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Andreas Hohlfeld^a; Chris Meier^a

^a Institute of Organic Chemistry, University of Hamburg, Hamburg, Germany

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

Andreas Hohlfeld and Chris Meier*

Institute of Organic Chemistry, University of Hamburg,
Hamburg, Germany

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

*Correspondence: Chris Meier, Institute of Organic Chemistry, University of Hamburg, Martin-Luther-King-Platz 6, D-20146 Hamburg, Germany; Fax: +49 404 2838 2495; E-mail: chris.meier@chemie.uni-hamburg.de.



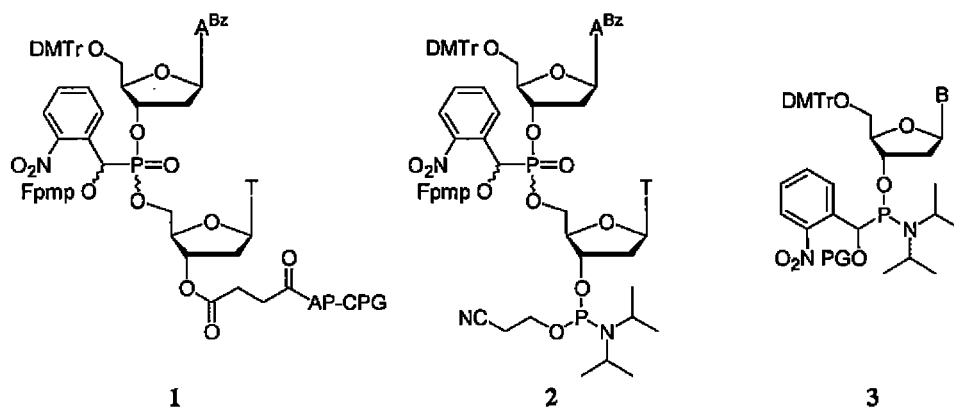


Figure 1. Structures of dimer building blocks **1** and **2** and the monomer target structure **3**.

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

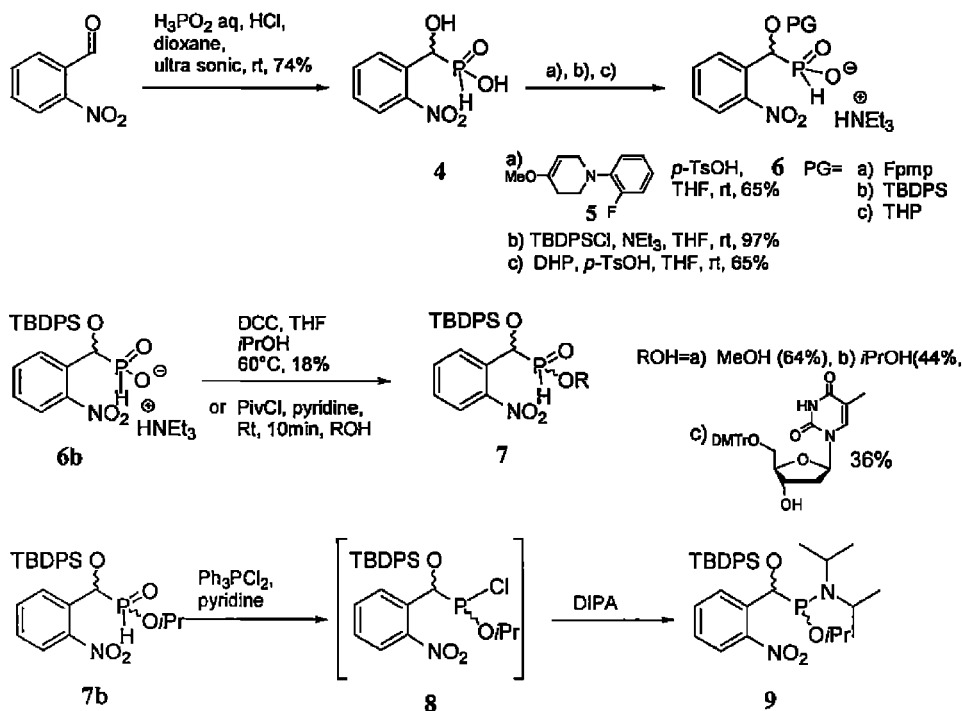


Figure 2. Reaction sequence for the synthesis of monomer building blocks.

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** (Fmp 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 diisopropylamine led to the protected (α -hydroxy-2-nitrobenzyl)-(isopropoxy)-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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