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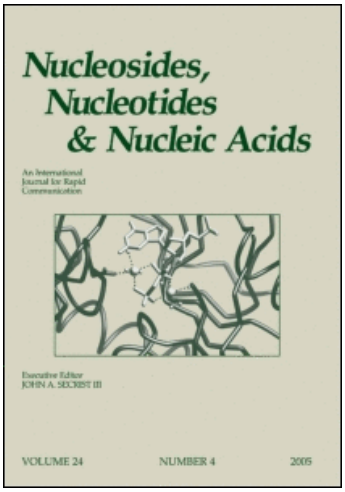

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Synthesis and Enzymatic Stability of Acyclic Thymidine Dimer Analogues having a Constrained Anti-Glycosidic Conformation

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SYNTHESIS AND ENZYMATIC STABILITY OF ACYCLIC THYMIDINE DIMER ANALOGUES HAVING A CONSTRAINED ANTI-GLYCOSIDIC CONFORMATION

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ABSTRACT: Our interest to design a novel class of antisense oligonucleotides has lead us to prepare acyclic thymidine dimer analogues having an unique constrained anti-glycosidic conformation. These dimer analogues showed remarkable resistance to nuclease degradation, such as Nuclease S1, Bovine Spleen Phosphodiesterase, and Snake Venom Phosphodiesterase.

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Antisense oligonucleotides are of great interest as potential therapeutic agents and as powerful molecular biological tools. In order to discover new oligonucleotide analogues which possess great resistance to nuclease and high affinity to their complementary strands, we have initiated the synthesis of nucleotide dimers containg an *anti*-glycosidic conformationally constrained acyclic thymidine as the building unit of oligonucleotide.

The target dimers were synthesized (Scheme 1) from 3,3-Bis(hydroxymethyl)-5-methyl-(1*H*,3*H*,4*H*,7*H*)-pyrimido[1,6-*c*][1,3]oxazine-6,8-dione (**1**). Tritylation of **1** with 4,4'-dimethoxytrityl chloride in dry pyridine gave a mixture of **T*-A** and **T*-B**. Coupling reaction of **T*-A** and **T*-B** with **T-CE**, **dA-CE**, **dC-CE**, **dG-CE**, followed by oxidation with iodine, cleavage with 25% ammonia water, deprotection with 80% acetic acid gave eight nucleotide dimers, **TpT*-A**, **dApT*-A**, **dCpT*-A**, **dGpT*-A**, **TpT*-B**, **dApT*-B**, **dCpT*-B**, and **dGpT*-B**, separately. These eight nucleotide dimers were converted to their sodium salts by elution through a column of Dowex 50W-400 cation exchange resin.

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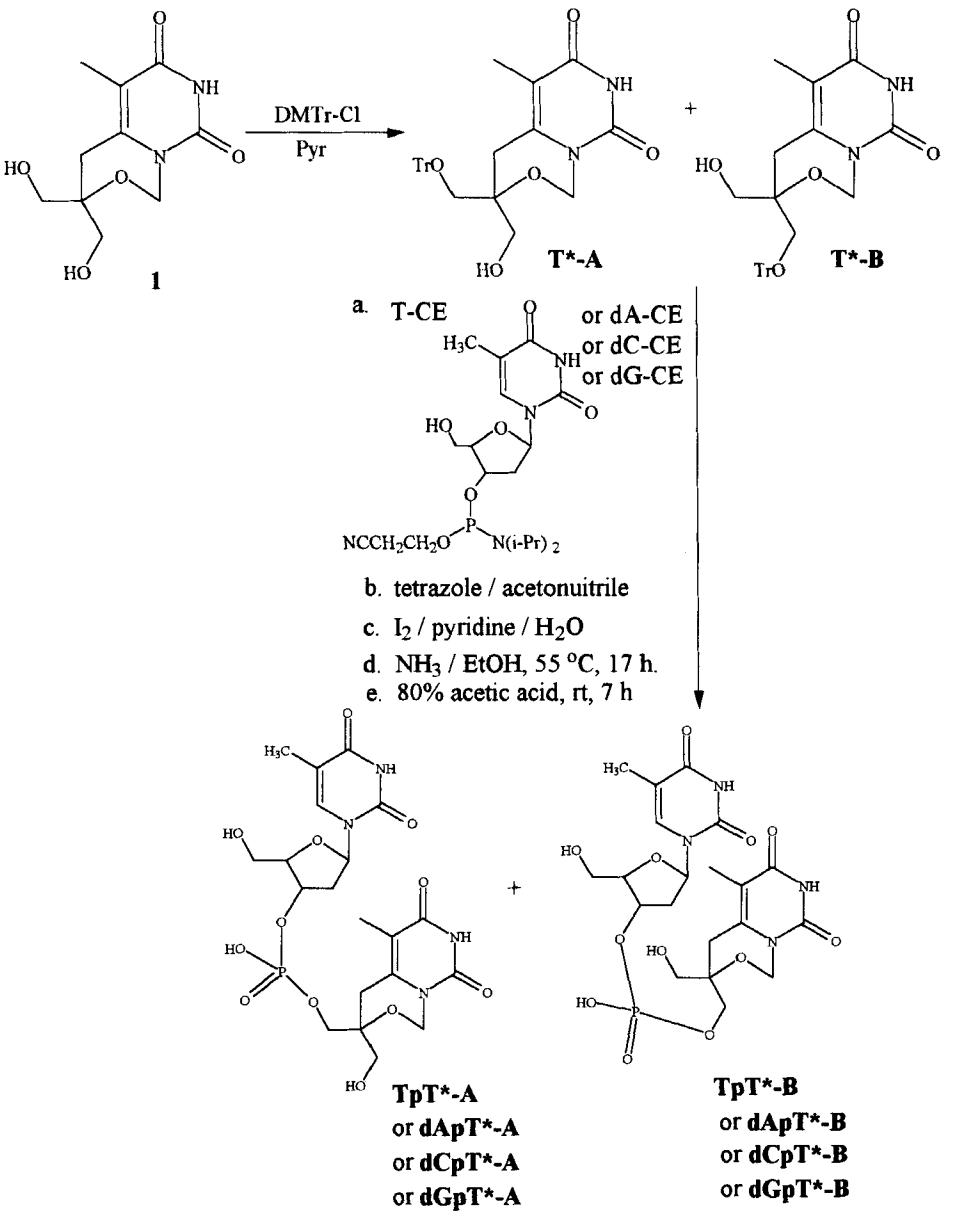
Scheme 1



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