



Nucleosides and Nucleotides

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Published online: 04 Oct 2006.

To cite this article: Anthony Romieu, Didier Gasparutto, Didier Molko & Jean Cadet (1999) Synthesis and Characterization of Oligodeoxynucleotides Containing 5',8-Cyclopurine-2'-Deoxyribonucleosides, Nucleosides and Nucleotides, 18:6-7, 1331-1333, DOI: [10.1080/07328319908044708](https://doi.org/10.1080/07328319908044708)

To link to this article: <http://dx.doi.org/10.1080/07328319908044708>

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SYNTHESIS AND CHARACTERIZATION OF OLIGODEOXYNUCLEOTIDES CONTAINING 5',8-CYCLOPURINE-2'-DEOXYRIBONUCLEOSIDES

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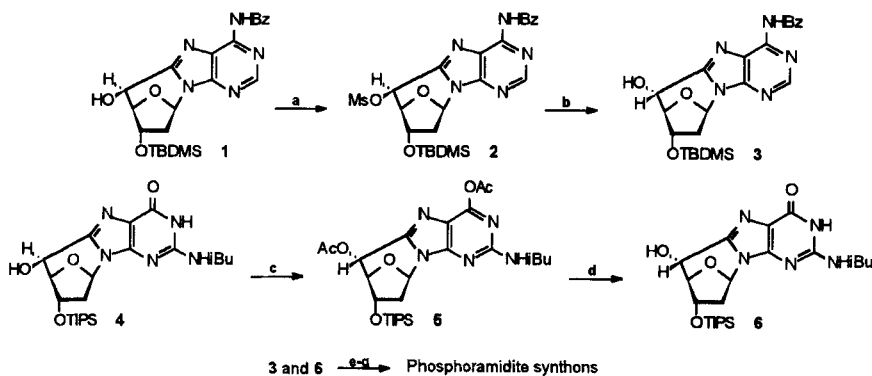
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ABSTRACT: Oligodeoxynucleotides containing the two 5'*R* and 5'*S* diastereoisomers of 5',8-cyclo-2'-deoxyadenosine (CyclodAdo) and 5',8-cyclo-2'-deoxyguanosine (CyclodGuo) have been synthesized using the phosphoramidite chemistry. The structural assignment and a few biochemical features of these modified DNA fragments are reported.

Highly reactive free radicals and particularly OH radical, generated by exposure to ionizing radiation, react with purine and pyrimidine nucleic acid components to produce a wide array of lesions. These include intramolecular cross link between the base and deoxyribose moieties of DNA. Indeed, the presence of 5',8-cyclopurine-2'-deoxyribonucleosides has been detected in γ irradiated aqueous solutions of 2'-deoxyadenosine and 2'-deoxyguanosine and in the enzymatic hydrolysates of irradiated calf thymus DNA.^{1,2} Such modified nucleosides which may be considered as tandem DNA lesions, the 2-deoxyribose and the purine residues being both altered, are likely to have a significant biological impact.³ In order to evaluate the biochemical and conformational consequences of 5',8-cyclopurine-2'-deoxyribonucleoside formation in DNA, it is necessary to prepare oligodeoxynucleotides that contain these double lesions at defined sites.

Recently, we reported the first site-specific incorporation of (5'*S*)-CyclodAdo into oligodeoxynucleotides using the phosphoramidite chemistry.⁴ In order to achieve the insertion of the other 5',8-cyclopurine-2'-deoxyribonucleosides, we have prepared the phosphoramidite synthons of (5'*R*)-CyclodAdo, (5'*R*)-CyclodGuo and (5'*S*)-CyclodGuo by

using a similar approach. However, the preparation of the 5'*R* diastereoisomers of CyclodAdo and CyclodGuo required the development of efficient methods for the epimerisation of C-5' carbon (Scheme 1). The protected alcohol **1** derived from (5'*S*)-CyclodAdo was converted into the (5'*R*)-epimer **3** via the mesyl derivative **2**, according to a procedure reported by Corey *et al.*⁵. Attempts to invert the C-5' stereoconfiguration of the protected alcohol **4** derived from (5'*S*)-CyclodGuo with this methodology were unsuccessful. The use of Mitsunobu esterification⁶ gave the (5'*R*) diacetyl derivative **5** which was further treated with sodium methylate to afford the (5'*R*)-5',8-cyclonucleoside **6**. Thereafter, dimethoxytritylation, desilylation and phosphitylation led to the phosphoramidite synthons. The modified phosphoramidites were incorporated efficiently into several oligonucleotides (3-mer, 14-mer and 22-mer). The presence and the integrity of 5',8-cyclonucleosides in the synthetic oligomers were confirmed by ESI mass spectrometry and NMR spectrometry for the 3-mers. The release of these modified nucleosides from the DNA fragments by endonucleases and exonucleases was also studied by means of HPLC and MALDI-TOF mass spectrometry analyses. These studies revealed that the digestion was affected and the enzymes act differently on the 5'*R* and 5'*S* epimers of the 5',8-cyclopurine-2'-deoxyribonucleosides.



Conditions: a) MsCl (2 eq), TEA (4 eq), CH₂Cl₂, rt, 3 h, 95%; b) KO₂ (3.6 eq), 18-C-6 (0.5 eq), DMSO/DME (1/1), rt, 9 h, 58%. c) DEAD (4 eq), PPh₃ (4 eq), AcOH (2 eq), THF, rt, 20 h, 80%; d) CH₃ONa (4 eq), THF, rt, 1 h, 95%; e) DMTrCl (3 eq), pyridine, 80°C, 4 h; f) TBAF (2 eq), THF, rt, 4 h (TBDMS), 16 h (TIPS); g) Cl-P(NiPr₂)O(CH₂)₂CN (1.1 eq), DIEA (2.2 eq), CH₂Cl₂, argon, 30 min.

SCHEME 1: Synthesis of the phosphoramidite synthons of (5'*R*)-CyclodAdo and -CyclodGuo.

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