Chiral Mono-, Di-, and Tri-chloromethylphosphonates and Phosphonothioates: Preparation, Absolute Configuration, and the Stereochemical Course of Their Reaction with Methoxide

C. Richard Hall,* Thomas D. Inch, Gary Peacock, Colin Pottage, and Nancy E. Williams
Chemical Defence Establishment, Porton Down, Salisbury, Wiltshire SP4 0JQ

Enantiomerically pure (+)-(*R*)-*O*-ethyl *S*-methyl dichloromethylphosphonothioate, prepared using (−)-ephedrine as a chiral template, is further chlorinated to the trichloro analogue using Bu^nLi–CCl_4 and dechlorinated by hydrogenolysis *via* the monochloro analogue to the corresponding methylphosphonothioate of known configuration. With methoxide, the trichloro derivative gives P–C bond cleavage with inversion and the dichloro derivative gives P–S bond cleavage with retention of configuration. In the monochloro derivative P–S and P–O bond cleavages are competitive, P–S bond cleavage occurring with 70% inversion. Under similar reaction conditions P–S bond cleavage occurs stereospecifically with inversion of configuration in methylphosphonothioates. Methoxide treatment of (+)-(*R*)-ethyl isopropyl trichloromethylphosphonate results in P–C bond cleavage with inversion while (−)-(*S*)-ethyl phenyl dichloromethylphosphonate loses the OPh group also with inversion. Possible reaction mechanisms are discussed.

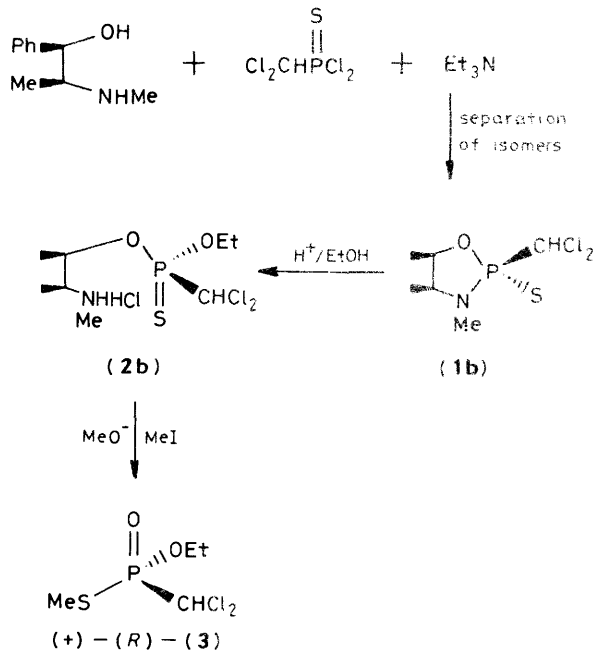
It has been suggested that the use of phosphonates as isosteric analogues of phosphates in studies of biosynthetic pathways and enzyme mechanisms is of restricted utility because the lower electronegativity of the methylene group (H–CH_2–) compared with oxygen (H–O–) causes a weakened acidity for phosphonates relative to phosphates, a reduced P=O stretching frequency, a downfield ^{31}P n.m.r. chemical shift, and diminished apicophilicity. Further, all these changes appear to be reversible if the α-positions in alkylphosphonates are halogenated, with a possible consequence that α-halogeno-alkylphosphonates might be good analogues of biological phosphates.[1,2]

Since the stereochemistry of reactions at phosphorus in biological processes may also be important and since no information was available on the stereochemistry of nucleophilic substitution in α-halogeno-alkylphosphonates, studies were undertaken to compare the stereochemistry of P–S bond cleavage by alkoxides in methylphosphonothioates and the corresponding α-halogeno derivatives. In contrast to most P–S bond cleavage reactions which occur with retention of configuration, alkylphosphonothioates undergo displacement with inversion of configuration, and it was possible that α-halogenation could cause a change from an inversion to the retention mechanism observed in phosphorothioates. Alternatively, halogen substitution which increases the acidity of remaining α-protons could facilitate an elimination step in the substitution mechanism. In this paper results are reported for reactions of alkoxides and mono-, di-, and tri-chloromethylphosphonothioates.

Results

(+)-(*R*)-*O*-Ethyl *S*-methyl dichloromethylphosphonothioate (**3**) was prepared, using (−)-ephedrine as a chiral template, by the route previously described for a range of other acyclic tetracovalent organophosphorus compounds[3,4] (Scheme 1). The configurations of (**1b**) and its phosphorus epimer (**1a**) were tentatively assigned on the basis of their rotations[5,6] and ^1H n.m.r. spectra.[5] Also, since all previously reported acid catalysed P–N bond cleaving reactions in 1,3,2-oxazaphospholidines have been shown to occur with inversion of configuration[5,7] and the final step (Scheme 1) does not cleave any bonds to phosphorus, the absolute configuration of (**3**) can be implied.

