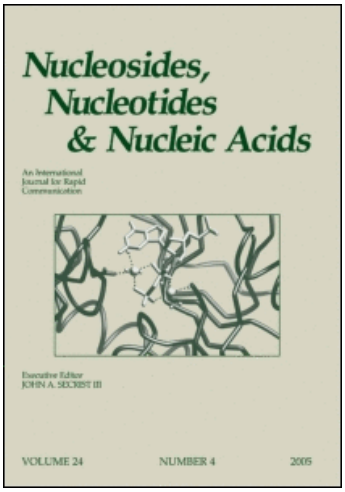

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Convenient Solid-Phase Method of Introduction of Sulfhydryl Groups into Oligodeoxyribonucleotides via 2'-O-Carbamate Linkage

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Convenient Solid-Phase Method of Introduction of Sulfhydryl Groups into Oligodeoxyribonucleotides via 2′-O-Carbamate Linkage

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A simple and convenient method for the synthesis of oligodeoxyribonucleotides (ODNs) carrying a linker with a terminal sulfhydryl group at the 2′-position of uridine residue has been developed.

First the synthesis of 2′-O-levulinyl protected uridine phosphoramidite (1) was accomplished. The synthesis contained 5 steps and included temporary blocking of 5′- and 3′-hydroxyl groups by tetra(isopropyldisiloxane)-1,3-diyl (Markiewicz) protective group, treatment by levulinyl anhydride, cleavage of the Markiewicz group, tritylation and phosphitylation.

After synthesis the ODNs immobilized on CPG, contained the uridine unit with 2′-hydroxyl group protected by levulinyl group at the chosen position of a strand. The 2′-hydroxyl group was selectively deblocked by hydrazine hydrate. Our method consists in the addition of diamines of different length to the functionalized 2′-hydroxyl group of uridine residue which was preliminarily included into ODN structure. For conjugation with diamines the treatment by one of bifunctional reagents

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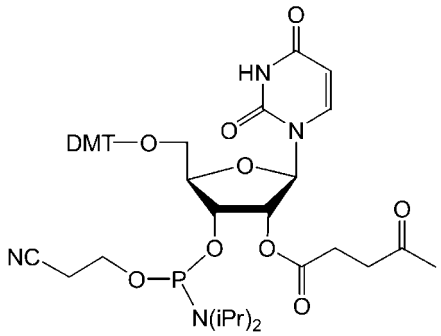


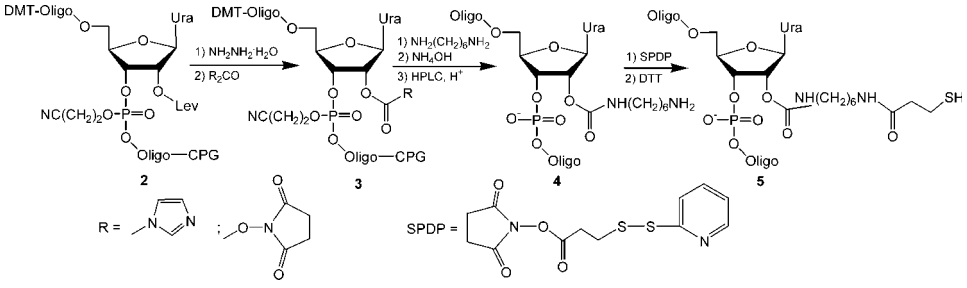
1

(N,N′-carbonyldiimidazole or N,N′-disuccinimidylcarbonate) was used. Both reagents showed a high efficiency in reaction with 2′-OH function and in following reaction with 1,6-hexamethylendiamine.

After cleavage from CPG and deprotection, the post-synthetical treatment of ODNs containing primary aliphatic amino groups was accomplished by the heterobifunctional linker – precursor (succinimidyl-3-(2-pyridyldithio)-propionate, SPDP) bearing both, the sulfhydryl group blocked by 2-pyridylthio protective group and the succinimidyl group reactive toward the amino groups. The thiol function can be selectively deprotected with dithiothreitol.

This approach allows creating ODNs carrying the sulfhydryl group into any desired position of a strand without any changes of standard protocol of ODN synthesis and purification procedure. A number of thiol containing ODNs of different length and sequence was obtained; also multiple insertions of sulfhydryl groups into single ODN strand were possible.

The use of the 2′-position as a modification point gives the possibility to keep hydrogen bonding and stacking abilities of modified nucleotide residues upon duplex formation and to avoid this way serious disturbance of double helix structure, thus preventing the substantial decrease of DNA duplex thermal stability.



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ODNs synthesized can be readily immobilized on gold surfaces and particles; they can be used to obtain conjugates with sulfur containing peptides and proteins. In our opinion, thiol containing ODNs obtained according to method proposed are especially suitable for a synthesis of DNA duplexes with covalently cross-linked strands. This is currently under investigation.

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