A CONVENIENT SYNTHESIS OF D-[1-^{11}C]GLUCOPYRANOSE AND D-[1-^{11}C]GALACTOPYRANOSE USING DIBORANE

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SUMMARY

Rapid chemical syntheses of D-[1-^{11}C]glucopyranose and D-[1-^{11}C]galactopyranose starting from D-arabinopyranose and D-lyxopyranose, respectively, are described. The use of diborane for reduction of intermediates in highly effective for reducing the time required.

Key Words: D-[1-^{11}C]glucopyranose, D-[1-^{11}C]galactopyranose, diborane.

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INTRODUCTION

The synthesis of D-glucopyranose labelled with positron emitting radionuclides has recently received much attention because their application to positron emission tomography proved useful in medical research.[1] D-Glucopyranose labelled with Carbon-11 (β^+ decay, $t_{1/2}$ = 20.4 min) has been synthesized by numerous biosynthetic methods.[2-6] However, all these methods suffer at least two serious disadvantages; labelled position is not defined and purity of the products is not satisfactory. In order to study the metabolism and disposition of D-hexopyranoses in the whole animal, we have chemically prepared D-glucopyranose and D-galactopyranose labelled at C-1 and describe herein the results.

RESULTS AND DISCUSSION

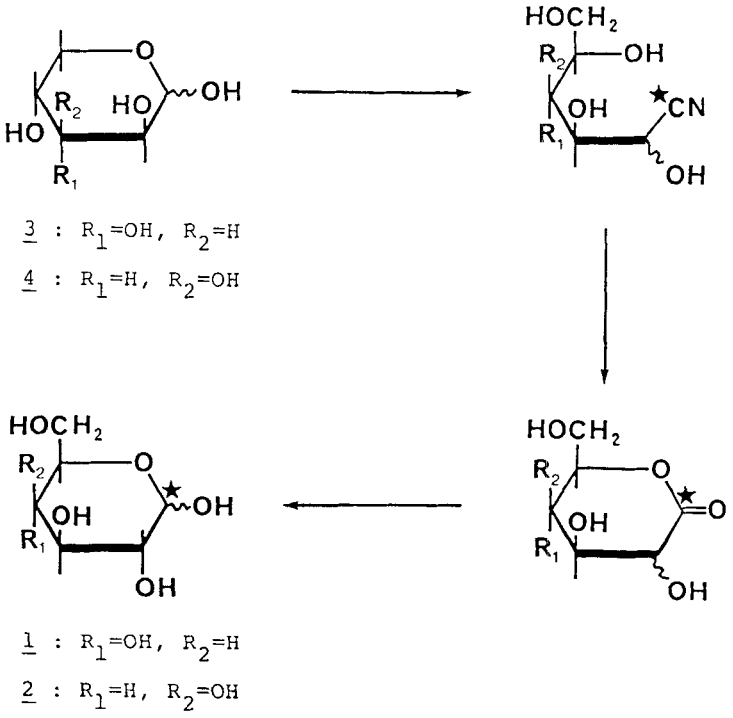
Hexopyranoses have been chiefly synthesized from pentopyranoses by the Kiliani-Fischer cyanohydrin method.[7,8] The method is composed of extension of the carbon atom chain of pentopyranose by treatment with cyanide and hydrolysis of the cyanohydrin followed by reduction. Various carbon-14 labelled hexopyranoses[9] have been synthesized by this method but it is not suitable for the syntheses of hexopyranoses labelled with carbon-11 because of the half-life time constraint. Recently, the applications of this method for preparing D-[1-^{11}C]glucopyranose (1) have been reported by Shiue and Wolf,[10] and by Hara and Nozaki.[11] We have also adapted this method to prepare (1) and D-[1-^{11}C]galactopyranose (2) with some modifications.

Bhattacharjee et al. have developed a new method for reduction of hexonic acid lactones with diborane, and reported the yield of D-glucopyranose from D-gluconolactone was optimal at room temperature and 3.5 hr reaction.[12] To shorten the

reaction time is prerequisite for the synthesis of compounds labelled with a short-lived radionuclide. We found that refluxing D-glucono-1,5-lactone with diborane in tetrahydrofuran for only 10 min gave the desired sugar. A change in reaction temperature brought about a considerable reduction of time required. Analyses with high performance liquid chromatography (HPLC) and thin-layer chromatography (TLC) confirmed that the reaction time of 10 min was adequate.

