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

Takeshi Sekine, Etsuko Kawashima, and Yoshiharu Ishido

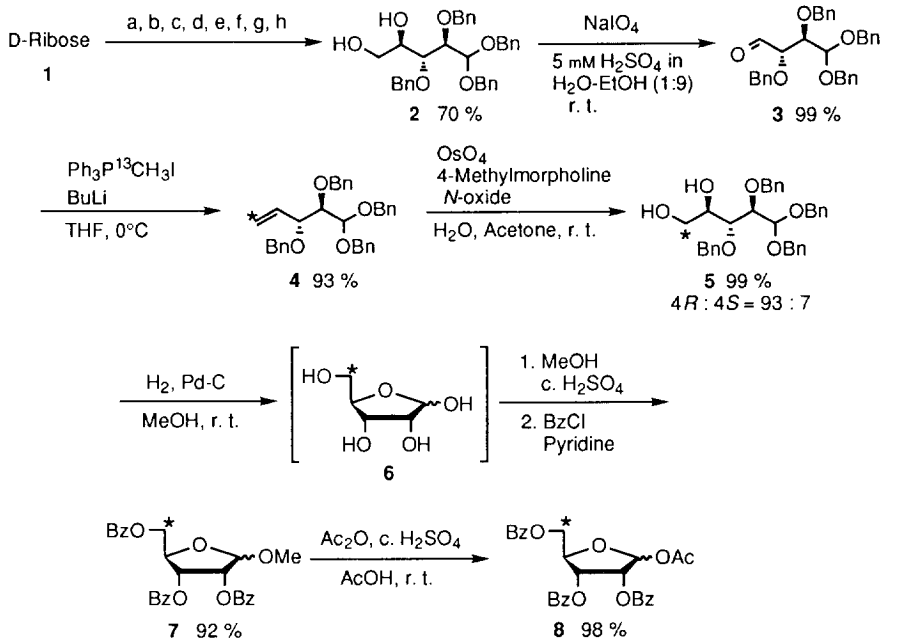
Laboratory of Pharmaceutical Chemistry, School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1, Horinouchi, Hachioji, Tokyo 192-03, Japan

Abstract: An approach to the synthesis of [5-^{13}C]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 ^{13}C into the 5-position of D-ribose by Wittig reaction using $Ph_3P^{13}CH_3I$ - BuLi, highly diastereoselective hydroxylation with OsO_4, and then debenzylation. Compound **6** with the necessary protecting groups and a leaving group was derived into [5'-^{13}C]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 ^{13}C 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'-^{13}C]adenosine and D-[5-^{13}C]ribose have been reported by Matwiyoff *et al.*[9] and by Serianni *et al.*[10] Matwiyoff *et al.* prepared [5'-^{13}C]adenosine[9] by the coupling reaction of an adenine derivative with a [5-^{13}C]ribose derivative which was synthesized by way of L-[1-^{13}C]ribonic acid obtained by the reaction of L-erythrose with [^{13}C]KCN, followed by hydrolysis under acidic conditions. Serianni *et al.*, on the other hand, synthesized D-[5-^{13}C]ribose from D-[6-^{13}C]glucose which was obtained by the reaction of 1,2-*O*-isopropylidene-α-D-*xylo*-pentdialdo-1,4-furanoside with [^{13}C]KCN.[10] These synthetic methods, however, inevitably involved multiple steps after the introduction of ^{13}C 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-^{13}C]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-^{13}C]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-*aldehydo*-2,3-di-*O*-benzyl-D-erythrose dibenzyl acetal (**3**) (99% yield) was then subjected to Wittig reaction[11] with $Ph_3P^{13}CH_3I$ (99 atom % ^{13}C) - BuLi in THF at room temperature, which is the first key step in introducing ^{13}C labeling as the 5-position of a pentose, to give 2,3-di-*O*-benzyl-4,5-didehydro-4,5-dideoxy-D-[5-^{13}C]ribose dibenzyl acetal (**4**) in 93% yield.[12] The second key step is to perform a diastereoselective hydroxylation of **4** with OsO_4;[13]

the treatment of **4** with OsO_4 (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-^{13}C]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 ^{1}H 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 debenzylation of **5** in methanol by the catalytic hydrogenation on palladium charcoal gave D-[5-^{13}C]ribose (**6**), which was then converted into 1-*O*-Ac-2,3,5-tri-*O*-benzoyl-D-[5-^{13}C]ribose (**8**) *via* methyl 2,3,5-tri-*O*-benzoyl-D-[5-^{13}C]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 $Ph_3P^{13}CH_3I$, *i.e.*, after introducing the ^{13}C labeling by Witting reaction, in contrast with the 4% overall yield of **8** from [^{13}C]KCN reported by Matwiyoff *et al.*[9] and 25% overall yield of **6** from [^{13}C]KCN reported by Serianni *et al.*[10] after introducing the ^{13}C label.



