A Facile One-pot Synthesis of N-[18F]Fluoroacetyl-D-mannosamine

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Introduction

We have made an effort to synthesize hexopyranoses labelled with positron emitting radionuclides such as those required for positron emission tomography. In a previous paper[1] we reported an efficient, one-pot synthesis of N-[^{18}F]fluoroacetyl-D-glucosamine, a potential diagnostic imaging agent, from ethyl bromoacetate. Its improved synthetic method and some biological characteristics have been reported.[2,3]

As a part of the synthetic study of hexopyranoses labelled with short-lived radionuclides, this paper describes a facile one-pot synthesis of N-[^{18}F]fluoroacetyl-D-mannosamine from ethyl bromoacetate.

Results and Discussion

The method for the synthesis of unlabelled N-fluoroacetyl-D-mannosamine has been described by Fondy and Emlich,[4] but it is impractical for the preparation of the ^{18}F-labelled sugar (I) because of the half-life time constraint.

The one-pot synthetic method of N-[^{18}F]fluoroacetyl-D-glucosamine starting from [^{18}F]fluoride and ethyl bromoacetate was developed by us.[1,2] This method is applied to synthesize the title sugar (I) and radiolabelling run has been carried out.

[^{18}F]fluoride was produced by the ^{18}O (p, n) ^{18}F nuclear reaction from a circulating 20 %-enriched [^{18}O]water target using the Tohoku University Cyclotron.[5] The ^{18}F nuclide thereby formed was converted to 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[2] to give the desired sugar (I) in an 18% radiochemical yield. The total synthesis time and

radiochemical purity were ca. 80 min and >98%, respectively. The synthetic pathway of I from [^{18}F]fluoride and ethyl bromoacetate is shown in Fig. 1.

It seems that the reactivity of [^{18}F]fluoroacetic acid and D-mannosamine (II) is similar to that of the acid and D-glucosamine. From the experimental fact, it may be concluded that our improved one-pot synthetic method is a general method for obtaining [^{18}F]fluoroacetyl compound from the corresponding aminosugar.

The medical use of I is currently being investigated and the results will be reported elsewhere.

Experimental

Kryptofix 222 and plates of thin-layer chromatography (TLC) 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. High performance liquid chromatographic (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 column [YMC-Pack PA-23 (10.0 x 250 mm), Yamamura Chem. Lab. Co., Jpn] was used in HPLC.

N-[^{18}F]Fluoroacetyl-D-mannosamine (I).

[^{18}F]Fluoride was produced from the proton bombardment of 20% enriched [^{18}O]water.[5] 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 resulting mixture was heated at 82°C for 10 min with stirring and cooled. 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 D-mannosamine (II) (0.2 mmol, 43.2 mg) and dicyclohexylcarbodiimde (0.5 mmol, 103 mg) in pyridine (0.5 ml) was added. The mixture was treated under similar conditions described in a previous paper[2] to afford the crude reaction product. The crude product was then submitted to preparative HPLC (Fig. 2). A radioactivity peak corresponding to I was then collected and the identity of the peak was confirmed by analytical HPLC. The total synthesis time, the radiochemical yield, and purity of I were ca. 80 min, 18% and >98%, respectively.

Acknowledgements

The use of the Tohoku University Cyclotron under directions of Professors Manabu Fujioka and Hikonojo Orihara, Tohoku University, is gratefully acknowledged. The present work was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

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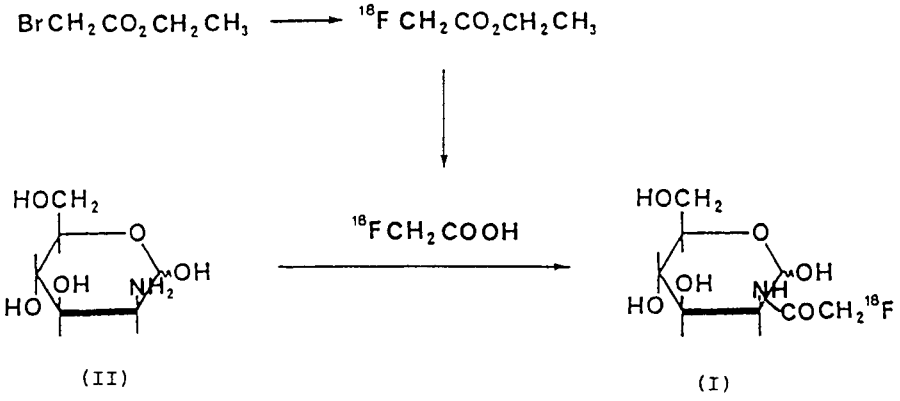
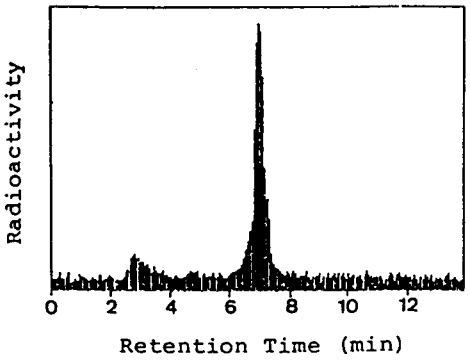


Fig. 1. Synthetic pathway of N-[^{18}F]fluoroacetyl-D-mannosamine (I) from ethyl bromoacetate.



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 chromatogram of reaction mixture. The main peak corresponds to compound I.