Pergamon

Tetrahedron Letters, Vol. 38, No. 8, pp. 1411-1412, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00080-4

A Multigram, Stereoselective Synthesis of D-[$^{13}C_5$]Ribose from D-[$^{13}C_6$]Glucose and Its Conversion into [$^{13}C_5$]Nucleosides

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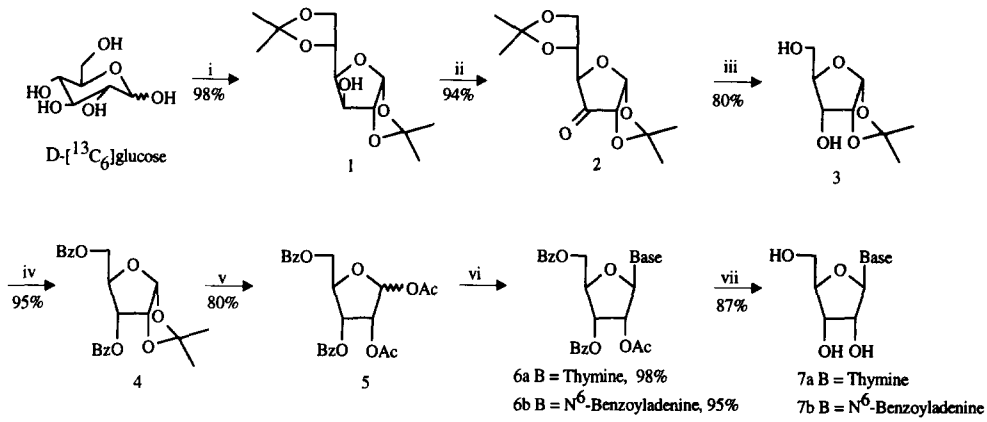
Abstract: The preparation of ^{13}C-labeled ribonucleosides starting from D-[$^{13}C_6$]glucose in 45% overall yield is described. The key of this short synthetic way is the dehomologation of di-O-isopropylidene hexofuranose **2** with periodic acid and $NaBH_4$ that afforded stereoselectively the labeled ribofuranose derivative **3** in high yield. © 1997 Elsevier Science Ltd. All rights reserved.

Nuclear magnetic resonance (NMR) spectroscopy provides unique information on the variation of the local structure and the dynamics of DNA and RNA under physiological condition which is potentially useful for understanding their biological function.[1-3] So, it has been largely used in studies of proteins-nucleic acids interactions. Unfortunately the overlap of proton resonance's between the two partners often precludes a complete assignment. One way of circumventing this difficulty is to use complexation of nucleic acids with ^{15}N uniformly labeled proteins.[4-6] Another is to use ^{13}C-labeled nucleic acids. The preparation of ^{13}C,^{15}N nucleosides have been reported from bacteria grown on minimal medium,[7-10] but isolation from cells is much less an economical way than synthetic way to obtain labeled nucleosides and especially deoxyribonucleosides. Therefore, this study reports an efficient and short way to obtain [$^{13}C_5$]nucleosides from the commercially available D-[$^{13}C_6$]glucose and follows our previously published work.[11-12] Incidentally, the chemical syntheses of [$^{13}C_5$]ribonucleosides have been reported by Schwalbe *et al*[13] who converted 3-O-mesyl-D-glucofuranose, as a key intermediate, to ribofuranose derivative with inversion at C-3 with tetrabutylammonium benzoate. This approach, however, inevitably involved multiple steps and was therefore considered not optimal enough, due to the cost of labeled precursors. Thus, more efficient process was still sought to obtain the labeled nucleosides. Our key step is the stereoselective dehomologation of 1,2:5,6-di-O-isopropylidene-3-oxo-D-glucofuranose.[14]

Chemical conversion of D-[$^{13}C_6$]glucose into D-[$^{13}C_5$]ribose was efficiently performed by the short sequence of reactions shown in Scheme 1. Commercially D-[$^{13}C_6$]glucose was successfully derived into [$^{13}C_6$]-1,2:5,6-di-O-isopropylidene-D-glucofuranose **1** in 98% yield from the consumed D-glucose.[15] In view of recent paper published by Robins *et al.*[14] on an efficient dehomologation of di-O-isopropylidenefuranose derivatives, compound **1** was oxidized by a suspension of pyridinium dichromate (PDC) in refluxed CH_2Cl_2 into the [$^{13}C_6$]-3-oxo- D-glucofuranose **2** in 94% yield. The resulting ketone **2** was submitted through a « one-pot » sequential transformation into the [$^{13}C_5$]-1,2-O-isopropylidene-α-D-ribofuranose **3** with periodic acid and sodium borohydride, in 80% yield. The hydride could only attack from the β-face resulting in [$^{13}C_5$]-α-D-ribofuranose as the exclusive product. This result has been also confirmed by NMR studies. Compound **3** was benzoylated to give the dibenzoylated [$^{13}C_5$]-α-D-ribofuranose derivative **4** in 95% yield, which was treated with Ac_2O/TFA to give [$^{13}C_5$]-1,2-di-O-acetyl-3,5-di-O-benzoyl-α,β-D-ribofuranose as crystalline product in 80% yield.



Scheme 1. Reagents: (i) $CuSO_4$, concentrated H_2SO_4, acetone; (ii) PDC, Ac_2O, CH_2Cl_2, reflux; (iii) H_5IO_6, EtOAc, then $NaBH_4$, EtOH; (iv) BzCl, Py; (v) Ac_2O, TFA; (vi) thymine (for **6a**) or N^6-benzoyladenine (for **6b**), HMDS, $(NH_4)_2SO_4$ then TMSOTf, DCE, 0 °C; (vii) NH_3/MeOH (for **6a**) or NaOH/MeOH/Pyridine (for **6b**).

The synthesis of [$^{13}C_5$]ribonucleosides was then achieved by the coupling reaction of persilylated nucleobases with compound **5** under Vorbrüggen conditions (trimethylsilyl trifluoromethane sulfonate as a promoter, 1,2-dichloroethane as solvent).[16] The protected [$^{13}C_5$]-5-methyluridine **6a** and the protected [$^{13}C_5$]-adenosine derivative **6b** were obtained in 98% and 95% yield respectively. Deprotection **6a** and **6b** with a saturated solution of NH_3-MeOH for 6a or NaOH/MeOH/pyridine for **6b** afforded **7a** and **7b** in 48% yield and 46% yield respectively from the consumed D-[$^{13}C_6$]glucose.[17] This method is well adapted for the synthesis of large scale of ^{13}C-labeled β-D-ribonucleosides, starting material for monomers of DNA or RNA oligomers.

Acknowledgments: This research was supported by grant from CNRS (ACC-SV5, Biologie Structurale) and the Fondation pour la Recherche Médicale.

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(*Received in France* 21 *November* 1996; *accepted* 14 *January* 1997)