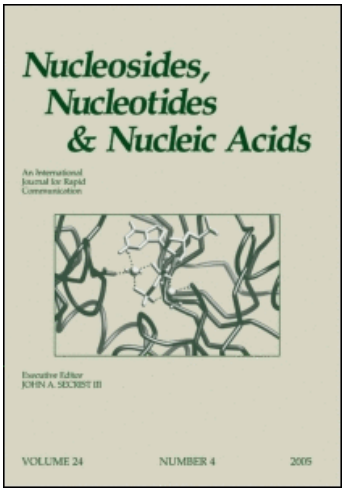

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A simple and efficient synthesis of nucleotides containing 5'-S- or 3'-S-phosphorothioate linkage.

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A simple and efficient synthesis of nucleotides containing 5'-S- or 3'-S-phosphorothioate linkage.

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Abstract: *A new efficient synthesis procedure leading to the nucleotide containing 5'-S or 3'-S-phosphorothioate linkage will be presented. The tittle compounds were prepared in the reaction anhydronucleoside with nucleoside phosphorodithioates. The second way is based on phosphitylation reaction using the nucleosidylphosphorofluoridites.*

Oligonucleosides containing internucleotide modification at phosphorus centre have received considerable attention oving to their applicability for various biochemical purposes and because of their potential use as antiviral drug.[1] The synthesis of nucleoside containing a 3'-S- or 5'-S-phosphorothiolate linkage has been the subject of an extensive development during these last years. These compounds, have been prepared:

a) : *via nucleophilic displacement of 3'-iodo-, 5'-tosyl-, or 5'-bromo-5'-deoxynucleosides by nucleoside 3'-phosphorothioates.*[2]

b) : *via phosphoramidide chemistry.*[3]

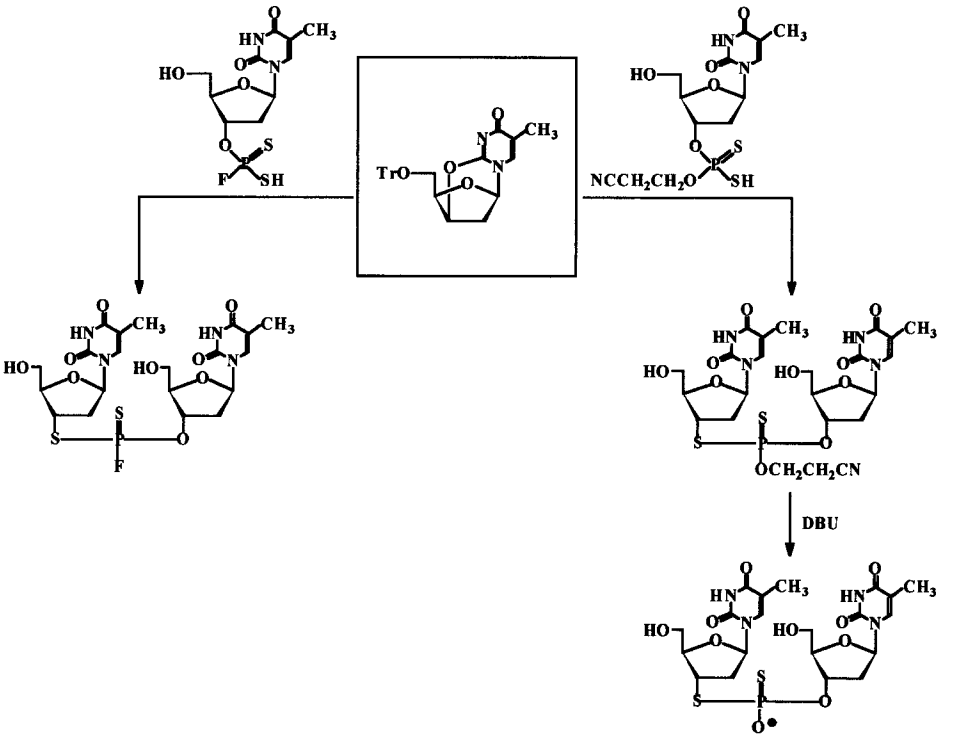
c) : *via Michaelisa-Arbusov reaction between a nucleosidyl 5'-phosphite and a nucleosidyl 3'-S-disulfide.*[4]

In spite of this approaches, formation of phosphorothiolate linkages requires laborious operations and depends on access to 3'- S or 5'- S thionucleosides, 5'- bromonucleoside or nucleosidyl-3'which are not readily available. For this reason we have sought an alternative strategy avoiding 3'- S- or 5'-S- thionucleosides. Our long-standing interest in the chemistry of sugar thiophosphates[5] and modified nucleotides also stimulated this work.[6]

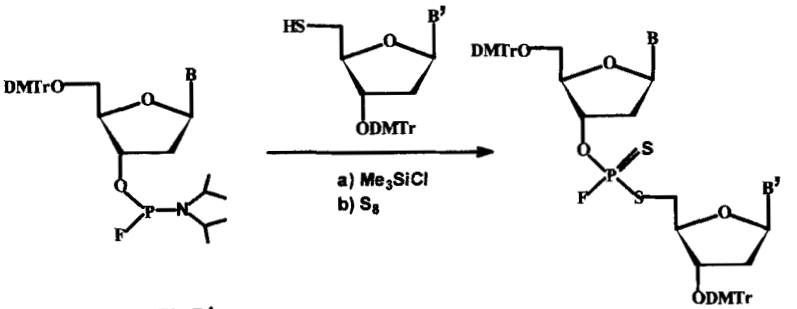
We discovered that 2,3'- anhydrothymidine reacts rapidly with phosphorus dithioacids RR'P(S)SH at ambient temperature in almost quantitative yield, and the ring opening proceeds with

inversion of configuration at the 3'- carbon. Phosphorus dithioacids, including those derived from nucleosides, are readily available.[7] Protonation of the anhydro-ring oxygen and the high nucleophilicity of phosphorus dithioacids make this procedure efficient and mild.

Our methodology is exemplified by reactions of 3'-*O*-trityl-2,5'anhydrothymidine or 5' *O*-trityl-2,3'-anhydrothymidine with *O*-[(5'-*O*-trityl)-thymidine-3'-yl]-*O*-(β-cyanoethyl) phosphorodithioate or phosphorofluoridodithioate. The dithioic acid was prepared in situ by treating its DBU salt with excess of 4-toluenenesulfonic acid monohydrate. Water introduced with 4-toluenesulfonic acid does not interfere with the ring opening reaction but effects the removal of the trityl group. The analogous reaction with the DBU salt of requiries severe conditions.



The dinucleoside (*O* 3' → *S* 5') phosphorofluoridodithioate can be prepared by an independent route from 5'-thio-5'-deoxynucleoside and deoxynucleoside- 3'-*O*-fluorophosphoramidite. The latter is easily accessible in almost quantitative yield from deoxynucleoside -3'-*O*-arylphosphoramidite in the reaction with tetrabutylamonium fluoride.[8]



B= Th, B'= Th
B= Ad(Bz), B'= Th

In conclusion we have reported a highly efficient synthesis of nucleotides containing 5'-S- or 3'-S-phosphorothioate linkage. The latter type of compounds are potentially useful for a 'antisense' approach in constructing antiviral drugs.

Acknowledgment.

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