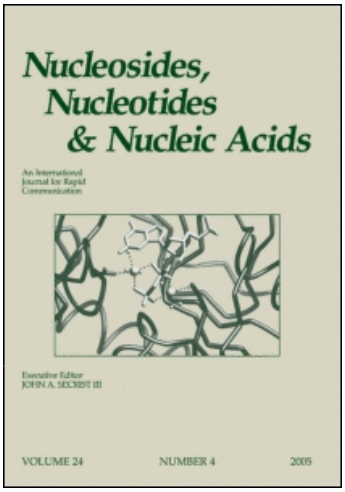

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Deoxyribonolactone Lesion in DNA: Synthesis of Fluorinated Analogues

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Online publication date: 09 August 2003

To cite this Article Crey, Caroline , Dumy, Pascal , Lhomme, Jean and Kotera, Mitsuharu(2003) 'Deoxyribonolactone Lesion in DNA: Synthesis of Fluorinated Analogues', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 1093 — 1095
To link to this Article: DOI: 10.1081/NCN-120022744
URL: http://dx.doi.org/10.1081/NCN-120022744

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, Nos. 5–8, pp. 1093–1095, 2003

Deoxyribonolactone Lesion in DNA: Synthesis of Fluorinated Analogues

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ABSTRACT

Mono- and difluorinated derivatives of 2-deoxyribonolactone were synthesized using diastereoselective Reformatski reaction as a key step.

Key Words: Fluorinated derivatives; Deoxyribonolactone; DNA damage; Synthesis.

Deoxyribonolactone in DNA is an oxidized abasic site damage that is produced by a variety of physical and chemical agents such as γ-irradiation and ene-diyne antibiotics. The extent and biological significance of the lesion are poorly documented due to the high lability of the damaged DNA. Recently we described the chemistry of deoxyribonolactone lesion in DNA that was investigated using oligonucleotides prepared, as already reported, from oligonucleotide precursors containing a photoactive nitroindole residue.[1–3] The cleavage kinetics were investigated using capillary

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DOI: 10.1081/NCN-120022744
1525-7770 (Print); 1532-2335 (Online)

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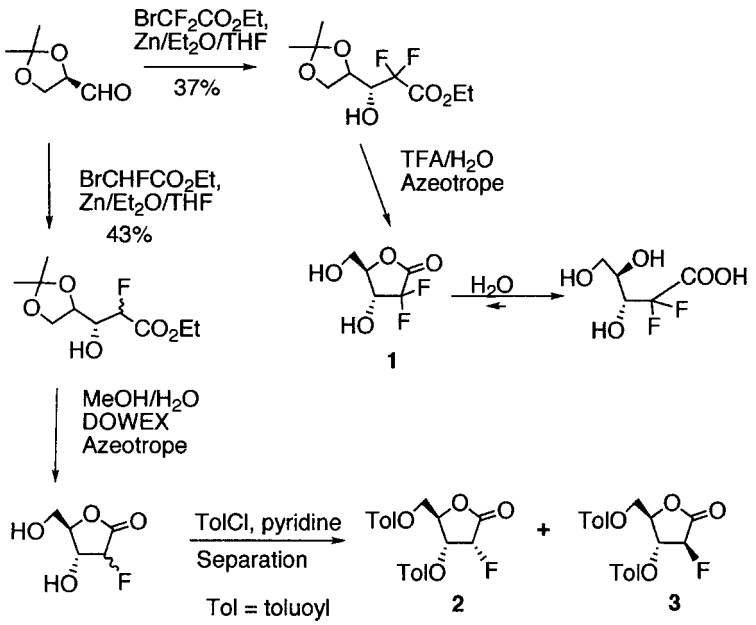

Scheme 1.

electrophoresis and it was found that the rate of cleavage of the lesion is extremely sensitive to pH, temperature. Here we describe the synthesis of fluorinated derivatives of deoxyribonolactone.

The fluorinated derivatives of deoxyribonolactone represent a new type of lesion model. When these residues are incorporated in DNA, they may be useful as stable analogs of the deoxyribonolactone lesion for future structural and biological studies. The synthetic route is outlined in the following schemes. Difluorodeoxyribonolactone **1** was synthesized in two steps as described previously using diastereoselective Reformatsky reaction as the first step.[4] It has been shown that the free difluorolactone **1** exists mainly as an open chain structure in aqueous solution. The two isomeric monofluorodeoxyribonolactones **2** and **3** were synthesized using the similar synthetic Scheme 1. The stereochemistry of two isomers was determined by 2D NOESY spectra. **2**: $R_f = 0.43$ (AcOEt:cyclohexane = 1:2), ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm = 7.92 (m, 2H); 7.82 (m, 2H); 7.25 (m, 4H); 5.74 (m, H-3); 5.48 (dd, H-2, $J = 48$ and 6 Hz); 4.97 (m, H-4); 4.66 (m, 2H, H-5); 2.41 (s, 6H). ^{19}F NMR (283 MHz, $CDCl_3$): δ ppm = −214.3 (d, $J = 48$ Hz). MS: (DCI, NH_3 + isobutane) m/z 387 $[M+H]^+$ *Anal. Calcd.* for $C_{21}H_{19}FO_6$: C, 65.28; H, 4.96; Found: C, 64.67; H, 4.88. **3**: $R_f = 0.37$ (AcOEt:cyclohexane = 1:2), ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm = 7.89 (m, 4H); 7.23 (m, 4H); 5.82 (m, H-3); 5.45 (dd, H-2, $J = 49$ and 5 Hz); 4.79 (m, H-4); 4.71 (m, 2H, H-5); 2.42 (s, 3H); 2.38 (s, 6H). ^{19}F NMR (283 MHz, $CDCl_3$): δ ppm = −199.5 (dd, $J = 49$ and 19 Hz). MS: (DCI, NH_3 + isobutane) m/z 387 $[M+H]^+$ *Anal. Calcd.* for $C_{21}H_{19}FO_6$: C, 65.28; H, 4.96; Found: C, 65.03; H, 4.86.

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