



Efficient Synthesis of D-[5-¹³C]Ribose from D-Ribose and Its Conversion into [5'-¹³C]Nucleosides

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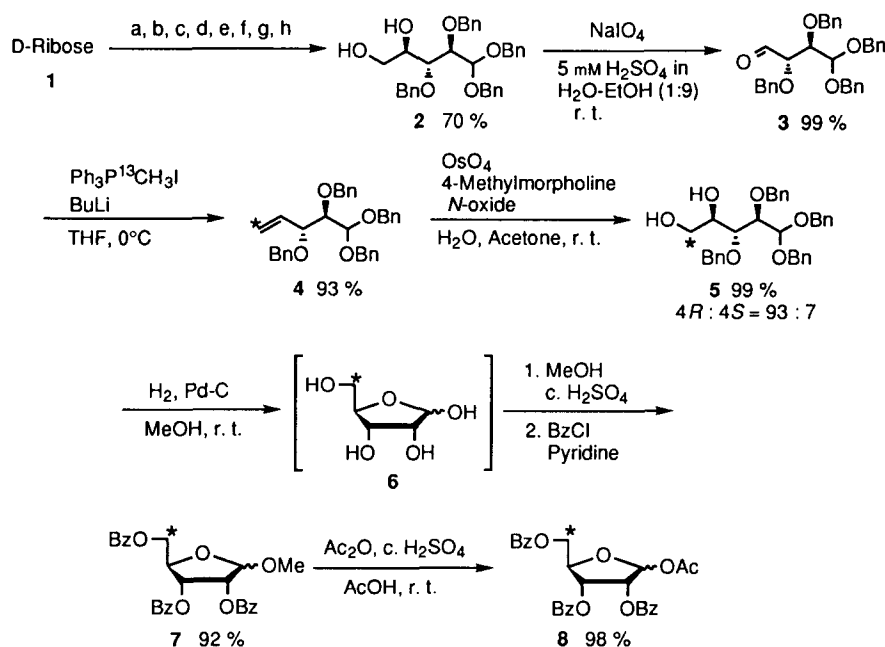
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Abstract: An approach to the synthesis of [5-¹³C]ribose (**6**) was achieved by a sequence reaction as follows: periodate oxidation of 2,3-di-*O*-benzyl-D-ribose dibenzyl acetal (**2**), which was derived from D-ribose (**1**) in 70% overall yield in 8 steps, followed by the introduction of ¹³C into the 5-position of D-ribose by Wittig reaction using Ph₃P¹³CH₃I - BuLi, highly diastereoselective hydroxylation with OsO₄, and then debenzylation. Compound **6** with the necessary protecting groups and a leaving group was derived into [5'-¹³C]ribonucleoside derivatives by the coupling reaction with persilylated nucleobases. Copyright © 1996 Elsevier Science Ltd

The conformational diversity of the sugar-phosphate backbone and/or the sugar moieties in nucleic acid is considered to be important in the elucidation of nucleic acid - protein or - drug recognition processes. The utility of ¹³C labeled RNAs and DNAs for the heteronuclear multidimensional NMR studies for nucleic acids has been shown in several reports.¹⁻⁸ Based on this background, the title nucleosides should be significantly useful for the conformational analysis of the sugar-phosphate backbone structure in nucleic acids. Incidentally, the chemical syntheses of [5'-¹³C]adenosine and D-[5-¹³C]ribose have been reported by Matwiyoff *et al.*⁹ and by Serianni *et al.*¹⁰ Matwiyoff *et al.* prepared [5'-¹³C]adenosine⁹ by the coupling reaction of an adenine derivative with a [5-¹³C]ribose derivative which was synthesized by way of L-[1-¹³C]ribonic acid obtained by the reaction of L-erythrose with [¹³C]KCN, followed by hydrolysis under acidic conditions. Serianni *et al.*, on the other hand, synthesized D-[5-¹³C]ribose from D-[6-¹³C]glucose which was obtained by the reaction of 1,2-*O*-isopropylidene- α -D-xylo-pentodialdo-1,4-furanoside with [¹³C]KCN.¹⁰ These synthetic methods, however, inevitably involved multiple steps after the introduction of ¹³C label, to attain the final product and, were therefore judged impractical. Thus, more efficient processes were sought to make the nucleosides more easily available.

