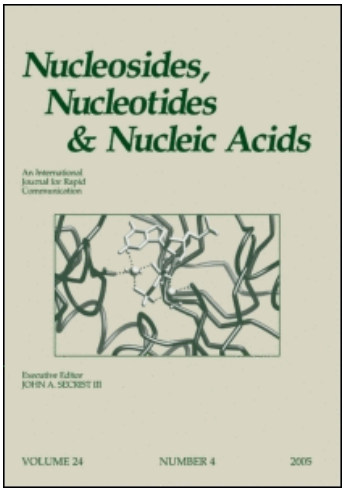

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SYNTHESIS OF OLIGODEOXYNUCLEOTIDES CONTAINING 4'-*C*-AMINOALKYLTHYMIDINES AND THEIR THERMAL STABILITY AND NUCLEASE-RESISTANCE PROPERTIES

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ABSTRACT: To find the nuclease-resistant oligodeoxynucleotides (ODNs) with natural phosphodiester linkages, we designed and synthesized ODNs containing 4'-*C*-aminoalkylthymidines (**1**-**4**). We found that the ODNs containing **1**, **2**, **3** or **4** were more resistant to nucleolytic hydrolysis by both snake venom phosphodiesterase (a 3'-exonuclease) and DNase I (an endonuclease) than unmodified ODNs.

To construct the nuclease-resistant oligodeoxynucleotides (ODNs) with natural phosphodiester linkages, we designed and synthesized ODNs containing 4'-*C*-aminoalkylthymidines (**1**-**4**) (FIG. 1). 4'-*C*-(2-Hydroxyethyl)thymidine, which is a precursor for the 4'α-*C*-(2-aminoethyl)thymidine (**2**) and 4'α-*C*-[2-[[*N*-(2-aminoethyl)-carbamoyl]oxy]ethyl]thymidine (**4**), was synthesized using a newly developed intramolecular radical cyclization reaction at the 4'-position of thymidine.[1,2,3] The 4'-phenylselenothymidine derivative **5**, which was prepared starting from thymidine, was converted to 3'-*O*-dimethylvinylsilyl thymidine derivative **8** (FIG. 2). The radical reaction was performed with Bu_3SnH using AIBN as a radical initiator, and the products were isolated after Tamao oxidation. When a solution of Bu_3SnH and AIBN in benzene was added slowly to a solution of **8** in benzene (0.01 M) at 80 °C, the desired 4'α-*C*-(2-hydroxyethyl)thymidine derivative **10** which was derived from a 5-*exo*-cyclized product **9**, was isolated in 87% yield. 4'-*C*-(3-Hydroxypropyl)thymidine (**11**) was also synthesized using the same intramolecular radical cyclization reaction with an allyldimethylsilyl group as a radical acceptor. Then, these 4'α-*C*-hydroxyalkylthymidines **10** and **11** were converted to the 4'α-*C*-aminoalkylthymidines **2**, **3**, and **4**. The nucleoside **1** was synthesized according to the method reported by Wang and Seifert.[4] The nucleosides **1**, **2**, **3** and **4** were incorporated into octadecamer. First, thermal stability of duplexes containing **1**, **2**, **3** and **4** were studied by thermal denaturation. It was found that

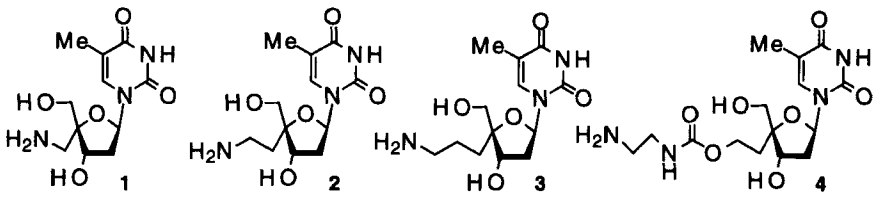

FIG. 1

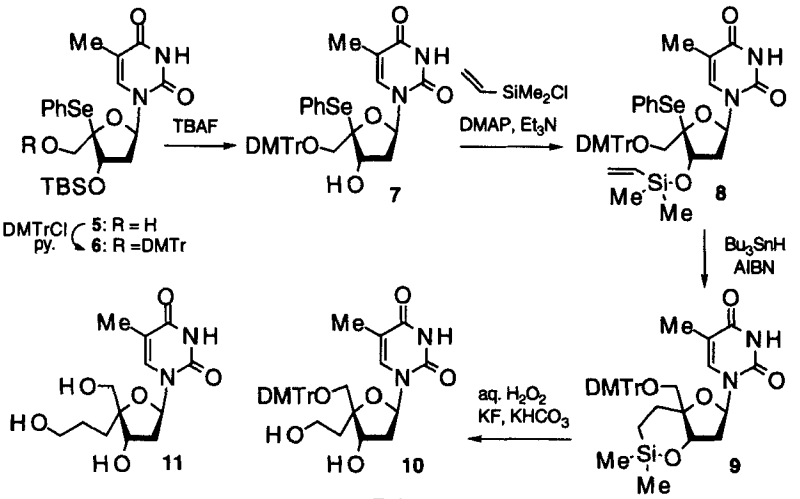

FIG. 2

ODNs containing these nucleosides stabilized the ODN-DNA duplexes and only slightly destabilized the ODN-RNA duplexes. However, these nucleosides did not largely destabilize ODN-RNA duplexes even when the numbers of the nucleoside analogs were increased. Next, the nuclease-resistant properties of ODNs containing **1**, **2**, **3** and **4** were examined. The ODNs labeld at the 5'-end of them with ^{32}P were incubated with an appropriate nuclease and the reaction was analyzed by polyacrylamide gel electrophoresis. We found that ODNs containing **1**, **2**, **3** or **4** were more resistant to nucleolytic hydrolysis by both snake venom phosphodiesterase (a 3'-exonuclease) and DNase I (an endonuclease) than unmodified ODNs. The half-lives of the ODNs containing five molecules of **1**, **2**, **3** or **4** against DNase I were 27, 29, 28, and 13 h, respectively, while that of the unmodified ODN was 22 min.

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