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Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

Dimeric Oligonucleotide Synthons Containing 2-Deoxy-3-*O*-Phosphonomethyl- α -D-erythro-pentofuranosyl Nucleosides

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To cite this Article Mikhailopulo, Igor A. , Kulak, Tamara I. , Tkachenko, Olga V. , Sentyureva, Svetlana L. and Seela, Frank(1999) 'Dimeric Oligonucleotide Synthons Containing 2-Deoxy-3-*O*-Phosphonomethyl- α -D-erythro-pentofuranosyl Nucleosides', Nucleosides, Nucleotides and Nucleic Acids, 18: 6, 1253 — 1254

To link to this Article: DOI: 10.1080/07328319908044682

URL: <http://dx.doi.org/10.1080/07328319908044682>

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DIMERIC OLIGONUCLEOTIDE SYNTHONS CONTAINING 2-DEOXY-3-*O*-PHOSPHONOMETHYL- α -D-*erythro*-PENTOFURANOSYL NUCLEOSIDES

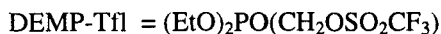
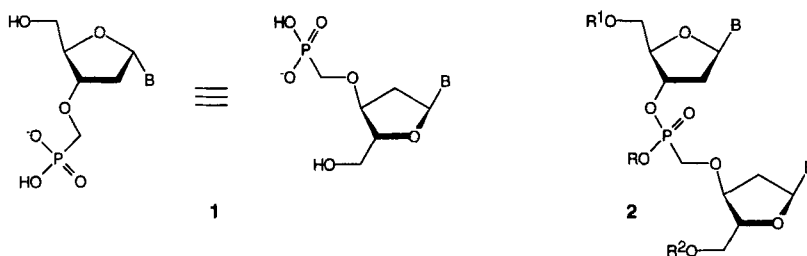
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ABSTRACT: The synthesis of 2'-deoxy-3'-*O*-phosphonomethyl- α -D-*erythro*-pentofuranosyl-thymine and -adenine (**1**, B is Thy or Ade) is described. Dimeric oligonucleotide synthons such as **2** containing isosteric phosphonate internucleoside linkage were prepared.

This communication describes the preparation of 3'-*O*-methanephosphonic acids **1** (B is Thy or Ade) and their use for the assembly of dimeric building blocks **2** suitable for the automated oligonucleotide synthesis.



The key step in the synthesis of **1** is the reaction of 5'-*O*-monomethoxytrityl-2'-deoxy- α -D-*erythro*-pentofuranosyl-thymine or -N⁶-benzoyladenine with diethyl [(trifluoromethylsulfonyl)oxy]methanephosphonate (DEMP-Tfl)¹ in the presence of

sodium hydride (the ratio of reactants 1.0:1.2:4.0+5.0, mol; THF, 0 °C, 1-2 h) resulting in the formation of the blocked 3'-*O*-phosphonates in *ca.* 60% yield. Treatment of fully blocked 3'-*O*-phosphonates with TMS-Br² in acetonitrile (r. t.), followed by column chromatography on DEAE-cellulose (HCO₃⁻ -form) afforded the 3'-*O*-methanephosphonic acids **1** (B = Thy, 76%; B = Ade, 65%).

In order to synthesize alternating α,β -oligonucleotides, we initiated our studies on preparation of dimeric synthons containing α - and β -nucleoside units bearing the internal 3'-*O*-phosphonomethyl linkage, *e.g.*, dimer **2**. In view of an automated synthesis of oligonucleotides, it was important to choose such a combination of protecting groups that enables an easy and selective deblocking of the 5'-hydroxyl group of the α -D-residue. The presence of two primary 5'-hydroxyl groups in the dimeric synthon like **2** adds complexity to the search for the 5'-blocking group of the α -D-residue that should be selectively removed before further manipulation.

Our initial selection of the protecting groups included the β -cyanoethyl group for the internal 3'-*O*-phosphonomethyl linkage and *t*-butyldimethylsilyl for the 5'-hydroxyl group of the α -D-sugar residue. The 5'-*O*-silylated derivative of phosphonate **1** (B = Thy) was reacted with β -cyanoethanol³ to afford the corresponding phosphonate monoester (45%) that was condensed with 5'-*O*-monomethoxytritylthymidine (TPS-Cl/Me-imidazole/pyridine, 20 °C, 16 h; 64%). After removal of the silyl group,⁴ the dimeric oligonucleotide synthon **2** (R = CNEt, R¹ = mMeOTr, R² = H; 62%) was obtained.

Investigations along the preparation of other dimeric synthons containing 2-deoxy-3-*O*-phosphonomethyl- α -D-*erythro*-pentofuranosyl nucleosides and their application for oligonucleotide synthesis are in progress.

Acknowledgments: Financial support from the Alexander von Humboldt-Foundation (Bonn/Bad-Godesberg, Germany), the Foundation for Advanced Studies (Belarus) and the NATO (HTECH.EV 970235) is gratefully acknowledged.

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