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SUGAR MODIFIED OLIGONUCLEOTIDES

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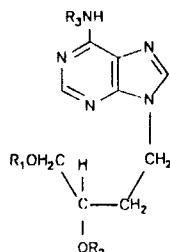
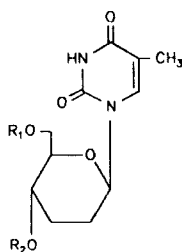
Abstract. The synthesis and enzymatic stability of oligonucleotides with 1-(2,3-dideoxy- β -D-erythro-hexopyranosyl)thymine and (S)-9-(3,4-dihydroxybutyl)adenine as monomeric units are described.

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 benzoyl group 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 $R_1 = \text{MMTr}, R_2 = H$
- 3 $R_1 = \text{MMTr}, R_2 = \text{P}(=\text{O})(\text{O}^-\text{Et}_3\text{NH}^+)(\text{H})$
- 4 $R_1 = \text{DMTr}, R_2 = \text{P}(=\text{O})(\text{O}^-\text{Et}_3\text{NH}^+)(\text{H})$
- 5 $R_1 = \text{DMTr}, R_2 = \text{C}(\text{H})(\text{O})\text{CH}_2\text{CH}_2\text{COOH}$

- 6 $R_1 = R_2 = R_3 = H$
- 7 $R_1 = R_2 = H, R_3 = \text{C}(=\text{O})\text{NH}_2$
- 8 $R_1 = \text{MMTr}, R_2 = H, R_3 = \text{C}(=\text{O})\text{C}_6\text{H}_5$
- 9 $R_1 = \text{MMTr}, R_2 = \text{P}(=\text{O})(\text{O}^-\text{Et}_3\text{NH}^+)(\text{H})$, $R_3 = \text{C}(=\text{O})\text{C}_6\text{H}_5$
- 10 $R_1 = \text{MMTr}, R_2 = \text{P}(=\text{O})(\text{O}^-\text{Et}_3\text{NH}^+)(\text{H})$, $R_3 = \text{C}(=\text{O})\text{C}_6\text{H}_5$
- 11 $R_1 = \text{DMTr}, R_2 = \text{P}(=\text{O})(\text{O}^-\text{Et}_3\text{NH}^+)(\text{H})$, $R_3 = \text{C}(=\text{O})\text{C}_6\text{H}_5$
- 12 $R_1 = \text{DMTr}, R_2 = \text{C}(\text{H})(\text{O})\text{CH}_2\text{CH}_2\text{COOH}, R_3 = \text{C}(=\text{O})\text{C}_6\text{H}_5$