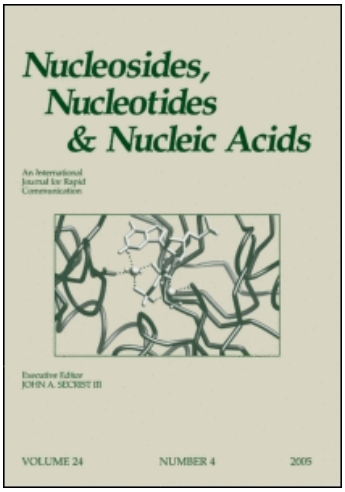

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Sugar Modified Oligonucleotides

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SUGAR MODIFIED OLIGONUCLEOTIDES

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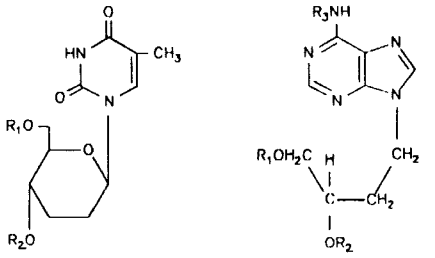
Abstract. The synthesis and enzymatic stability of oligonucleotides with 1-(2,3-dideoxy-β-D-erythro-hexopyranosyl)thymine and (S)-9-(3,4-dihydroxybutyl)adenine as monomeric units are described.

In view of the recent interest in antisense oligonucleotides as antiviral or antitumor agents, we became interested in the synthesis of nuclease-resistant oligonucleotides. Because modifications of the phosphate moiety have been the subject of intensive research (e.g. the synthesis of phosphorothioates, phosphorodithioates and methylphosphonates), we concentrated our efforts on sugar-modified oligonucleotides. We describe here the synthesis and enzymatic stability of oligonucleotides containing 1-(2,3-dideoxy-β-D-erythro-hexopyranosyl)thymine **1** and (S)-9-(3,4-dihydroxybutyl)adenine **6** as monomers.

The condensation of 3,4,6-tri-O-acetyl-D-glucal and bistrimethylsilylthymine in the presence of trimethylsilyl trifluoromethanesulfonate yielded 1-(4,6-di-O-acetyl-2,3-dideoxy-β-D-erythro-hex-2-enopyranosyl)thymine. This gave compound **1** following hydrogenation and deacetylation. The synthesis of the acyclic monomer started from (S)-1,2-O-isopropylidene-1,2,4-butanetriol. After mesylation we obtained (S)-4-O-methanesulfonyl-1,2-O-isopropylidene-1,2,4-butanetriol. The reaction of this product with adenine in the presence of sodium hydride afforded (S)-9-(3,4-O-isopropylidene-3,4-dihydroxybutyl)adenine. Subsequent protection of the exocyclic aminofunction of adenine with a benzoylgroup followed by acidic hydrolysis yielded compound **7**.

The primary hydroxyl group of both **1** and **7** was protected with a monomethoxytrityl group to afford **2** and **8**. The secondary hydroxyl group of **2** and **8** was functionalised to yield the phosphoramidite **9** and the H-

phosphonates **3** and **10**. These were used as building blocks to synthesize several dimers using the phosphoramidite or the H-phosphonate approach. The following dimers were synthesized: T^*pT^*; T^*pT; TpT^*; A^*pA^*; A^*pA; ApA^* [T^* = **1**, A^* = **6**, T = thymidine, A = 2'-deoxyadenosine]. Compared with the dimers TpT and ApA, all dimer analogues have an improved stability against the hydrolytic activity of nuclease S_1, snake venom phosphodiesterase and bovine spleen phosphodiesterase. For the synthesis of longer oligonucleotides we made use of the analogs **4** and **11** functionalized with a dimethoxytrityl protecting group. We also prepared **5** and **12** which were linked to a LCAA-CPG support. Synthesis was done on an Applied Biosystems 381A model using the H-phosphonate approach. The stepwise coupling yields were around 95% for the unmodified nucleotides and around 90% for the modified nucleotides. Following oligonucleotides were prepared: $T^*T_{11}T^*$, $T^*T^*T_9T^*T^*$, $T^*T_5T^*T_5T^*$, $T_6T^*T_6$, T^*_{13} and the adenosine oligomers $A^*A_{11}A^*$, $A^*A^*A_9A^*A^*$, $A^*A_5A^*A_5A^*$, $A_6A^*A_6$, A^*_{13}. Determination of thermal stabilities of these oligomers with the natural A_{13} and T_{13} are underway.



1 $R_1 = R_2 = H$
2 R_1 = MMTr, $R_2 = H$
3 R_1 = MMTr, R_2 = H-phosphonate Et_3NH^+ salt
4 R_1 = DMTr, R_2 = H-phosphonate Et_3NH^+ salt
5 R_1 = DMTr, R_2 = $-CO-CH_2-CH_2-COOH$

6 $R_1 = R_2 = R_3 = H$
7 $R_1 = R_2 = H$, R_3 = formyl
8 R_1 = MMTr, $R_2 = H$, R_3 = benzoyl
9 R_1 = MMTr, R_2 = $-P(N^iPr_2)-OCH_2CH_2CN$, R_3 = benzoyl
10 R_1 = MMTr, R_2 = H-phosphonate Et_3NH^+ salt, R_3 = benzoyl
11 R_1 = DMTr, R_2 = H-phosphonate Et_3NH^+ salt, R_3 = benzoyl
12 R_1 = DMTr, R_2 = $-CO-CH_2CH_2COOH$, R_3 = benzoyl