D-Arabinopyranose (3) and potassium cyanide were heated at 100 °C for 10 min in the presence of alkali. After removal of cation, the resulting mixture was evaporated to dryness and the residue was treated with diborane for 10 min. After removal of ionic substances, D-glucopyranose was obtained by HPLC technique in a 17% yield based on cyanide, and was then converted into penta-O-acetyl-α-D-glucopyranose by the conventional method.[13] TLC showed that there was no detectable amount of pentaacetyl-D-mannopyranose in this reaction product. The reaction was reproducible at scales ranging from 150 mg for the preparation of quantities of unlabelled D-glucopyranose to 30 mg for the radiolabelled run. D-Lyxopyranose (4) was treated in an analogous fashion to give *ca.* 50% yield of D-galactopyranose, and D-talopyranose was not detected in the product.

Carbon-11 nuclide was produced from the proton bombardment of nitrogen by ^{14}N (p, α) ^{11}C nuclear reaction using the Tohoku University Cyclotron. The ^{11}C nuclide thereby formed was converted into hydrogen [^{11}C]cyanide by the ordinary procedure.[14] Sugar (3) was treated with hydrogen [^{11}C]cyanide to afford (1) in *ca.* 10% radiochemical yield. Its radiochemical purity was >95% and the total preparation time of (1), including HPLC purification, is *ca.* 60 min. Under the optimal conditions, 600 μCi of (1) was obtained. Compound (4) was treated as in the



3 : R_1=OH, R_2=H

4 : R_1=H, R_2=OH

1 : R_1=OH, R_2=H

2 : R_1=H, R_2=OH

★ indicates ^{11}C-label.

procedure described above to give (2) in ca. 10% radiochemical yield. The radiochemical purity and the preparation time are >96% and ca. 1 h, respectively.

Additionally, these syntheses of (1) and (2) using diborane as reducing agent are suitable for their automated syntheses because the simple apparatus and easy operations have been used.

EXPERIMENTAL

Diborane and TLC silica gel plates were purchased from Aldrich Chemical Co. and E. Merck AG., respectively. The purity of each compound was always checked by TLC on silica gel. HPLC analyses were carried out either with a Waters Associates model 6000 equipped with a refractive index (RI) detector or with a Waters Associates model 4500 equipped with a radioactivity monitor.

D-[1-^{11}C]Glucopyranose (1). Hydrogen [^{11}C]cyanide[14] was transferred into a solution of D-arabinopyranose (3) (30 mg) in 0.05 M potassium hydroxide aq. solution (0.2 mL) and then heated at 100 °C for 10 min. The reaction solution was passed through a resin column (Dowex 50, H^+ form, 2 mL) and eluted with water. After removal of the solvent, the residue was suspended in tetrahydrofuran (1 mL). After addition of 1 M diborane in tetrahydrofuran (2 mL) the suspension was refluxed for 10 min. The resulting solution was treated with water to decompose an excess of diborane and evaporated to dyness under a reduced pressure. To the residue, was added methanol (5 mL). The methanol solution was evaporated to dryness *in vacuo* to remove a large portion of boric acid. The residue was dissolved in water and the solution was chromatographed over an ion retardation resin (AG 11-A8, 2 mL) column using water as elution solvent. The eluent was then subjected to preparative HPLC (Column: Aminex HPX-87C/250 x 4 mm. Eluent: Water. Flow rate: 0.8 mL/min. Temperature: 85 °C). A radioactivity peak corresponding to (1) was then collected and the identity of the peak was comfirmed by analytical HPLC (Column: μ-Bondapak carbohyd. Eluent: Acetonitrile/water, 85:15 v/v. Flow rate: 2.0 mL/min). The total synthesis time, the radiochemical yield, and purity of (1) are *ca.* 60 min, *ca.* 10%, and >95%, respectively. The radioactivity of (1) is 600 μCi under the optimum conditions.

D-[1-^{11}C]Galactopyranose (2). D-Lyxopyranose (4) (30 mg) was treated in a similar manner as in (1) to afford (2) in *ca.* 10% radiochemical yield. The radiochemical purity and the total synthesis time are ≥96% and *ca.* 60 min, respectively.

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