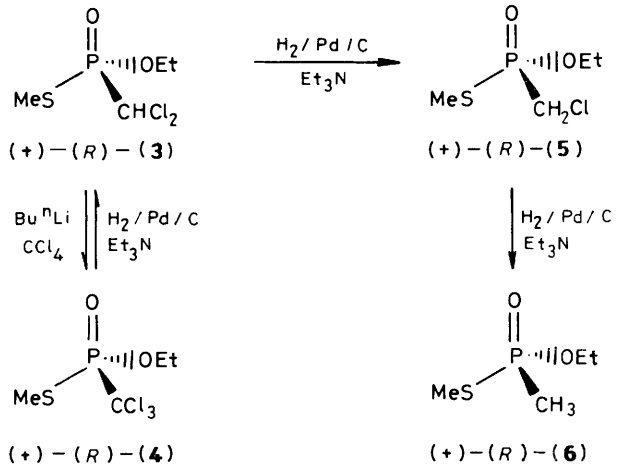
Compound (+)-(*R*)-(**3**) is converted into its trichloro analogue (+)-(*R*)-(**4**) by treatment with n-butyl-lithium and quenching of the resulting anion with carbon tetrachloride (Scheme 2).[8] Hydrogenolysis of (+)-(*R*)-(**4**) in the presence of triethylamine results in the stepwise loss of chlorine. This not only enables the preparation of the monochloro derivative (+)-(*R*)-(**5**) but also, since none of the reactions in Scheme 2 involve cleavage of bonds to phosphorus and the absolute configuration of the unchlorinated derivative (+)-(*R*)-(**6**) has already been established,[9] it confirms the absolute configuration of (**3**), (**4**), and (**5**) as (*R*) and supports the assignment of (**1b**) and (**2b**).



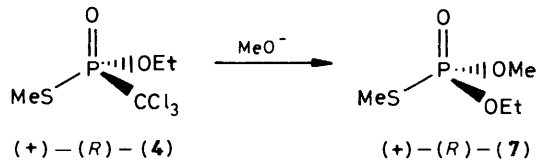
Scheme 1.

Treatment of the trichloro derivative (+)-(*R*)-(**4**) with a controlled amount of sodium methoxide results in enantiomerically pure (+)-(*R*)-ethyl *O*,*S*-dimethyl phosphorothioate (**7**).[5] The reaction therefore involves P–C bond cleavage with inversion of configuration (Scheme 3).

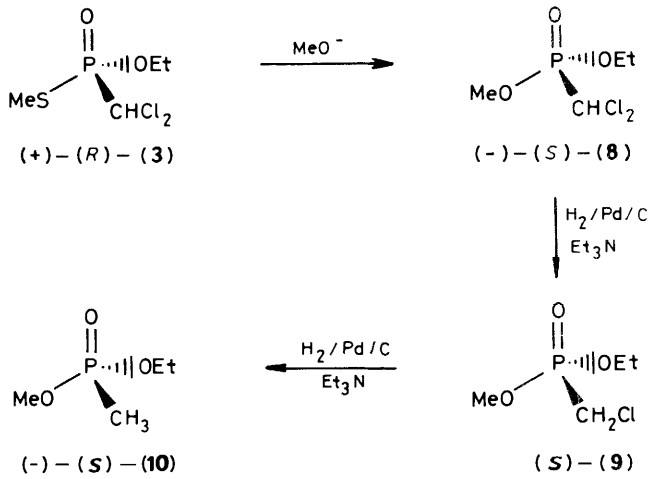
The reaction of the dichloro derivative (+)-(*R*)-(**3**) with methoxide also results in a single enantiomer, in this case (−)-



Scheme 2.

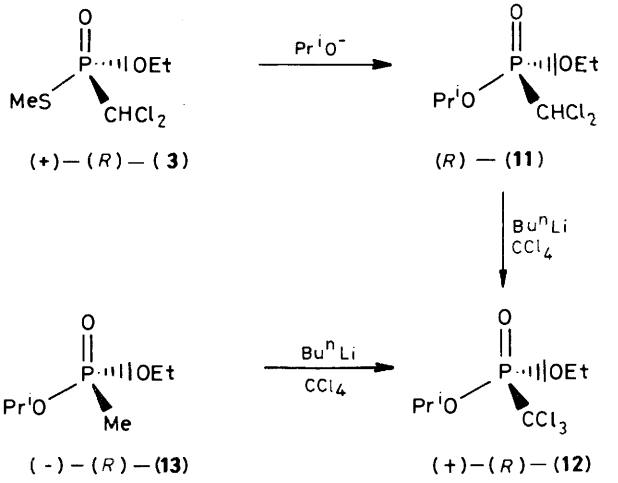


Scheme 3.



