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Synthesis of an Oligonucleotide Analogue of Ethenoadenosine

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ABSTRACT

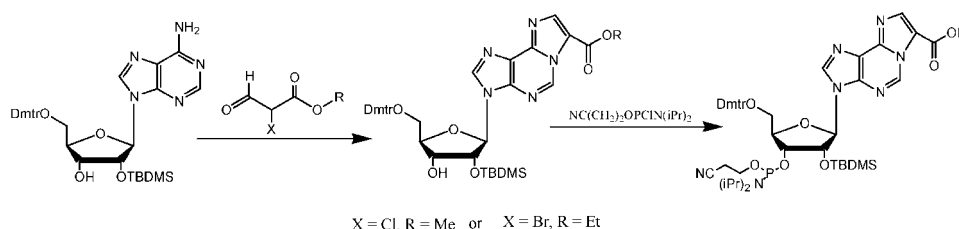
A phosphoramidite building block derived from 11-carboxy-1,*N*⁶-ethenoadenosine has been prepared to be used in a solid supported oligonucleotide synthesis.

DNA damage by toxic agents compromises the coding potential and strand integrity of genetic material. An increasing number of bifunctional chemical agents are known to form covalent cyclic adducts with DNA bases by bridging two nitrogen atoms on a single base. While cyclic adducts as such may be classified as mutagenic DNA lesion, those bearing additional functional groups that are able to interfere with the base-pairing are of particular interest. Besides miscoding, such adducts may possibly give rise to inter- or intrastrand cross-linking of DNA, or they may result in irreversible binding of proteins to the DNA backbone. Halogen substituted malonaldehydes, formed intracellularly from mutagenic halo compounds,^[1] are known to give 11-formyl-1,*N*⁶-etheno adducts when reacted with adenosine,^[2–4]

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and under oxidative stress conversion to 11-carboxy-1,*N*⁶-etheno adducts appears plausible. To learn more about the effects that the latter base modification exerts on the duplex stability and coding properties of DNA, convenient methods for the insertion of the adduct in any position within any oligonucleotide sequence are needed. For this purpose, the adducted nucleoside should be converted to a building block which is compatible with conventional protocols of solid-supported oligonucleotide without any marked modifications. We now report on preparation of such a phosphoramidite building block derived from 11-carboxy-1,*N*⁶-ethenoadenosine. The synthesis is outlined below.



RESULTS AND DISCUSSION

A possible route to obtain 11-carboxy-1,*N*⁶-ethenoadenosine involves oxidation of 11-formyl-1,*N*⁶-ethenoadenosine known to be formed in a relatively high yield upon treatment of adenosine with 2-bromomalonaldehide in aqueous solution at low pH.^[4] This approach, as well as the reaction of 3-alkoxy-2-halo-3-oxopropanal with adenosine in aqueous solution, however, leads to laborious purification. By contrast, 5'-*O*-(4,4'-dimethoxytrityl)-2'-*O*-(*tert*-butyldimethylsilyl)adenosine when reacted with 2-bromo-3-ethoxy-3-oxopropanal in aqueous dioxane (dioxane:water 2:1, *v/v*) gave protected 11-ethoxycarbonyl-1,*N*⁶-ethenoadenosine in a 60% yield. Similarly, the reaction with 2-chloro-3-methoxy-3-oxopropanal gave protected 11-methoxycarbonyl-1,*N*⁶-ethenoadenosine, but in a lower yield. The 3'-hydroxy group was then phosphitylated with 2-cyanoethyl-*N,N,N',N'*-tetraisopropylphosphoramidite to obtain a building block that can be used in a solid-supported oligonucleotide chain assembly by a normal phosphoramidite strategy. Studies at a monomer level have shown that the ethoxycarbonyl group may be hydrolyzed in aqueous alkali to a carboxylate group without other modifications in the ethenoadenine ring system. Accordingly, brief treatment of the fully protected oligonucleotide with aqueous sodium hydroxide before ammonolytic deprotection of the base moieties should give the carboxyetheno adducted oligomer. By contrast, direct ammonolysis of the protected oligonucleotide will give a carbamoyletheno adduct that is highly fluorescent.^[5] On using amines as a cleaving agent instead of ammonia, various *N*-alkyl- or *N*-arylcaramoyletheno adducts are obtained.

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