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Synthesis of 2'-Deoxy[5'-¹³C]Ribonucleotides and HMQC-Noesy NMR Study of the Dickerson's Dodecamer with ¹³C-Labeling at the 5' Positions

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SYNTHESIS OF 2'-DEOXY[5'-¹³C]RIBONUCLEOTIDES AND HMQC-NOESY NMR STUDY OF THE DICKERSON'S DODECAMER WITH ¹³C-LABELING AT THE 5' POSITIONS

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ABSTRACT: In addition to the synthesis of 2'-deoxy[5'-¹³C]ribonucleosides (6) *via* the D-[5-¹³C]ribose derivative (4), the construction of the corresponding dodecanucleotide with the Dickerson's sequence and its HMQC-NOESY NMR analysis are described.

An efficient synthetic method for 2'-deoxy[5'- 2 H]ribonucleosides (5'S:5'R = ca. 2:1) has been developed with the expectation that they would enable us to assign unambiguously both of the H5' and H5" signals of an oligodeoxyribonucleotide and to analyze its sugar-phosphodiester backbone conformation NMR spectroscopically.\(^1\) The construction of a dodecadeoxyribonucleotide with the Dickerson's sequence from these components proved their utility in 2D \(^1\text{H}-\frac{31}{P}\) HSQC\(^2\) and DQF-COSY spectroscopy.\(^3\)

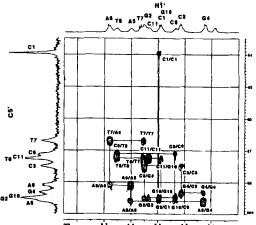
From another point of view, site-specific labeling of the 5' position of nucleosides with ¹³C could be expected to facilitate conformational studies of an oligonucleotide chain, in terms of heteronuclear multidimensional NMR spectroscopy. Consequently, an efficient method for the synthesis of 2'-deoxy[5'-¹³C]ribonucleosides (6) starting from D-ribose via D-[5-¹³C]ribose was successfully developed in our laboratory⁴, and construction of the Dickerson's dodecamer with ¹³C-labeling at its 5' positions for the NMR study was conducted; the detailed results thus obtained will be described herein.

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The coupling reaction of the D-[5-13C]ribose derivative 4 with a silvlated nucleobase through the Vorbrüggen's approach, followed by dehydroxylation at the 2' position, gave 6 (99 atom % ¹³C) in excellent yields. The synthesis of D-[5-¹³C]ribose is characterized by the introduction of a ¹³C-label at the 5 position of D-ribose through the Wittig reaction using Ph₃P¹³CH₃I, and subsequent highly asymmetric dihydroxylation using OsO_4 - 4-methylmorpholine N-oxide. It is of great interest that the latter reaction gave the D-[5-13]C]ribose derivative [(4R)-3; 3,4-anti] isomer] predominantly over the Llyxose derivative [(4S)-3; 3,4-syn] isomer] as shown below, in accordance with the empirical rule⁵ proposed by Kishi et al and Stork et al.

The resulting 6 were then converted into the corresponding 3'-phosphoramidite derivatives, and were used for the construction of d(C*G*C*G*A*A*T*T*C*G*C*G)2 (7) by conventional automated synthesis.

HMOC-NOESY NMR spectroscopic study of 7 revealed the correlation between C5'(i)-C6H(i), C8H(i), and the sequential NOEs of C5'(i)-C1'H(i-1), C5'(i)-C2"H(i-1),and C5'(i)-C2H(i-1). Moreover, all of C6H, C8H, C1'H, C2'H, C2"H, C3'H, C5', and C5"H, as well as C4'H for the seven residues therein, were unambiguously assigned.



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