a) MeOH, c. H_2SO_4, 0°C; b) DMTrCl, Pyridine, r. t,; c) BnBr, NaH, DMF, r. t.;
d) 3% CCl_3COOH in $CHCl_3$, r. t.; e) EtSH, c. HCl, 0°C;[14] f) Ac_2O, DMAP, CH_2Cl_2, r. t.;
g) HgO, $HgCl_2$, $CaSO_4$, BnOH, 70°C;[15] h) 2.0 M NaOH aq., MeOH, r. t

Scheme 1

Compound **8** was finally subjected to a coupling reaction[16] with a persilylated nucleobase (persilylated N^6-benzoyladenine,[17] N^2-acetyl-O^6-diphenylcarbamoylguanine,[17] N^4-benzoylcytosine,[18]

thymine, [19] and uracil[18]) to give [5'-^{13}C]ribonucleoside derivatives in good yields (80%, 79%, 96%, and 78%, respectively).

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

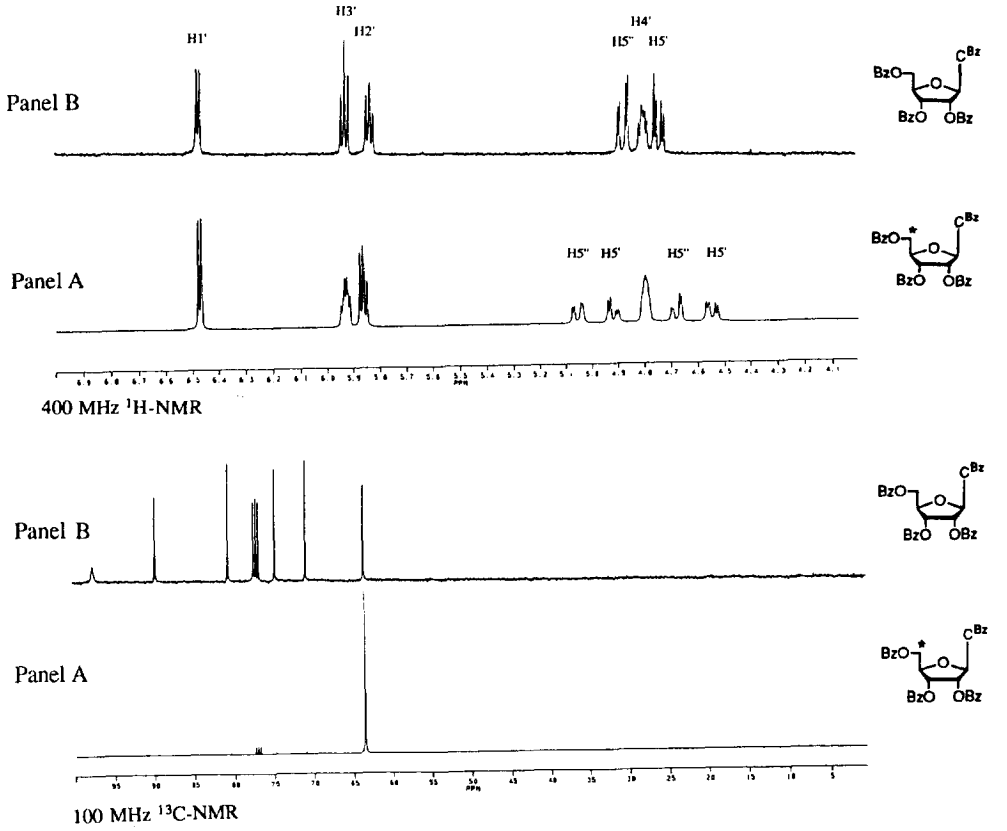


Fig. 1

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

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12. 2,3-di-*O*-benzyl-4,5-didehydro-4,5-dideoxy-D-[5-^{13}C]ribose dibenzylacetal(**4**) ^{1}H-NMR ($CDCl_3$) : 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, H5'), 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). ^{13}C-NMR ($CDCl_3$) : 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 $C_{32}{}^{13}CH_{36}O_6$ .0.1H_2O: C, 79.85 H, 6.95. Found: C, 79.75 H, 7.03.
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