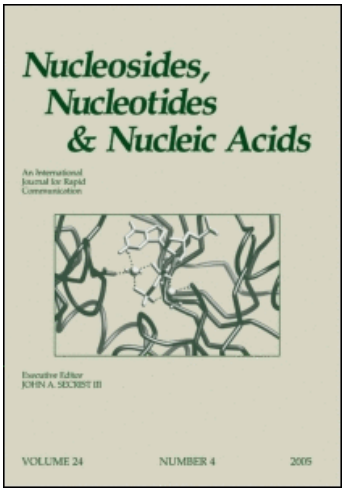

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Dimeric Oligonucleotide Synthons Containing 2-Deoxy-3-*O*-Phosphonomethyl-α-D-*erythro*-pentofuranosyl Nucleosides

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

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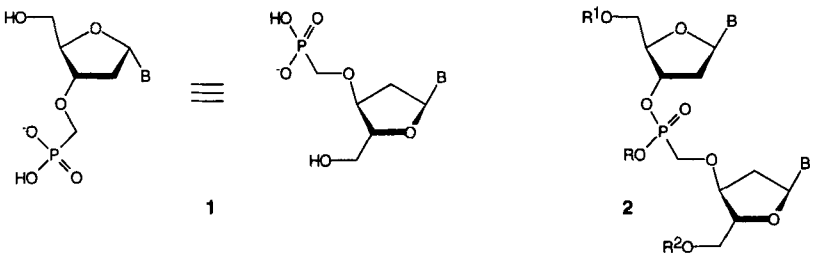
ABSTRACT: The synthesis of 2'-deoxy-3'-*O*-phosphonomethyl-α-D-*erythro*-pentofuranosyl-thymine and -adenine (**1**, B is Thy or Ade) is described. Dimeric oligonucleotide synthons such as **2** containing isosteric phosphonate internucleoside linkage were prepared.

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.



DEMP-Tfl = $(EtO)_2PO(CH_2OSO_2CF_3)$

The key step in the synthesis of **1** is the reaction of 5'-*O*-monomethoxytrtyl-2'-deoxy-α-D-*erythro*-pentofuranosyl-thymine or -N^6-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-Br[2] in acetonitrile (r. t.), followed by column chromatography on DEAE-cellulose (HCO_3^- -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-cyanoethanol[3] 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, R^1 = mMeOTr, R^2 = 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.

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