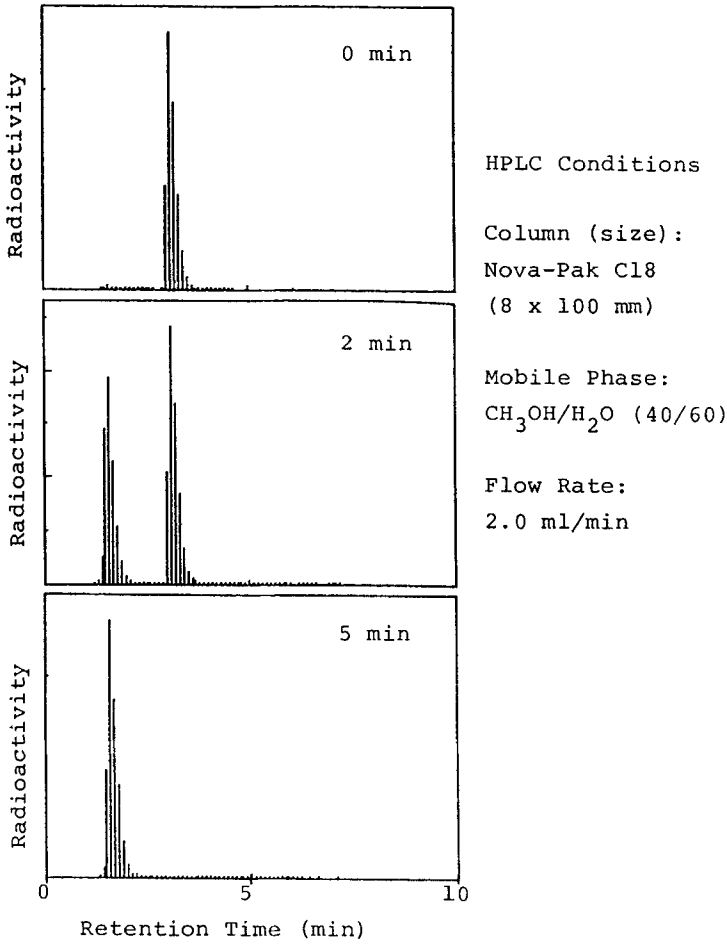


Fig. 1 Analytical HPLC Chromatograms of Dependence of Alkaline Hydrolysis of Ethyl [^{18}F]Fluoroacetate on Reaction Time.

The treatment of aminosugar (6) in an analogous fashion gave an 18% radiochemical yield of the desired sugar (2), as well as isomeric sugar (1). No difference in reactivity

between the two aminosugars (5 and 6) towards [^{18}F]fluoroacetic acid was observed.

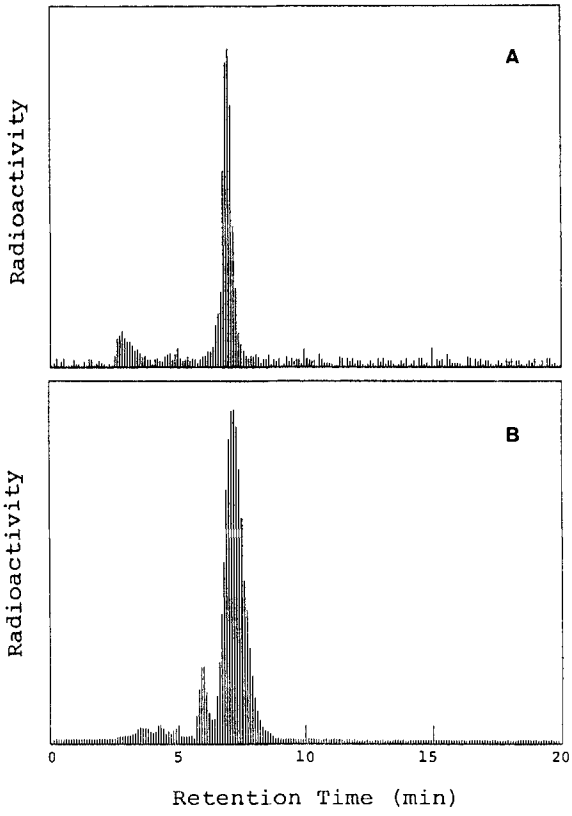
The medical uses of compounds (1 and 2) are being investigated and the results will be reported elsewhere.

