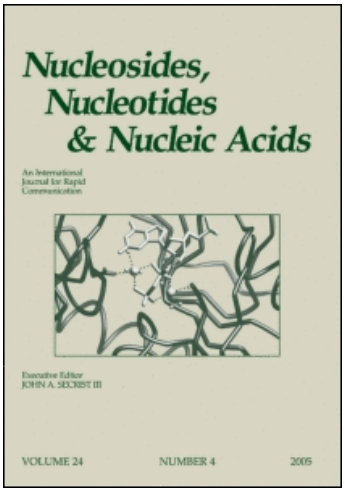

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Synthesis of Oligodeoxynucleoside Phosphorodithioates by a Phosphortriester Method

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SYNTHESIS OF OLIGODEOXYNUCLEOSIDE PHOSPHORODITHIOATES BY A PHOSPHORTRIESTER METHOD

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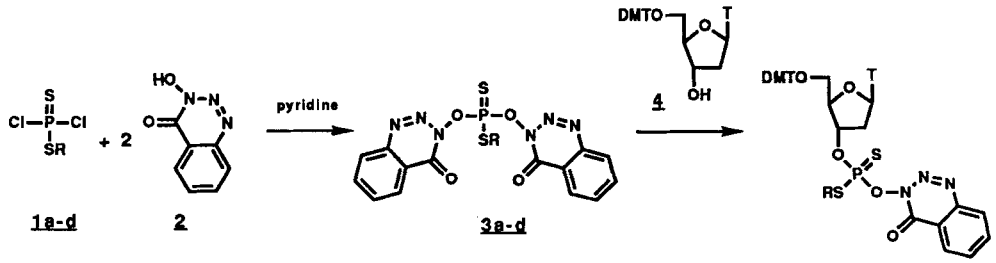
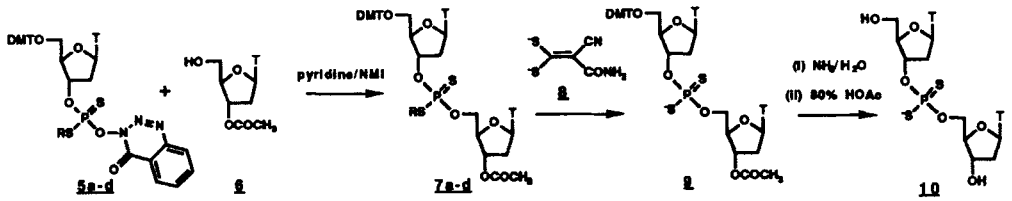
Abstract: A new method for preparation of oligodeoxynucleoside phosphorodithioates using a phosphortriester approach is presented.

Oligonucleoside phosphorodithioates are potential antisense oligonucleotide analogs in which both nonbonding oxygen atoms in the phosphate diester group are substituted by sulphur. Several methods have been developed recently in order to syntesize these interesting analogs[1-13], but only the thioamidite method is currently applicable to solid phase synthesis[9-10]. One serious disadvantage of this method is the susceptibility of the tervalent thiophosphorus compounds to undergo dismutations which leads to impurities, mainly phosphorothioates.

We now present a new approach to the synthesis of oligonucleoside phosphorodithioates, based on van Boom's HOBt method[14], in which the phosphorodithioates **5a-d** are used as the reactive monomers.





The phosphorodithioate monomers **5a-d** were prepared *in situ* from the dithiophosphorodichloridates **1a-d**[13]

To prepare the phosphorodithioate dimers **7a-d**, the solution of **5a-d** was evaporated to a gum, dissolved in anhydrous acetonitrile (5 ml), and a mixture of pyridine/N-methylimidazole (0.15 g, 1.8 mmol / 0.58 g, 7.2 mmol) and **6** (0.71 g, 2.5 mmol) was added. The coupling was complete in 1 h at r.t.

7 was deprotected with an excess of **8** (1.7 M in DMF, ca. 26 C, $t_{1/2}$ ca. 3 min.).Unfortunately, this resulted in cleavage of the dimers **7a-c** (20 %, 35 % and 4 % resp.), but for **7d** only the pure dimer product **9** was detected. The completely deblocked dimer **10** was obtained by standard treatment with conc. aq. ammonia followed by 80 % aq. acetic acid.

5d is promising for a solid support synthesis of oligonucleoside phosphorodithioates that avoids the sulphurization step and the unstable tervalent thiophosphorus reagents used in the thioamidite method. Work is in progress to improve the relative slow coupling rate of **5d**.

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