Therefore, the present synthetic study on D-[5-¹³C]ribose (**6**) from D-ribose (**1**) was undertaken to overcome the drawback described above, and the results thus obtained will be described herein. Chemical conversion of D-ribose (**1**) into D-[5-¹³C]ribose (**6**) was efficiently performed by the sequence of reactions shown in Scheme 1. Compound **1** was successfully derived into 2,3-di-*O*-benzyl-D-ribose dibenzyl acetal (**2**) in 70% overall yield in 8 steps. After periodate oxidation of **2**, the resulting 4-*aldehyde*-2,3-di-*O*-benzyl-D-erythrose dibenzyl acetal (**3**) (99% yield) was then subjected to Wittig reaction¹¹ with Ph₃P¹³CH₃I (99 atom % ¹³C) - BuLi in THF at room temperature, which is the first key step in introducing ¹³C labeling as the 5-position of a pentose, to give 2,3-di-*O*-benzyl-4,5-didehydro-4,5-dideoxy-D-[5-¹³C]ribose dibenzyl acetal (**4**) in 93% yield.¹² The second key step is to perform a diastereoselective hydroxylation of **4** with OsO₄;¹³

the treatment of **4** with OsO₄ (0.05 molar equiv.) in the presence of 4-methylmorpholine *N*-oxide as a co-oxidizing agent gave a 93:7 mixture of 2,3-di-*O*-benzyl-D-[5-¹³C]ribose dibenzyl acetal (**5**) and the corresponding L-lyxo derivative in 99% yield. Such a high diastereoselectivity (4*R*/4*S* = 93/7) was confirmed by 400 MHz ¹H NMR spectroscopy after 4,5-di-*O*-benzoylation. The stereochemistry to give the excellent diastereoselectivity might be explained in terms of the concept described by Kishi *et al.*¹³ Subsequent debenzoylation of **5** in methanol by the catalytic hydrogenation on palladium charcoal gave D-[5-¹³C]ribose (**6**), which was then converted into 1-*O*-Ac-2,3,5-tri-*O*-benzoyl-D-[5-¹³C]ribose (**8**) via methyl 2,3,5-tri-*O*-benzoyl-D-[5-¹³C]ribofuranoside (**7**) by the usual method. The efficiency of the present approach from **1** to **8** is characterized by the 62% overall yield of **8** from Ph₃P¹³CH₃I, *i.e.*, after introducing the ¹³C labeling by Wittig reaction, in contrast with the 4% overall yield of **8** from [¹³C]KCN reported by Matwiyoff *et al.*⁹ and 25% overall yield of **6** from [¹³C]KCN reported by Serianni *et al.*¹⁰ after introducing the ¹³C label.



- a) MeOH, c. H₂SO₄, 0°C; b) DMTrCl, Pyridine, r. t.; c) BnBr, NaH, DMF, r. t.;
 d) 3% CCl₃COOH in CHCl₃, r. t.; e) EtSH, c. HCl, 0°C;¹⁴ f) Ac₂O, DMAP, CH₂Cl₂, r. t.;
 g) HgO, HgCl₂, CaSO₄, BnOH, 70°C;¹⁵ h) 2.0 M NaOH aq., MeOH, r. t.

Scheme 1

Compound **8** was finally subjected to a coupling reaction¹⁶ with a persilylated nucleobase (persilylated *N*⁶-benzoyladenine,¹⁷ *N*²-acetyl-*O*⁶-diphenylcarbonylguanine,¹⁷ *N*⁴-benzoylcytosine,¹⁸

thymine,¹⁹ and uracil¹⁸) to give [5'-¹³C]ribonucleoside derivatives in good yields (80%, 79%, 96%, and 78%, respectively).

The ¹H- and ¹³C-NMR spectra of *N*⁴, *O*²,*O*³,*O*⁵-tetrabenzoyl[5'-¹³C]cytidine (Panel A) and *N*⁴, *O*²,*O*³,*O*⁵-tetrabenzoylcytidine (panel B) for comparison are illustrated in Fig. 1.

