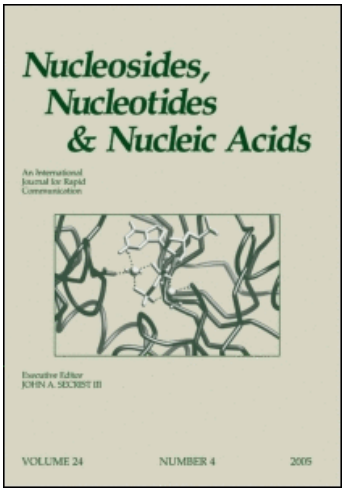

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Novel Oligonucleotide Analogues Derived From Serine and 4-Hydroxyproline

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NOVEL OLIGONUCLEOTIDE ANALOGUES DERIVED FROM SERINE AND 4-HYDROXYPROLINE

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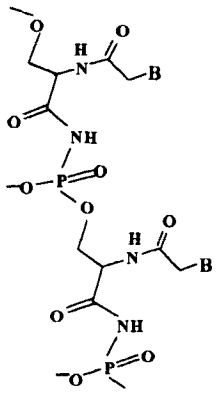
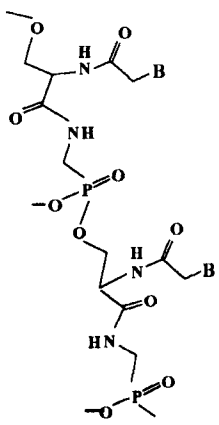
ABSTRACT. A set of DNA analogues derived from serine and 4-hydroxyproline and containing carboxamidomethyl phosphonate and carboxamidophosphate bonds between monomeric units was synthesized.

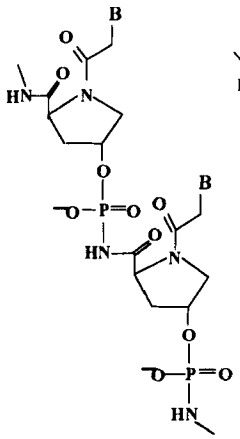
Earlier, the synthesis of oligonucleotide analogues derived from serinol[1,2] or from 4-hydroxy-N-acetylprolinol[3] with phosphodiester bonds between monomers was described, and their properties as potential antisense and antigene reagents were examined. In this communication, we report the synthesis of a set of nucleic acid analogues on the base of L-serine (1, 2) and trans-4-hydroxy-L-proline (3,4) Procedures to obtain novel building blocks from methyl esters of amino acids (5 a,b) and thymine via carboxylic derivative (6) to give either phosphoramidites (7a,b) or phosphonate monomers (8a,b) were developed (Scheme 1)[4]. The homo-thymine oligomers (1) and (3) were synthesized by solid phase technique using monomers of type (6) and protocols published earlier for the synthesis of oligonucleotides containing N-acylphosphoramidate internucleotide linkages[5]. Whereas analogues (2) and (4) were obtained



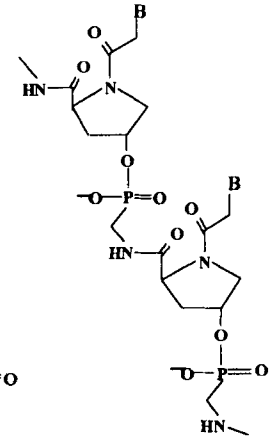
(1)



(2)

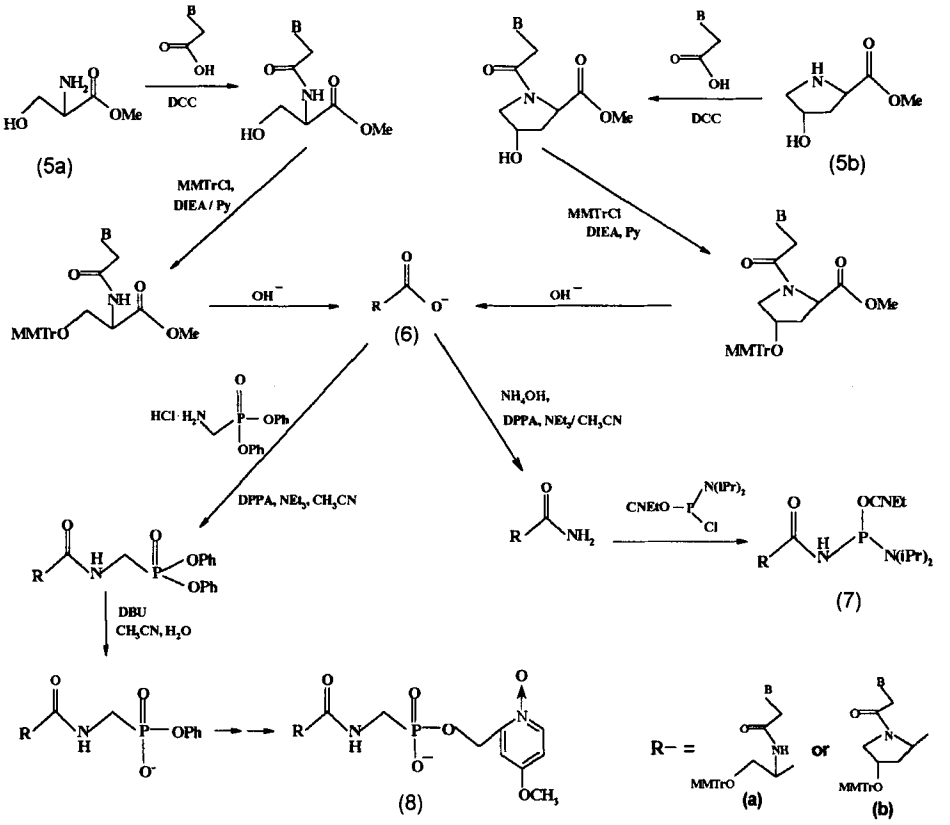


(3)



(4)

SCHEME 1



according the protocols developed by us for the synthesis of oligonucleotide analogues with carboxamidomethyl phosphonate internucleoside linkages[6]. After the purification by anion-exchange chromatografy, the binding behaviour of the oligomers (1-4) to natural DNA and RNA strands were examined. It was found that in contrast to the carboxamidomethyl phosphonate oligonucleotide analogues[6] and acyclic analogues on the base of 1-phenylserinol[2], these oligomers were not able to form stable complexes with complementary DNA and RNA strands under physiological conditions, that may be the disadvantage of their use as antisense compounds.

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