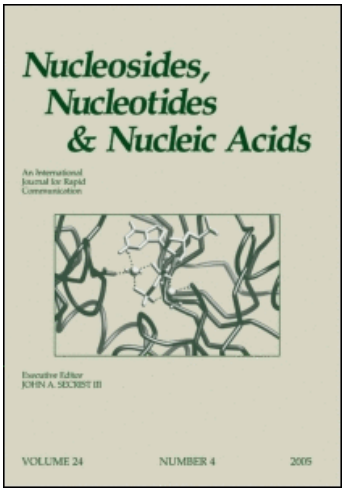

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α-Hydroxybenzylphosphonate Modified Oligonucleotides: Synthesis, Properties, and a Novel Route via Monomer Building Blocks

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α-Hydroxybenzylphosphonate Modified Oligonucleotides: Synthesis, Properties, and a Novel Route via Monomer Building Blocks

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ABSTRACT

In general, α-hydroxybenzylphosphonate modified 2′-deoxyadenosine-thymidine dimer building blocks **1**, **2** are utilized for the incorporation into α-hydroxybenzylphosphonate pro-oligonucleotides. For a universal application of our pro-oligonucleotide concept on biologically relevant oligonucleotides a route for the synthesis of modified monomer building blocks **3** was developed and is presented herein.

Key Words: Antisense pro-oligonucleotides; Hydroxybenzylphosphonate modification; Building blocks; Phosphinamidites.

In previous studies, we presented that $(T)_{15}$ oligonucleotides, containing the α-hydroxybenzylphosphonate modification showed significant enhancement in the stability towards 3′- and 5′-exonucleases (SVP and CSP) compared to the unmodified

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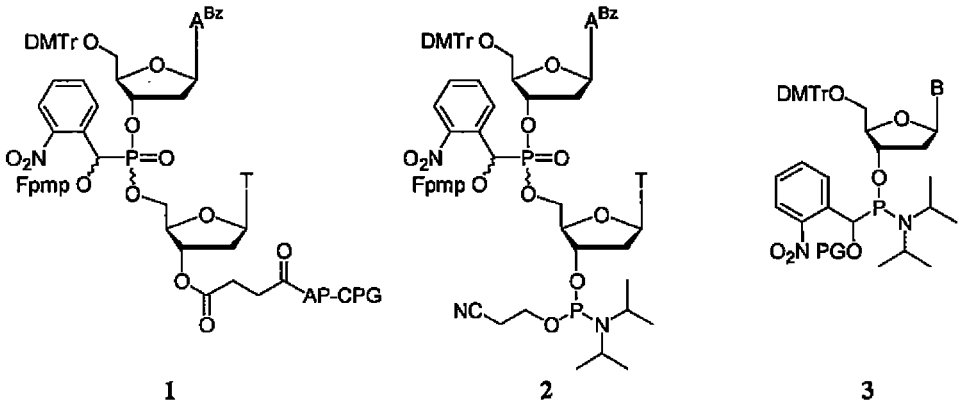

Figure 1. Structures of dimer building blocks **1** and **2** and the monomer target structure **3**.

oligonucleotide. Also, the observed T_m-values of the hybridized DNA and RNA point to a possible application as antisense oligonucleotides.[1,2]

We synthesized dimer building blocks **1** and **2** (Fig. 1) for the incorporation into an anti h-*ras* sequence (5′-TATTCCGTCAT-3′). With this concept of dimer building blocks it is possible to determine the absolute configuration at the phosphorus center

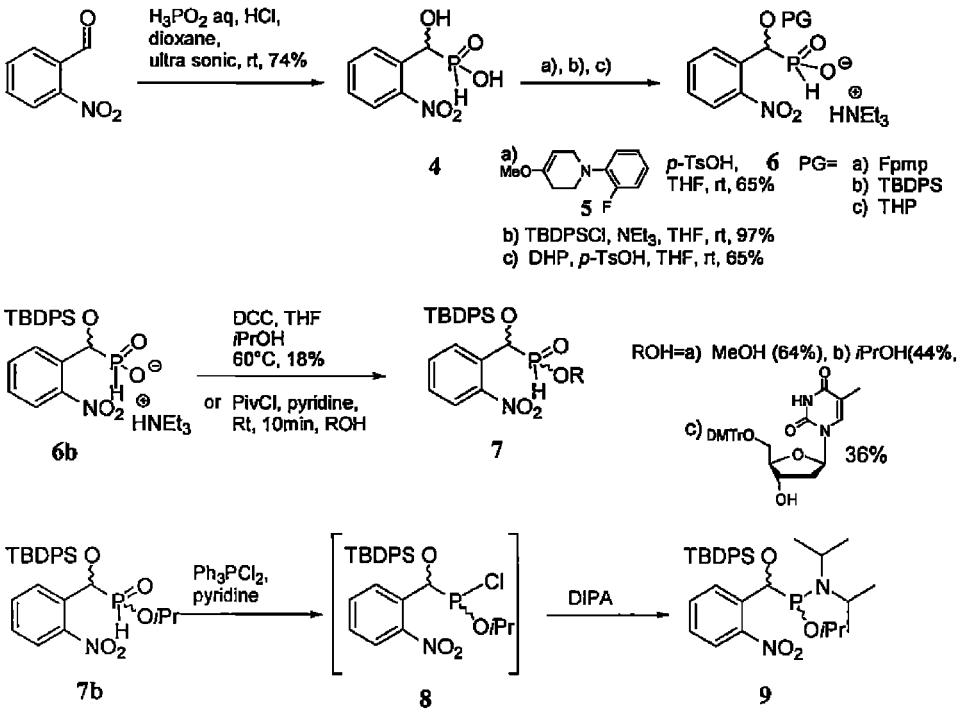

Figure 2. Reaction sequence for the synthesis of monomer building blocks.

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of the resulting oligonucleotides and to study the possible effects on the activity as antisense pro-oligonucleotides.

For a wide application as a potential antisense pro-oligonucleotide system, it is necessary to find a synthetic way to prepare monomer building blocks **3**, which should be suitable for solid phase synthesis. For the synthesis of α-hydroxybenzylphosphinamidites **3** (Fig. 1), the α-hydroxy-(2-nitrobenzyl)-phosphinic acid **4** was synthesized by an acid catalyzed nucleophilic addition of hypophosphinic acid to 2-nitrobenzaldehyde. The hydroxy group was protected, e.g., by TBDPSCl, DHP or enolether **5** (Fpmp precursor) resulting the phosphinic acids **6a–c**. Esterification of the protected phosphinic acid **6b** was achieved using DCC as coupling agent or by pivaloyl chloride activation, yielding the phosphinic acid esters **7a–c**. Chlorination of the protected phosphinic ester **7b** to the chlorophosphine **8** and following transformation with di*iso*propylamine led to the protected (α-hydroxy-2-nitrobenzyl)-(*iso*propyloxy)-phosphinamidite **9** (Fig. 2).

We developed a route to the novel α-hydroxybenzylphosphinamidites. With this method it should be possible to synthesize α-hydroxybenzyl-nucleosyl-phosphinamidites **3** and in further work the synthesis of these modified monomer building blocks as well as the synthesis of modified oligonucleotides will be presented.

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