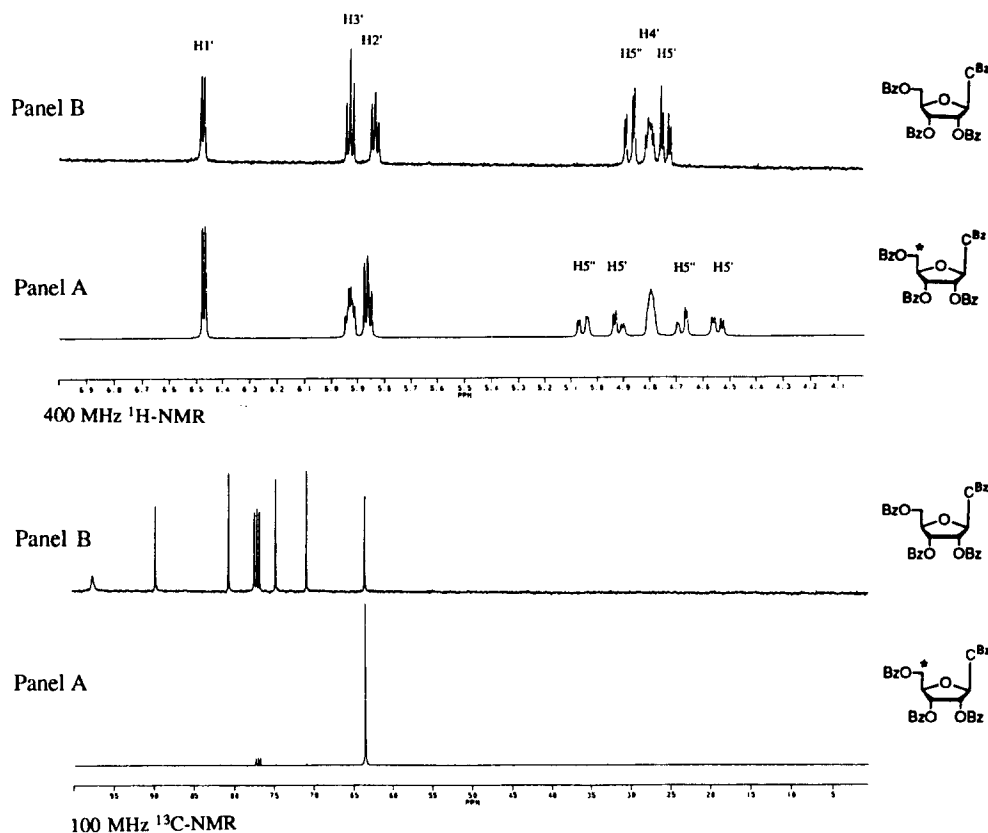


Fig. 1

An approach to the synthesis of [5'-¹³C]ribonucleosides was thus achieved by the coupling reaction of persilylated nucleobases with D-[5-¹³C]ribose derivative (9). The products were derived into the corresponding 2'-deoxy[5'-¹³C]ribonucleoside derivatives by the established method.²⁰

References and Notes

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12. 2,3-di-*O*-benzyl-4,5-didehydro-4,5-dideoxy-D-[5-¹³C]ribose dibenzylacetal(**4**) ¹H-NMR (CDCl₃): δ 7.2-7.4(20H, m, Ph-H), 5.96(1H, ddd, J_{3,4} = 8.0 Hz, J_{4,5} = 17.4 Hz, J_{4,5'} = 10.4 Hz, H₄), 5.29(1H, ddd, J_{4,5'} = 10.4 Hz, J_{5,5'} = 1.9 Hz, J_{5',C5} = 158.4 Hz, H_{5'}), 5.17(1H, ddd, J_{4,5} = 17.4 Hz, J_{5,5'} = 1.9 Hz, J_{5,C5} = 155.2 Hz, H₅), 4.87(1H, d, J = 11.5 Hz, Bn-CH), 4.78(1H, d, J = 11.5 Hz, Bn-CH), 4.70(1H, d, J_{1,2} = 6.4 Hz, H₁), 4.58-4.68(4H, m, Bn-CH X 4), 4.49(1H, d, J = 11.7 Hz, Bn-CH), 4.32(1H, d, J = 12.0 Hz, Bn-CH), 4.10(1H, dd, J_{2,3} = 3.3 Hz, J_{3,4} = 8.0 Hz, J_{3,C5} = 4.3 Hz, H₃), 3.98(1H, dd, J_{1,2} = 6.4 Hz, J_{2,3} = 3.3 Hz, H₂). ¹³C-NMR (CDCl₃): δ 138.80, 138.68, 138.21, 137.72, 134.99(d, J_{4,5} = 68.8 Hz), 128.36, 128.32, 128.26, 12, 127.93, 127.83, 1.66, 127.54, 127.38, 127.34, 119.30, 101.61, 81.69, 81.24, 74.41, 70.16, 69.51, 69.03. Anal. Calcd. for C₃₂H₃₆O₆ · 0.1H₂O: C, 79.85 H, 6.95. Found: C, 79.75 H, 7.03.
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