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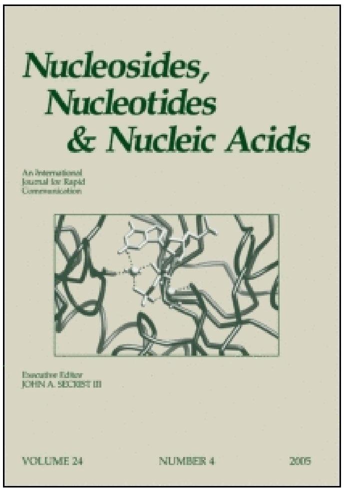

Nucleosides, Nucleotides and Nucleic Acids

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Stereoselective Synthesis of Nucleoside Phosphorofluoridates

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NUCLEOSIDES & NUCLEOTIDES, 10(1-3), 283-286 (1991)

STEREOSELECTIVE SYNTHESIS OF NUCLEOSIDE PHOSPHOROFLUORIDATES

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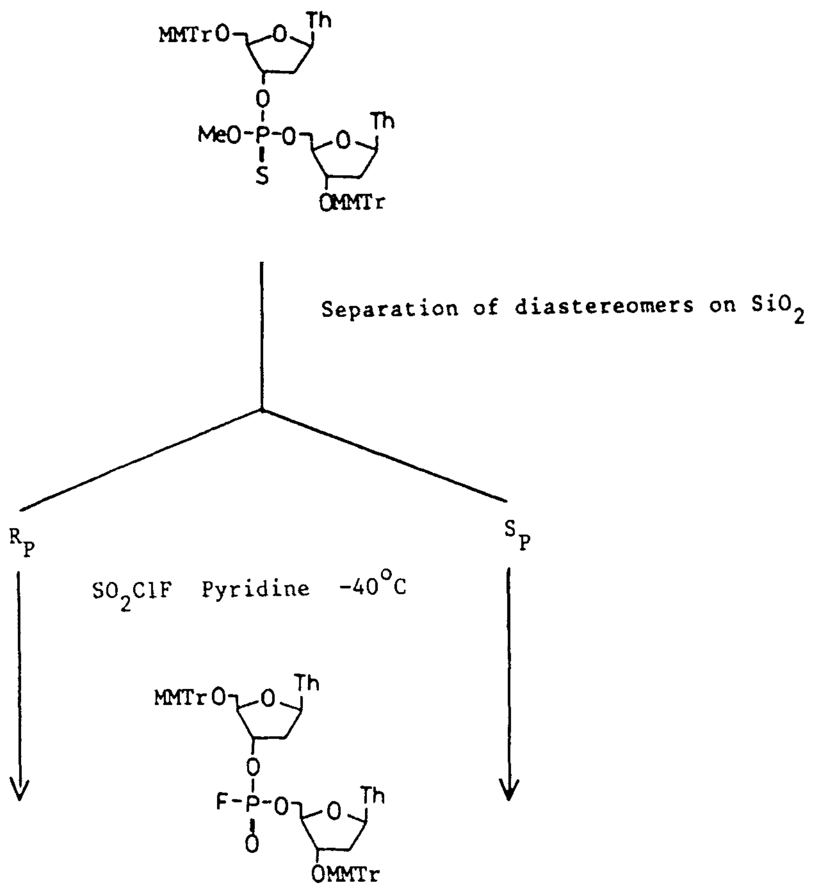
Abstract: The reaction of diastereoizomeric 3'-[5'-O-(monomethoxytrityl)thymidyl]-5'-(3'-O-monomethoxytrityl)thymidine O-methyl phosphorothioate and 3'-[5'-O-(monomethoxytrityl)thymidyl]-5'-(3'-O-monomethoxytrityl)-N^6-benzoyladenosine O-methyl phosphorothioate with sulfuryl-chloride fluoride leads to the corresponding diastereoisomeric phosphorofluoridates in highly stereoselective manner.

