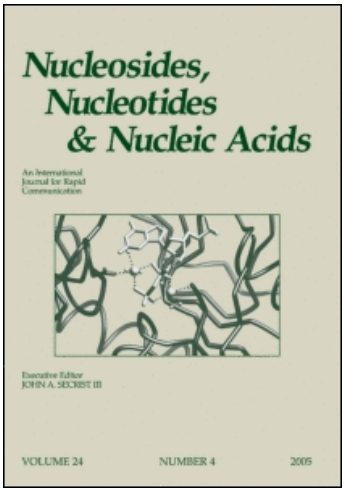

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Dinucleotides Incorporating Isomeric Nucleosides: Synthesis, Structural and Stereochemical Characterization, and Enzymology

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DINUCLEOTIDES INCORPORATING ISOMERIC NUCLEOSIDES: SYNTHESIS, STRUCTURAL AND STEREOCHEMICAL CHARACTERIZATION, AND ENZYMOLOGY

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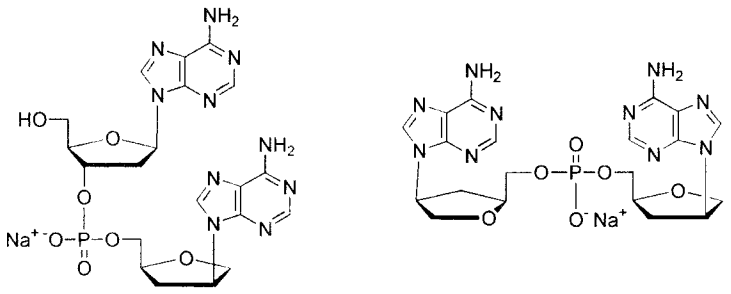
ABSTRACT: The synthesis, stability toward nucleases, and conformational properties of 3'→5' and 5'→5' dinucleotides bearing an isomeric nucleoside component is described.

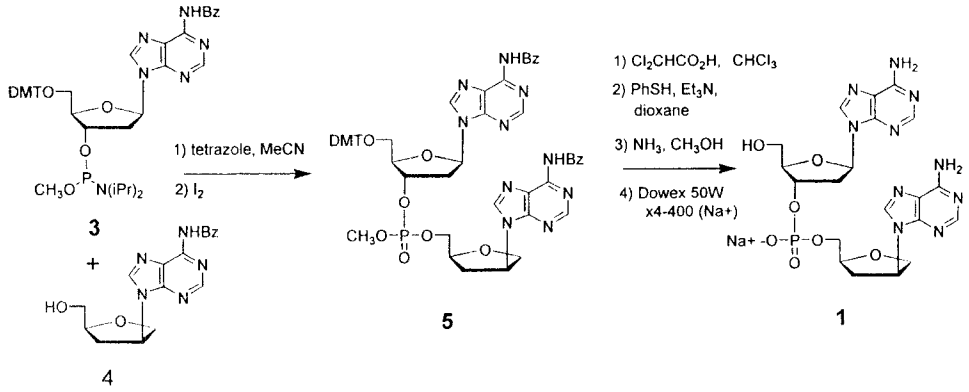
4(*S*)-(6-Amino-9H-purin-9-yl)tetrahydro-2(*S*)-furanmethanol [(*S,S*)-IsoddA] triphosphate synthesized in our laboratory has been discovered to be a powerful inhibitor (K_i 16 nM) of HIV reverse transcriptase (RT), a key enzyme encoded by HIV.[1] This compound, an L-related nucleoside triphosphate, is incorporated in the structure of HIV viral DNA and behaves as a chain terminator of this DNA. We have been interested in the synthesis, structural studies, and behavior toward enzymes of di- and higher nucleotides incorporating isomeric nucleosides. The focus of this paper is on two dinucleotides **1** and **2** incorporating the L-related and anti-HIV active dideoxynucleoside, (*S,S*)-IsoddA (Scheme 1).

