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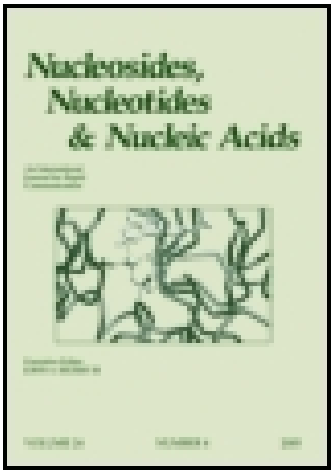

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Synthesis of Protected 3′,5′-Di-2′-Deoxythymidine-(α-hydroxy-2-nitrobenzyl)-phosphonate Diesters as Dimer Building Blocks for Oligonucleotides

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NUCLEOSIDES & NUCLEOTIDES, 14(3-5), 803-804 (1995)

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SYNTHESIS OF PROTECTED 3',5'-DI-2'-DEOXYTHYMIDINE-(α-HYDROXY-2-NITROBENZYL)-PHOSPHONATE DIESTERS AS DIMER BUILDING BLOCKS FOR OLIGONUCLEOTIDES

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ABSTRACT: The synthesis of 3'-succinyl-CPG bound 3',5'-di-2'-deoxythymidyl-(α-hydroxy-2-nitrobenzyl)-phosphonate diester **1** and the 3'-phosphoamidite derivative **2** is descibed. The hydroxyl-groups of the backbone modification were protected with trialkylsilyl groups: TES and TBS. Compounds **1, 2** are suitable blocks for oligonucleotide synthesis.

DNA- or RNA-antisense oligonucleotides are an important possibility to treat viral diseases. The mode of action is the hybridization of an antisense-oligonucleotide with a complementary sequence of the sense-RNA target strand [1]. In order to stabilize an antisense oligonucleotide against degradation by nucleases different chemically modified oligonucleotides have been introduced: methylphosphonates, phosphorothioates, phosphorodithioates and phosphotriesters as backbone modifications were synthesized [2]. All these modifications are more lipophilic than the natural phosphodiester oligonucleotide and much more stable against exonucleases. We want to introduce now our α-hydroxybenzyl-phosphonate chemistry into oligonucleotides as new a backbone modification [3].

We present here the synthesis of the dimer building blocks **1, 2** containing our new backbone modification suitable for oligonucleotide synthesis. We synthesized different derivatives of the dimer building block: the 3'-phosphoamidite **1** as well as the 3'-CPG-succinate **2**. These dimers allow the incorporation of the new backbone modification into an oligonucleotide following the phosphoamidite chemistry at different positions: at the 3'-, at the 5'-terminus as well as mixed modified oligonucleotides containing internal and terminal modifications. The synthesis of **1, 2** is summarized in Scheme 1. The synthesis uses H-phosphonate chemistry starting from thymidyl-3'-H-phosphonate **3** which was coupled with

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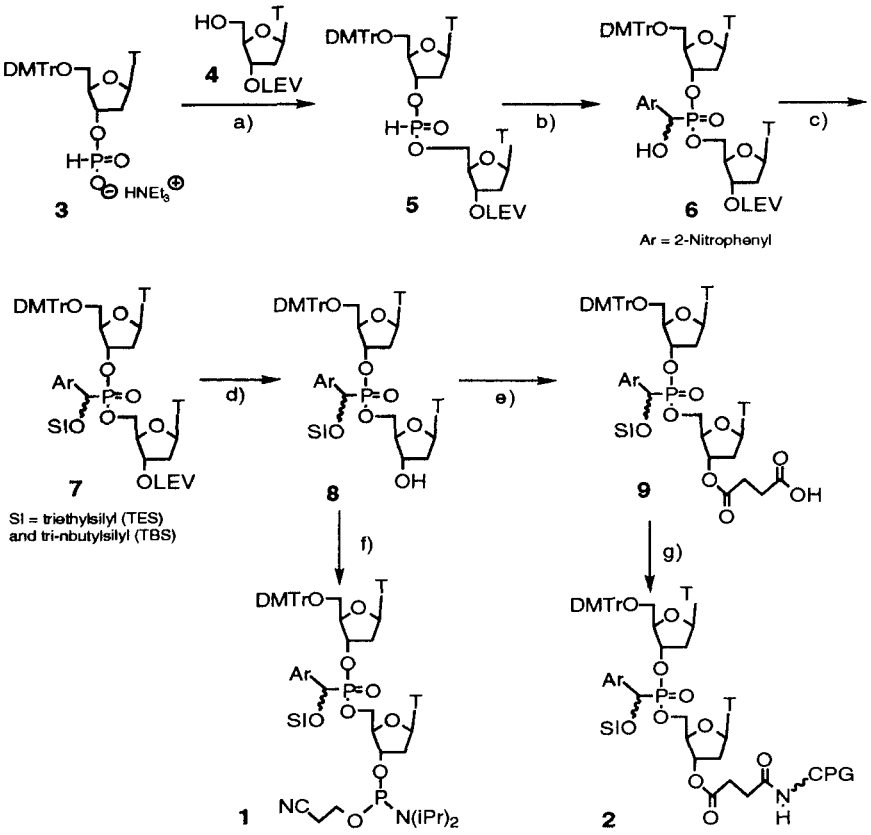

Conditions: a) Pivaloylchloride, pyridine, rt, 5 min.[4]; b) 2-nitrobenzaldehyde, NEt_3 (cat.), CH_2Cl_2, rt, 5h[6]; c) trialkylsilylchloride, pyridine, rt, 8h; d) hydrazinehydrate, pyridine/HOAc 3:2, rt, 3 min.; e) succinic acid anhydride, pyridine, DMAP, rt, 3 days; f) β-cyanoethyl-diisopropyaminochlorophosphine, CH_3CN, 0°C, 1h; g) TBTU, DMF, N-ethylmorpholine, CPG-support, rt, 16h.

SCHEME 1: Synthesis of the two dimer building blocks for oligonucleotide synthesis

3'-levulinylthymidine **4** to yield the H-phosphonate diester **5** [4]. **5** was reacted with 2-nitrobenzaldehyde to give the α-hydroxy-2-nitrobenzylphosphonateester **6** [3,5]. The hydroxyl group of **6** was protected using the TES or TBS group to give **7**. Compound **8** is the key intermediate for **1** and **2**, which were synthesized using standard methods.

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