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Acylphosphonates. 6.[1] Reaction Mechanism of Zn/Me_3SiCl Mediated Conversion of 2,2,2-Trichloroethoxycarbonylphosphonates to Silyl Phosphites

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Summary: It was elucidated by ^{31}P nmr spectroscopy that the conversion of 2,2,2-trichloroethoxycarbonylphosphonates to dialkyl trimethylsilyl phosphites by treatment with Me_3SiCl-Zn-acetylacetone proceed with retention configuration at phosphorus. In this study, optical active dinucleoside 2,2,2-trichloroethoxycarbonylphosphonates were synthesized and employed as the reaction substrates.

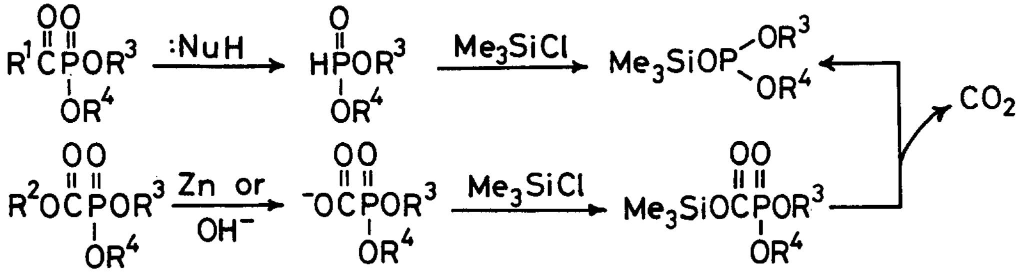
Optical active phosphorus compounds have proved to been available not only for stereoselective transformations of organic compounds but also for elucidation of the mechanism of enzyme reactions.[2,3] Especially, optical active analogs of oligonucleotides having P=S bonds in place of P=O bonds in internucleotidic phosphates have been of central interest in the field to molecular biologists since they served as specific substrates of various enzymes, such as venom phosphodiesterase, that recognized the chiral center of the phosphorus atom.

In our previous papers,[4,5,6] we have reported two methods for the conversion of five-valent dialkyl acylphosphonates to tervalent dialkyl trimethylsilyl phosphites .

One of them involves deacylation of dialkyl acylphosphonates with primary amines followed by silylation. The others involve the use of the ethoxycarbonyl and 2,2,2-trichloroethoxycarbonyl groups as the P-H bond blockers which are removed by treatment with alkali and zinc powder, respectively. In these methods, the resulting carboxylphosphonates were converted to silyl phosphites by the successive silylation (Scheme 1).

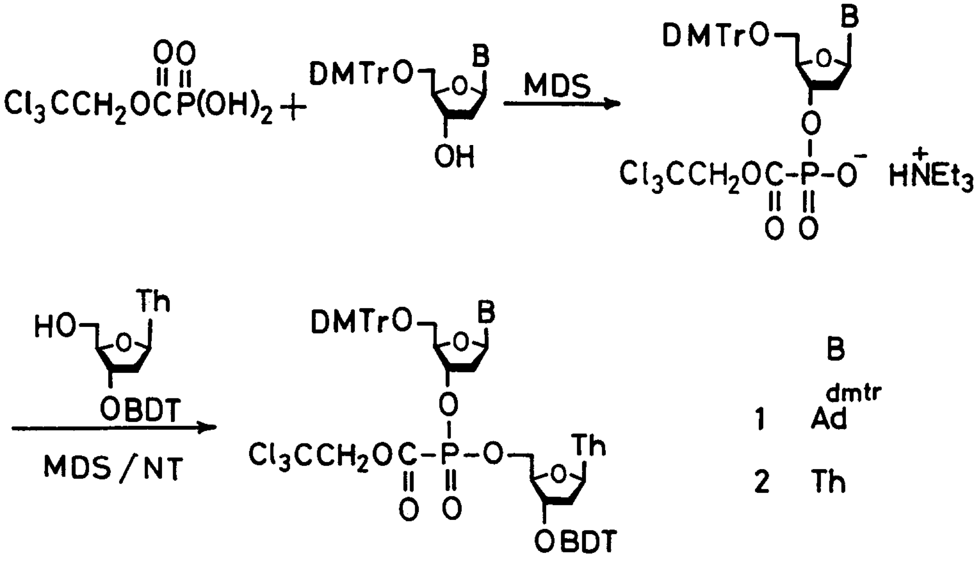
In order to examine stereochemistry of the transformation of acylphosphonates to silylphosphites, we synthesized dinucleoside 2,2,2-trichloroethoxycarbonylphosphonates (1 and 2), protected with the 4,4'-dimethoxytrityl (DMTr) group at the 5'- and N^6-positions and 1,3-benzodithiol-2-yl (BDT)[7] group at the 3'-position, in a method similar to that described in a previous paper (Scheme 2).[4] In each case the diastereomers (1a,b or 2a,b) derived from the chirality of the phosphorus atom were separated by preparative liquid chromatography using Waters Prep System 500 A (Silica gel, EtOAc). The isolated yields of 1a,b and 2a,b were 15-18%.[8] The ratios of diastereomers were nearly 1:1.

Scheme 1



Sulfurization of optical active trialkyl phospites with elemental sulfur is well known to proceed with retention.[9] The initial products obtained by treatment of 1 and 2 with Zn-Me$_3$SiCl-acetylacetone (AcAc)[5,10] were further in situ converted to the phosphorothioates (3,4) by addition of sulfur to make sure the configuration of the tervalent phosphorus intermediates (Scheme 3).

