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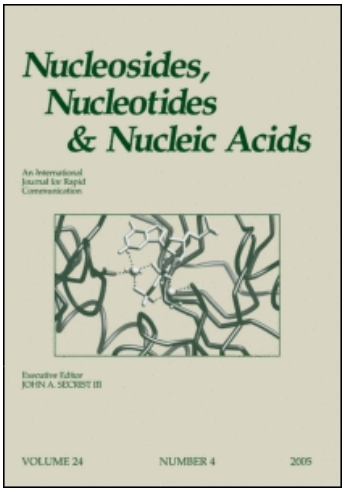

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Synthesis and Characterization of Oligodeoxynucleotides Containing 5',8-Cyclopurine-2'-Deoxyribonucleosides

Anthony Romieu[a]; Didier Gasparutto[a]; Didier Molko[a]; Jean Cadet[a]
[a] Laboratoire des Lésions des Acides Nucléiques, Grenoble Cedex, (France)

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

Anthony Romieu, Didier Gasparutto, Didier Molko and Jean Cadet*

Laboratoire des Lésions des Acides Nucléiques,
DRFMC/SCIB/CEA-Grenoble / 38054 Grenoble Cedex 9 (France)

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.

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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

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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 esterification[6] 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 phosphytilation 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.

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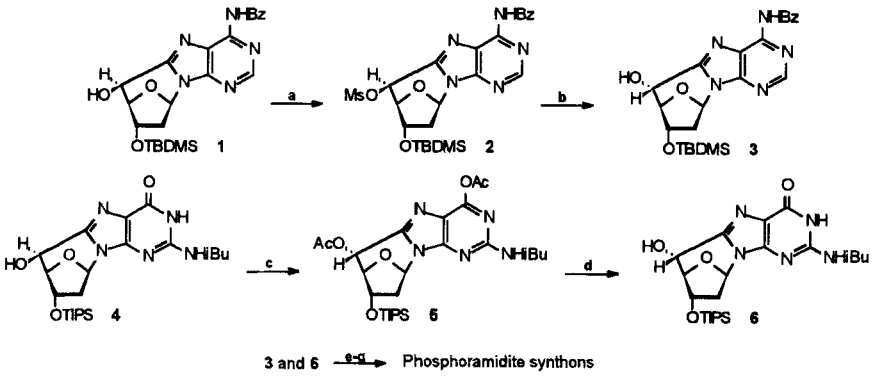

Conditions: a) MsCl (2 eq), TEA (4 eq), CH_2Cl_2, rt, 3 h, 95%; b) KO_2 (3.6 eq), 18-C-6 (0.5 eq), DMSO/DME (1/1), rt, 9 h, 58%. c) DEAD (4 eq), PPh_3 (4 eq), AcOH (2 eq), THF, rt, 20 h, 80%; d) CH_3ONa (4 eq), THF, rt, 1 h, 95%; e) DMTrCl (3 eq), pyridine, 80°C, 4 h; f) TBAF (2 eq), THF, rt, 4 h (TBDMS), 16 h (TIPS); g) Cl-P(NiPr$_2$)O(CH$_2$)$_2$CN (1.1 eq), DIEA (2.2 eq), CH_2Cl_2, argon, 30 min.

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

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