Fluoro derivatives of phosphorus containing direct phosphorus-fluorine bond are of great importance in the chemistry of both these elements. Fluoro derivatives of compounds of pentavalent phosphorus can be potent enzyme inhibitors. Some years ago we drew our attention towards nucleoside phosphorofluoridates, wherein the phosphodiester moiety is replaced by the non-ionic fluorophosphoryl group. These compounds provide a new model for testing properties of modified oligonucleotides.

In 1963 Wittman described the synthesis of the nucleoside 5'-phosphorofluoridates by reaction of nucleoside 5'-phosphates and 2,4-dinitrofluorobenzene.[1]

This synthesis of nucleoside 3'- or 5'-phosphorofluoridates was also employed by other authors.[2] However, the reported yields were usually low and the method could not be extended for preparation of the dinucleotides containing phosphorofluoridate grouping.



one diastereomer (100%)

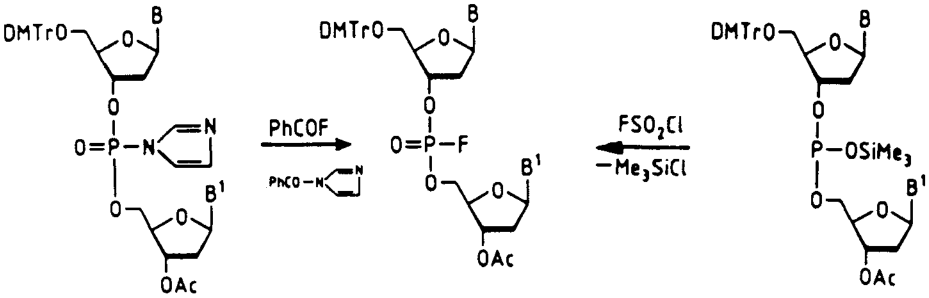
B	$\delta^{31}P$	J_{P-F} Hz
Th	-8.9	975.8
Ad(bz)	-8.5	976.0

two diastereomers

B	$\delta^{31}P$	J_{P-F} Hz	
Th	-8.9; -9.4	975.7; 970.1	1:4
Ad(bz)	-8.4; -8.9	976.0; 980.1	1:3

Fig. 1

In our previous reports we have described two efficient methods leading to nucleoside 3'- and 5'-phosphorofluoridates. The nucleoside phosphoroazolides react with acyl fluorides to give the corresponding phosphorofluoridates in excellent yield.[3] The dinucleoside trimethylsilylphosphite, which are readily available via modified Letsinger-Carruthers reagent or direct silylation of dinucleoside hydrogen phosphonates,[4] react with sulfuryl chloride fluoride SO_2ClF in dry pyridine solution at -30°C. This strongly exothermic reaction leads to the dinucleoside phosphorofluoridates in high yield.[5]



Both methods are not suitable for the stereoselective synthesis of diastereoizomeric nucleoside phosphorofluoridates.

It has been discovered in Łódź Laboratories that sulfuryl chloride fluoride is an excellent fluorinating reagent in organophosphorus chemistry.[6] According to our preliminary observations sulfuryl chloride fluoride does not react with purine and pyrimidine bases under conditions which are used for fluorination at the phosphorus center. Therefore this new fluorinating reagent can be used even without protection of nucleoside base and sugar hydroxyl group.

The phosphorothionates derived from nucleoside are readily available in pure diastereoizomeric forms.[7] We were able to demonstrate that diastereoizomeric dinucleoside O-methylphosphorothionates react with sulfuryl chloride fluoride in highly stereoselective manner.

The reaction of sulfuryl chloride fluoride with the diastereoizomer R_P is stereospecific whereas with the S_P it is highly stereoselective. The phosphorofluoride prepared from the diastereoizomers S_P can be readily separated by chromatography to yield a second pure izomeric phosphorofluoridate. Both diastereoizomers exhibit high degree of optical stability.

Although mechanistic considerations of the reaction leading to the phosphorofluoridates are indicative for the inversion of configuration at the P center, further experimental studies are required.

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