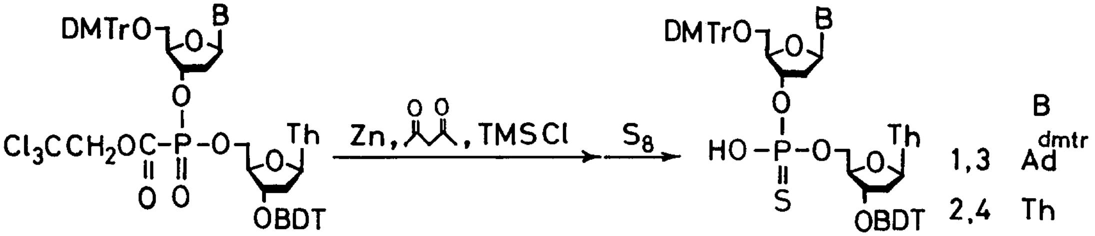
Scheme 2



(1 , 2)

It was found that treatment of 1a with zinc powder (10 equiv.) in pyridine in the presence of trimethylsilyl chloride (10 equiv.) and acetylacetone (10 equiv.) for 1h and with elemental sulfur (10 equiv.) for 1h gave the sole product in 89% yield and it was identified with Sp-Ap(s)T (3a) by comparison with their ^{31}P nmr spectra.[3] On the other hand, the other isomer, 1b was similarly converted to Rp-Ap(s)T (3b) in 90% yield as shown in Figure 1.

Scheme 3



(1,2)

(3,4)

	3a	3b	4a	4b
yield (%)	89	90	88	94

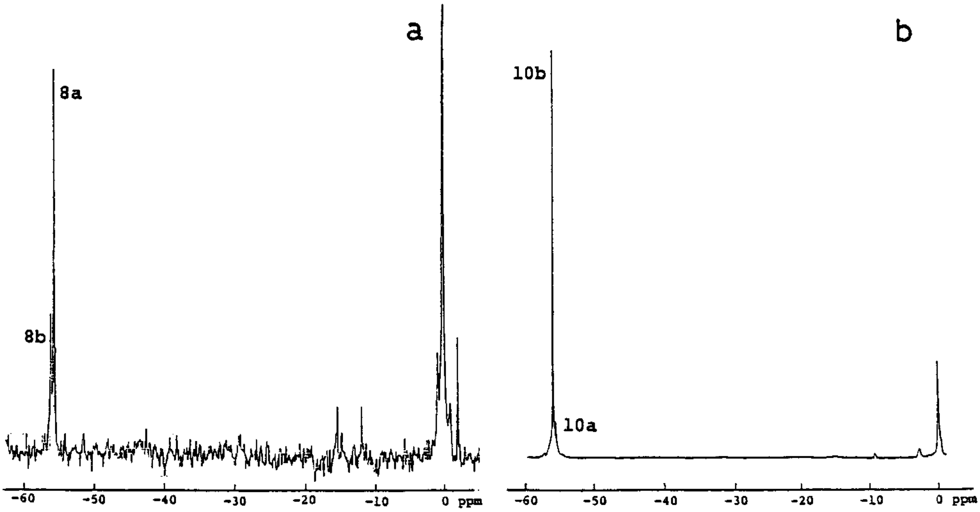
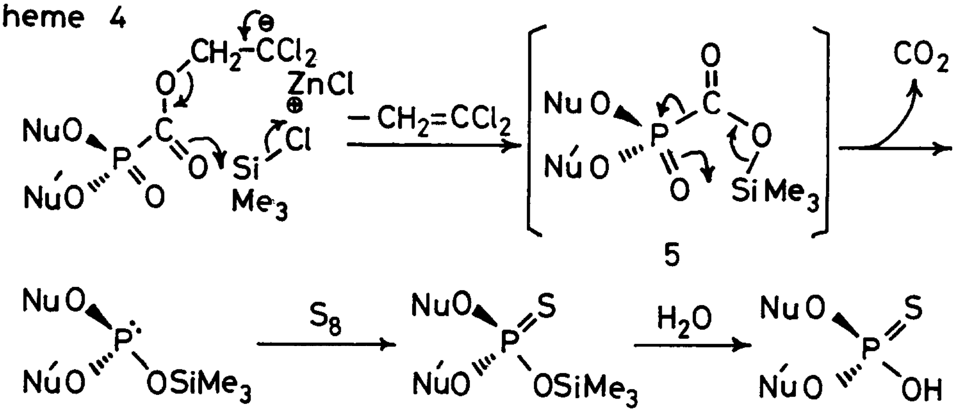


Figure 1 ^{31}P nmr spectra ($CDCl_3$/Py,3:1,v/v) of 3 obtained by treatment of 1 with Zn-Me_3SiCl-AcAc following elemental sulfur. The chemical shifts were relative to an external standard of 85% H_3PO_4 (aq.).

These results suggest that the conversion of 1 to 3 proceeded without racemization. No racemization was proved also in the case of the transformation of 2a (δ -7.29) or 2b (δ -8.26) to Sp-Tp(S)T (4a, δ -56.22) or Rp-Tp(S)T (4b, δ -56.78). These results indicate that the chirality of 1 or 2 at phosphorus was preserved during the whole reaction process. Therefore, we proposed the following conversion mechanism from acyloxyphosphonate to phosphorothioate (Scheme 4).

Scheme 4



The reductive removal of the 2,2,2-trichloroethyl group proceeded more rapidly in the presence of trimethylsilyl chloride than in the absence of it.

From these facts, we concluded that the conversion of 1 or 2 to 3 or 4 proceed via a five-membered ring transition state as depicted in 5.

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