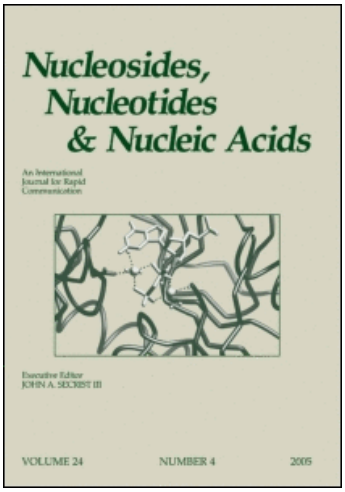

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Synthesis of 2'-Deoxy[5'-^{13}C]Ribonucleotides and HMQC-Noesy NMR Study of the Dickerson's Dodecamer with ^{13}C-Labeling at the 5' Positions

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

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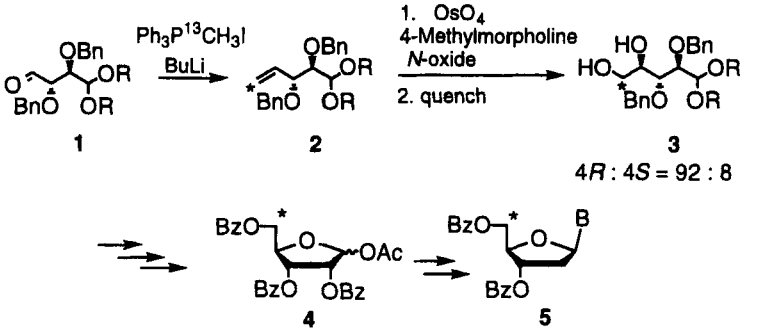
ABSTRACT: In addition to the synthesis of 2'-deoxy[5'-^{13}C]ribonucleosides (**6**) *via* the D-[5-^{13}C]ribose derivative (**4**), the construction of the corresponding dodecanucleotide with the Dickerson's sequence and its HMQC-NOESY NMR analysis are described.

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}H-^{31}P HSQC[2] and DQF-COSY spectroscopy.[3]

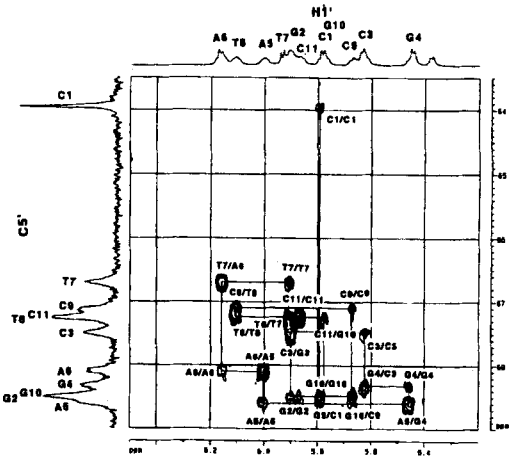
From another point of view, site-specific labeling of the 5' position of nucleosides with ^{13}C could be expected to facilitate conformational studies of an oligonucleotide chain, in terms of heteronuclear multidimensional NMR spectroscopy. Consequently, an efficient method for the synthesis of 2'-deoxy[5'-^{13}C]ribonucleosides (**6**) starting from D-ribose *via* D-[5-^{13}C]ribose was successfully developed in our laboratory[4], and construction of the Dickerson's dodecamer with ^{13}C-labeling at its 5' positions for the NMR study was conducted; the detailed results thus obtained will be described herein.

The coupling reaction of the D-[5-^{13}C]ribose derivative **4** with a silylated nucleobase through the Vorbrüggen's approach, followed by dehydroxylation at the 2' position, gave **6** (99 atom % ^{13}C) in excellent yields. The synthesis of D-[5-^{13}C]ribose is characterized by the introduction of a ^{13}C-label at the 5 position of D-ribose through the Wittig reaction using $Ph_3P^{13}CH_3I$, 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 [(4*R*)-**3**; 3,4-*anti* isomer] predominantly over the L-lyxose derivative [(4*S*)-**3**; 3,4-*syn* isomer] as shown below, in accordance with the empirical rule[5] 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.

An HMQC-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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