Compound **1,** a 3'→5' dinucleotide [2'-deoxyadenylyl-(3'→5')-isodideoxyadenosine], was designed as a model system to represent the terminus of HIV DNA on incorporation of (*S,S*)-IsoddA. This compound was synthesized using the solution phase phosphoramidite methodology[2] by coupling N^6-benzoyl-5'-O-(4,4'-dimethoxytrityl)-2'-deoxyadenosine-O-methylphosphoramidite (**3**) with N^6-benzoyl IsoddA (**4**)[3,4] as described previously by us.[5] The target compound (produced in 34% overall yield) was converted from its ammonium to its sodium salt with Dowex 50Wx 4-400 (Na^+ form). Compound **1** as its sodium salt was purified by reversed phase HPLC on a C-18 column



1 2

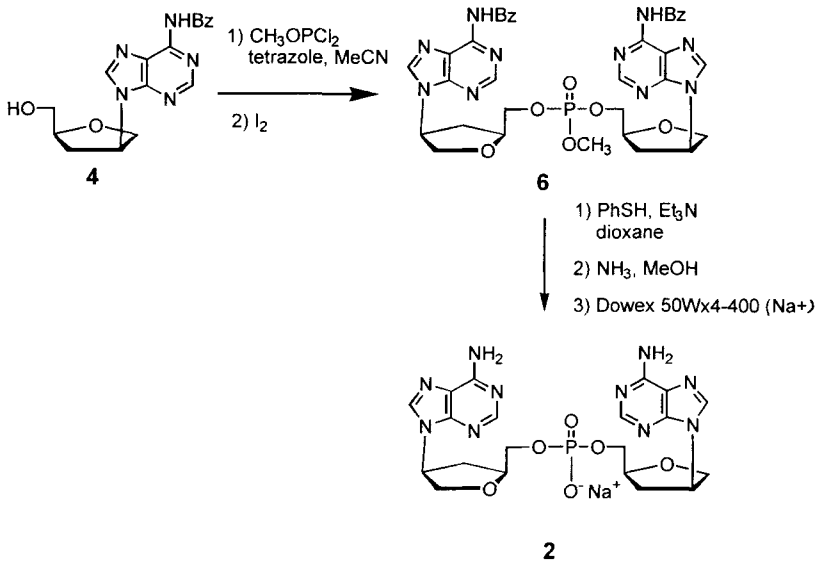
Scheme 1



Scheme 2

(water/ methanol elution). Structural confirmation came from UV and multinuclear NMR spectra, mass spectral data and elemental analysis.

The phosphoramidite coupling methodology used very successfully for the synthesis of the 3'→5' dinucleotide **1** proved unsuccessful for the 5'→5' dinucleotide **2.** The triester **6** was finally prepared from **4** in 50 % yield by using methyl dichlorophosphite as the coupling reagent followed by oxidation with iodine (Scheme 3). Deprotections were achieved by treatment of **6** first with thiophenol and triethylamine in dioxane, and subsequently with methanolic ammonia. The ammonium salt was converted into the sodium salt by Dowex 50W×4-400 (Na^+) to give the target molecule **2** (54% yield from



Scheme 3

Table 1. UV Maxima and Molar Extinction Coefficients (in H_2O)

Compound	λ_{max}	ε
Deoxyadenosine	259	15,000
IsoddA	260	14,700
dApisoddA (**1**)	258	24,000
isoddApisoddA (**2**)	259	30,400

6). Compound **2** was purified by reversed-phase HPLC (Amberlite XAD-4 resin, 0-10% EtOH/H_2O) and its structure was confirmed by multinuclear NMR spectra, and UV and HR-FABMS data: UV λ_{max} 259 (30,465); ^{1}H NMR (300 MHz, D_2O) δ 2.07-2.18 (m, 2H), 3.99-4.22 (m, 8H), 4.31-4.33 (m, 2H), 5.15 (m, 2H), 8.02 (s, 2H), 8.05 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.7, 57.2, 68.8 (d), 75.4, 80.7 (d), 120.2, 142.2, 150.7, 154.7, 157.5; ^{31}P NMR (125 MHz, $CDCl_3$) δ −1.81. HRMS-FAB: calculated for $C_{20}H_{25}N_{10}NaO_6P$ (MH^+), 555.1594; found, 555.1593.

Various spectroscopic methods have been used to study the conformational properties of dinucleotides including hypochromicity and circular dichroism. Quantitative UV data of the 3'→5' dinucleotide **1** (Table 1) exhibit clear evidence of hypochromicity, an indication of base stacking interaction between the chromophores. The data for compound **2**, however, do not show any indication of hypochromicity. Further support for base stacking in **1** is clearly present in the CD data for this compound determined in water at temperatures from 5 °C to 55 °C. The spectra showed well-defined isodichroic points, changes in the intensity of the CD maxima and minima with temperature, and λ_{max} and λ_{min} values which were independent of temperature.

The question of the stability of the 3'→5' internucleotide bond of a dinucleotide bearing an isomeric nucleoside was also examined. Dinucleotide **1** showed marked resistance toward internucleotide bond cleavage by both 3'→5' and 5'→3' exonucleases.

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