EXPERIMENTAL

Kryptofix 222 and TLC plates were purchased from E. Merck AG. Ethyl bromoacetate was from Wako Chemical Ltd. and distilled under a reduced pressure. The other reagents were obtained commercially (Wako) and used without further purification. The purity of each compound was always checked by TLC. HPLC analyses were carried out either with a Waters Assoc. model 6000 equipped with a refractive index detector or with a Waters Assoc. model 4500 equipped with a radioactivity monitor. The packed columns [Nova-Pak C18 (8 x 100mm), Waters Assoc. USA and YMC-Pack PA-23 (10.0 x 250mm), Yamamura Chem. Lab. Co., Jpn] were used in HPLC.

2-Deoxy-2-[^{18}F]fluoroacetamido-D-mannopyranose (1). [^{18}F]Fluoride was produced from the proton bombardment of 20% enriched [^{18}O]water by the ^{18}O (p, n) ^{18}F nuclear reaction at the Cyclotron (8). To the aqueous solution of [^{18}F]fluoride, a mixture of aqueous potassium carbonate (33 μmol/0.2 ml) and Kryptofix 222 (72 μmol, 27 mg) was added. The resulting solution was dried at 90°C in a stream of dry nitrogen gas. To the residue, a solution of ethyl bromoacetate (0.2 mmol, 33.4 mg) in acetonitrile (1 ml) was added. The mixture was heated at 82°C for 10 min with stirring. After addition of 1 N aqueous potassium hydroxide (0.4 ml), the reaction mixture was heated for additional 5 min. To the resulting mixture, a mixture of hydrochloride of (5) (0.2 mmol, 43.2 mg) and dicyclohexylcarbodiimide (0.5 mmol, 103 mg) in pyridine (0.5 ml) was then added. The mixture was heated at 82°C for 20 min

with stirring, diluted with water (2 ml) to decompose an excess of the carbodiimide, and filtered. The filtrate was washed with ethyl ether (10 ml x 2) and evaporated to dryness under a reduced pressure. The residue was dissolved in water (0.5 ml) and the solution was chromatographed over an ion retardation resin (AG 11-A8, 2 ml) column using water as elution solvent. The eluate was then mixed with an approximately equal portion



A: The large peak is compound (1).
B: The large peak is compound (2).

HPLC Conditions:
Column;
YMC-Pack PA-23.
Column Size;
10.0 x 250 mm.
Mobile Phase;
CH_3CN/H_2O (75/25).
Flow Rate;
5.0 ml/min.

Fig. 2 Preparative HPLC Chromatograms of Reaction Mixtures.

of acetonitrile, passed through a Millex-HA filter unit (Millipore), and eluted with aqueous acetonitrile (1:1, v/v). The effluent was concentrated to 1/10 of its original volume

and then subjected to preparative HPLC. The radio-chromatogram is shown in Fig. 2-A. A radioactivity peak corresponding to (1) was then collected and the identity of the peak was confirmed by analytical HPLC. The total synthesis time, the radiochemical yield, and purity of (1) are ca. 80 min, an 18%, and >98%, respectively.

2-Deoxy-2-[^{18}F]fluoroacetamido-D-galactopyranose (2). The treatment of hydrochloride of (6) under similar conditions gave (2) in an 18% radiochemical yield. The total synthesis time and radiochemical purity are ca. 80 min and >98%, respectively. A preparative HPLC chromatogram is shown in Fig. 2-B.

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REFERENCES

1. Tada M., Oikawa A., Iwata R., Fujiwara T., Kubota K., Matsuzawa T., Sugiyama H., Ido T., Ishiwata K., and Sato T. - J. Labelled Compds. Radiopharm. 27: 1317 (1989)
2. Fujiwara T., Matsuzawa T., Kubota K., Tada M., Iwata R., Hatazawa J., Fukuda H. and Ido T. - CYRIC Ann. Rep. (Tohoku University), 174 (1988)
3. Aspinall G. O., Percival E., Rees D. A., and Rennie M. - in "Rodd's Chemistry of Carbon Compounds" (2nd Edition), Vol. 1., Part F, ed. Coffey S., Elsevier Publishing Company, Amsterdam, 1967, p 596.
4. Penglis A. A. E. - Adv. Carbohydr. Chem. Biochem. 38: 195 (1981)

5. Fondy T. P. and Emlich C. A. - J. Med. Chem. 24: 848 (1981)

6. Fondy T. P. Roberts S. B., Tsiftsoglou A. S., and Sartorelli A. C. - J. Med. Chem. 21: 1222 (1978)

7. Tada M., Oikawa A., Iwata R., Sato K., Matsuzawa T., Kubota K., Fujiwara T., Sugiyama H., Abe Y., Sato T., Takahashi H., Wakui A. and Ido T. - CYRIC Ann. Rep. (Tohoku University), in press

8. Iwata R., Ido T., Brady F., Takahashi T. and Ujiie A. - Appl. Radiat. Isot. 38: 979 (1987)