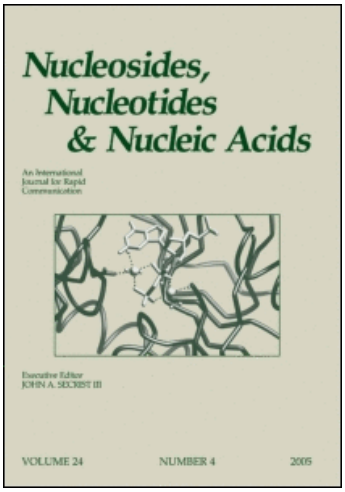

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EFFICIENT CHEMICAL SYNTHESIS OF OLIGONUCLEOTIDES CONTAINING THE 2-DEOXYRIBONOLACTONE SITE

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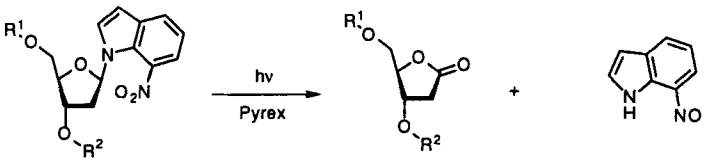
ABSTRACT: A highly efficient synthetic method for incorporation of the deoxyribonolactone lesion into oligonucleotides was developed using the photochemical properties of 7-nitroindole.

The deoxyribonolactone lesion (**2**, dL) is a common abasic site induced in DNA *via* radical H1' abstraction by a variety of oxidative agents[1]. This lesion has been shown to be highly mutagenic and suspected to play an important role in carcinogenesis[2]. However, until now, no efficient methodology has been described for the synthesis of oligonucleotides incorporating this lesion at preselected positions. The conventional phosphoramidite approach is unsuitable for this synthesis because of the alkali-sensitive nature of this lesion.



1

a $R^1=R^2=$*p*-Toluoyl
b $R^1=R^2=H$
c R^1=5'-TGp, R^2= pAC-3'
d R^1=5'-ATp, R^2=pCG-3'
e R^1=5'-CGCACp, R^2=pCACGC-3'

2 + 3

We were interested to design a new building block to be incorporated efficiently in a short oligonucleotide and then converted to the dL moiety by photochemical reaction. As nitro aromatic compounds are known to be able to abstract hydrogen *via* the n,π^* triplet

state[3], we expected that a simple 2-deoxyribose derivative containing an appropriate nitroindole moiety could generate 2-deoxyribonolactone *via* photoreaction initiated by anomeric hydrogen abstraction.

Early molecular modeling study of the 7-nitroindole derivative **1a** predicted close proximity between a photoreactive oxygen of the nitro group and the anomeric hydrogen. Nucleosides **1a** and **1b** were thus prepared. Indeed, the X-ray study of **1b** indicated a 2.4 Å distance for H1'-O[3]. This proximity also exists in the liquid state as shown by NMR. Upon irradiation[4], 1-deoxyribosyl-7-nitroindole **1a** yielded quantitatively the deoxyribonolactone **2a** and 7-nitrosoindole **3**.

Using the phosphoramidite method, the 7-nitroindole nucleoside was successfully incorporated into oligonucleotides **1c-e**. The irradiation[4] of these oligomers afforded cleanly the desired dL containing oligonucleotides **2c-e** which were fully characterized by ES-MS and by NMR spectrometry.

The structural study[5] of a dL containing duplex (**2e** and its complementary strand with T in the middle position) was performed by NMR and molecular modeling. The simulated duplex structure shows only little perturbation relative to the regular B-DNA conformation.

In summary these results demonstrate the usefulness of the newly developed methodology of dL site incorporation into oligonucleotides for study of common DNA oxidative damage. The method is applicable for specific abasic site incorporation without any restriction concerning the base sequence.

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(4) The photolysis lamp, suspended in a jacketed, water-cooled immersion well, is a 100 W high pressure mercury arc Hanovia lamp with pyrex filter (**1a**→**2a** in CH_3CN, **1c-e**→**2c-e** in 5 mM sodium phosphate buffer, pH 6.0, C = 15 μM).

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