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Synthesis of ^2H , ^{13}C -Labelled 2'-Deoxynucleosides and Their Site Specific Incorporation into Oligo-DNA for Structural Studies via Relaxation Time Measurements

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SYNTHESIS OF ^2H , ^{13}C -LABELLED 2'-DEOXYNUCLEOSIDES AND THEIR SITE SPECIFIC INCORPORATION INTO OLIGO-DNA FOR STRUCTURAL STUDIES *VIA* RELAXATION TIME MEASUREMENTS

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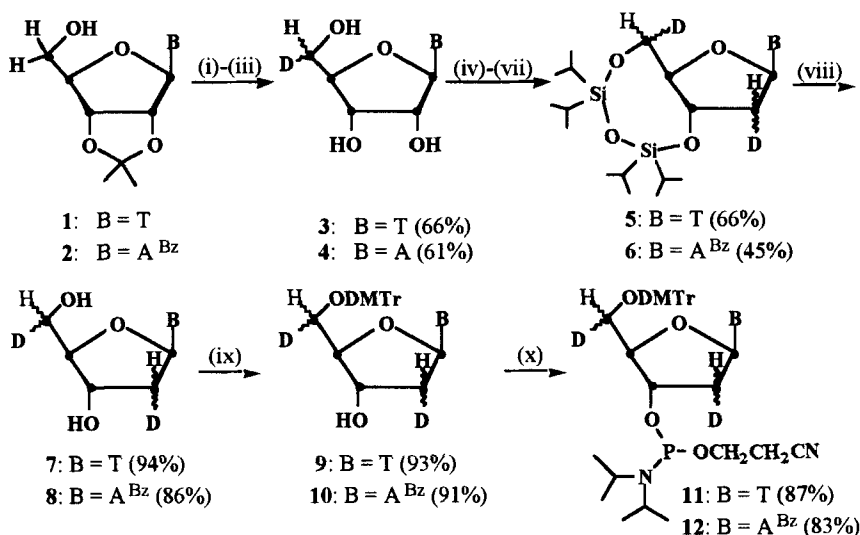
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ABSTRACT: We have recently shown¹ the usefulness of ^2H , ^{13}C -labelled 2'-deoxynucleoside building blocks for structural studies *via* relaxation time measurements. The synthesis of phosphoramidite blocks **11** and **12** for their site-specific incorporation (indicated by underlines) into the $\text{d}^5'(\text{C}^2\text{G}^3\text{A}^4\text{T}^5\text{T}^6\text{A}^7\text{A}^8\text{T}^9\text{C}^{10}\text{G})_2^{3'}$ is briefly described for studying the T_1 and $T_{1\rho}$ relaxations of ^2H and ^{13}C at specific deuterated carbons in a large molecule.

At the outset of our work, it was anticipated, that the use of $^{13}\text{C}/^2\text{H}$ labelled 2'(R/S), 5'(R/S)- $^2\text{H}_2$ -1',2',3',4', 5'- $^{13}\text{C}_5$ -2'-deoxynucleosides makes it possible to perform ^2H relaxation measurements only at C2' and C5' of the double-labelled nucleosides through a $^1\text{H} \rightarrow ^{13}\text{C} \rightarrow ^2\text{H} \rightarrow ^{13}\text{C} \rightarrow ^1\text{H}$ polarisation transfer, since the absence of $^2\text{J}_{\text{HH}}$ couplings in these residues allows the filtration of all other non-double labelled ^{13}C -fragments.

The 5'-deuteration of ribonucleosides with uniformly ^{13}C -labelled sugar moiety² was achieved by Moffatt-oxidation³ of the 2',3'-*O*-isopropylidene derivatives **1** and **2**, followed by reduction of the 5'-aldehyde with NaBD_4 to give a ~1:1 R/S mixture of deuterio-isotopomers. The cleavage of the isopropylidene group with 10% aqueous acetic acid at elevated temperature gave substantial loss of adenosine derivative most probably due to depurination. Nucleosides **3** and **4** were converted to the 3',5'-*O*-(1,1,3,3-tetraisopropyl-disiloxan-1,3-diyl)-2'-*O*-phenoxythiocarbonyl derivatives which were reduced with tributyltin deuteride⁴ to afford the diastereomeric 2'-deuterio derivatives (~85% ^2H at R; ~15% ^2H at S) **5** and **6** (after additional *N*⁶-benzoylation step). After removal of sugar protection upon a treatment with 1.0 M TBAF, the 2'-deoxynucleoside blocks **7** and **8** were converted to the appropriate phosphoramidite derivatives **11** and **12** through phosphitylation⁵ of the 5'-*O*-dimethoxytrityl nucleosides **9** and **10**. All intermediates were

satisfactorily characterised by their ^1H -, ^{13}C - and ^{31}P -NMR spectra recorded on a Jeol JNM GX 270 spectrometer at 270.17, 67.94 and 109.37 MHz, respectively. The labelled 10-mer $\text{d}^5(1\text{C}^2\text{G}^3\text{A}^4\text{T}^5\text{T}^6\text{A}^7\text{A}^8\text{T}^9\text{C}^{10}\text{G})_2^{3'}$ was prepared by the solid phase method on a Pharmacia LKB Gene Assembler Special synthesiser^{1b}.



Scheme 1. (i) DMSO, DCC, dichloroacetic acid, rt; (ii) NaBD₄ in ethanol, rt; (iii) 10% aq. acetic acid, ~90 °C (followed by NH₃ in methanol for compound 4); (iv) TPDS-Cl₂ in dry pyridine, rt; (v) phenoxythiocarbonyl chloride, methylimidazole in dry dichloromethane, rt; (vi) tributyltin deuteride, AIBN in dry toluene, ~85 °C; (vii) (to get compound 6) benzoyl chloride in dry pyridine; (viii) TBAF in dry THF, rt; (ix) DMTTr-Cl in dry pyridine, rt; (x) (2-cyanoethoxy)bis(N,N-diisopropylamino)phosphine, N,N-diisopropylammonium tetrazolide in dry dichloromethane, rt.

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