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PHOSPHORAMIDATE ANALOGUES OF DIRIBONUCLEOSIDE MONOPHOSPHATES

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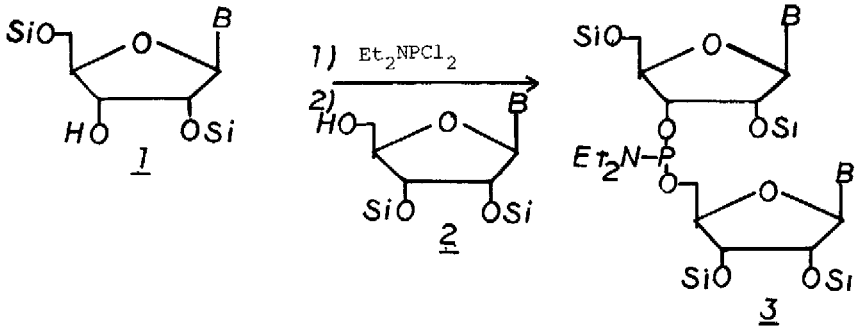
The synthesis of thio, seleno, and imino analogues of diribonucleoside phosphoramidates is described

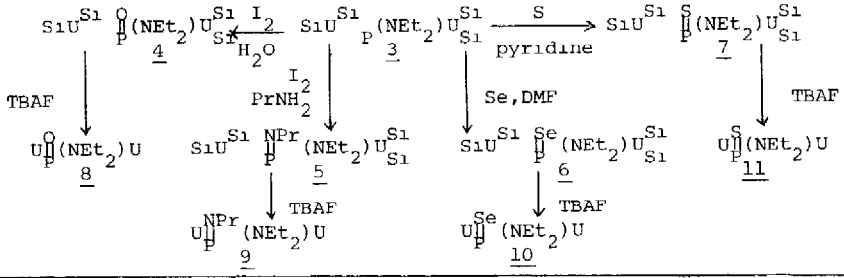
Since the original publication by Letsinger(1) in which he described the use of dichlorophosphites for the rapid synthesis of deoxynucleotides, these reagents have been widely used for the synthesis of oligonucleotides (2-4) In the previous two articles in this issue, we have described the preparation of dinucleoside phosphites and their conversion into several new nucleotide analogues. In this report we wish to describe the use of dichlorophosphoramidites for the synthesis of the phosphoramidite analogues of natural nucleotides and their conversion into several new nucleotide analogues.

The procedure is illustrated by the synthesis of compound 3 A solution of 2',5'-diTBDMS-uridine (1, 236 mg, 0 5 mmole) in THF (0 5 ml) was added dropwise to dichlorodiethylphosphoramidite (Et_2NPCl_2, 82 µl, 1.1 eq) in THF (0 3 ml) at 20°C and after 15 min 2',3'-diTBDMSuridine (2, 189 mg, 0 4 mmole) in THF (0.8 ml) was added. After an additional 60 min, the solvents were removed at reduced pressure and the product 3 (mp 101-106°C, λ_{max}^{EtOH} 262 nm, ^{31}P, -135 8, -134 9) was isolated in 68% yield Compound 3 was stable for at least a week when stored under nitrogen but in the presence of air it is slowly converted to the phosphoramidate 4 (~ 15% after 1 week).

Very few nucleoside phosphoramidates have been reported (5-8) but it has been noted (5) that the choice of protecting group is critical since phosphoramidates have been reported to be unstable to both acid and base conditions (5) during removal of protecting groups The silyl groups are ideal in this respect in that they can be removed with TBAF without cleaving the phosphoramidate linkages.

Compound 3 can readily be converted into the analogues 4-7 For example, after 5 min with iodine-water in THF, 3 is quantitatively converted to 4 while iodine in THF with n-propylamine gives 5 as the only product after 5 min Treatment of 3 with selenium in DMF or sulfur in pyridine for 3 h produces 6 and 7 respectively Compounds 3-7 on treatment with TBAF yield the deprotected compounds 8-11, none of which are degraded by snake venom, spleen, or ribonuclease A enzymes. Compounds 3-7 are all obtained as a mixture of diastereomers, some of which are easily separated on TLC





Compound	R_f^*	^{31}P (rel 85% H_3PO_4)
$SiU^{Si}_{P}(NEt_2)U^{Si}_{Si}$ (3)	0 41	-135 8, -134 9
$SiU^{Si}_{P}(O)(NEt_2)U^{Si}_{Si}$ (4)	0 21, 0 10	-11.4, -9 6
$SiU^{Si}_{P}(NPr)(NEt_2)U^{Si}_{Si}$ (5)	0 07	-8 9, -8 4
$SiU^{Si}_{P}(Se)(NEt_2)U^{Si}_{Si}$ (6)	0.46, 0 38	-72 5, -70 4
$SiU^{Si}_{P}(S)(NEt_2)U^{Si}_{Si}$ (7)	0 43, 0 36	-91.4, -90 5

*Silica Gel TLC, solvent ether hexane (3 1), 2 developments

The compounds reported in this article are all readily prepared and easily isolable and represent several new analogues of nucleotides These compounds are currently undergoing biological testing.

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