Scheme 4.

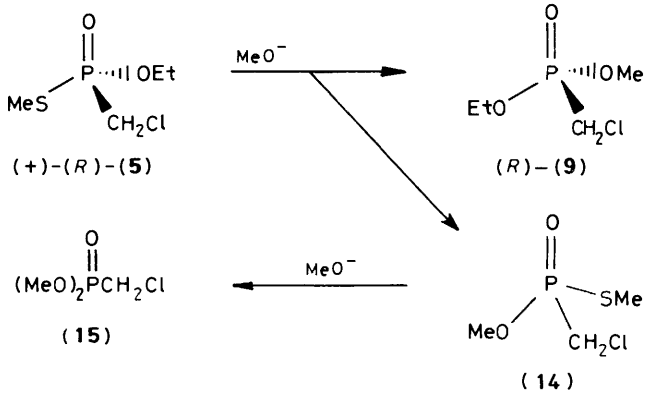
(*S*)-(**8**) (Scheme 4). The reaction however must be carried out with great care because both excess methoxide and the displaced MeS^- rapidly *O*-dealkylate the primary product. Also (−)-(*S*)-(**8**) is prone to transesterification. Hydrogenolysis of (−)-(*S*)-(**8**) results firstly in the monochloromethylphosphonate (*S*)-(**9**) then the already configurationally established unchlorinated derivative (−)-(*S*)-(**10**) (Scheme 4).[10] P–S Bond cleavage by methoxide in (+)-(*R*)-(**3**) therefore occurs with *retention* of configuration at phosphorus. This is supported by the sequence outlined in Scheme 5. Treatment of (+)-(*R*)-(**3**) with isopropoxide results in the dichloromethylphosphonate (*R*)-(**11**) which, on treatment with n-butyl-lithium followed by carbon tetrachloride, gives the trichloro analogue (**12**). ^1H N.m.r. spectroscopy in the presence of the chiral shift reagent tris-{3-[heptafluoro(hydroxy)butylidene]-(+)-camphorato}europium(III), [Eu(hfc)$_3$], shows[3] that this sample is approximately a 4:1 mixture of the (+)-(*R*):(−)-(*S*)



Scheme 5.

enantiomers. The loss in enantiomeric purity presumably occurs during the conversion of (**3**) into (**11**), but this could not be confirmed since none of the ^1H n.m.r. signals in (**11**) were usefully resolved in the presence of Eu(hfc)$_3$ (at 60 or 100 MHz). The loss could be a result of either a not completely stereospecific P–S bond cleaving reaction, or of transesterification of the product.[31]P N.m.r. spectroscopy suggests that transesterification of (**11**), at least with other alkoxides, does occur at a significant rate but no preparative experiments were successful because dealkylation reactions were always competitive (these were considerably accelerated in the presence of thiol). Enantiomerically pure (+)-(*R*)-(**12**) was generated by treating the already configurationally established (−)-(*R*)-(**13**)[5] with n-butyl-lithium followed by carbon tetrachloride. Since neither chlorination reaction involves a change in configuration at phosphorus, P–S bond cleavage by isopropoxide in (+)-(*R*)-(**3**) (Scheme 5) must occur with at least 80% retention of configuration.

^{31}P N.m.r. monitoring of the reaction between the monochloro derivative (+)-(*R*)-(**5**) and methoxide clearly reveals a competitive reaction. The major primary product is (*R*)-(**9**) (Scheme 6). ^1H N.m.r. spectroscopy in the presence of [Eu(hfc)$_3$]



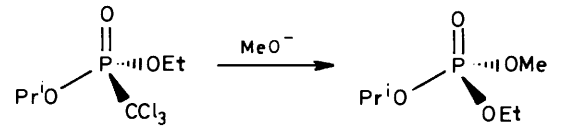
Scheme 6.

shows that this sample contains ≤30% of the *S* enantiomer. P–S Bond cleavage in (+)-(*R*)-(**5**) therefore occurs with ≥70% inversion of configuration at phosphorus. The minor primary product is (**14**) which results from P–O rather than P–S bond cleavage in (+)-(*R*)-(**5**). It was not possible to isolate (**14**), and thus establish its configuration, since its concentration in the reaction mixture never exceeds 5% that of (+)-(*R*)-(**5**) and it

reacts rapidly with methoxide to give (**15**) which is then dealkylated.

It has been reported previously[5] that methylphosphonothioates react with alkoxides to give the product of P–S bond cleavage with ≈80% inversion of configuration. In fact, the exact percentage depends on both the reaction conditions and the other groups at phosphorus. Under the same conditions as for the mono- and di-chloromethyl derivatives reported above, *O*-ethyl *S*-methyl methylphosphonothioate reacts with methoxide with ≥90% inversion of configuration.

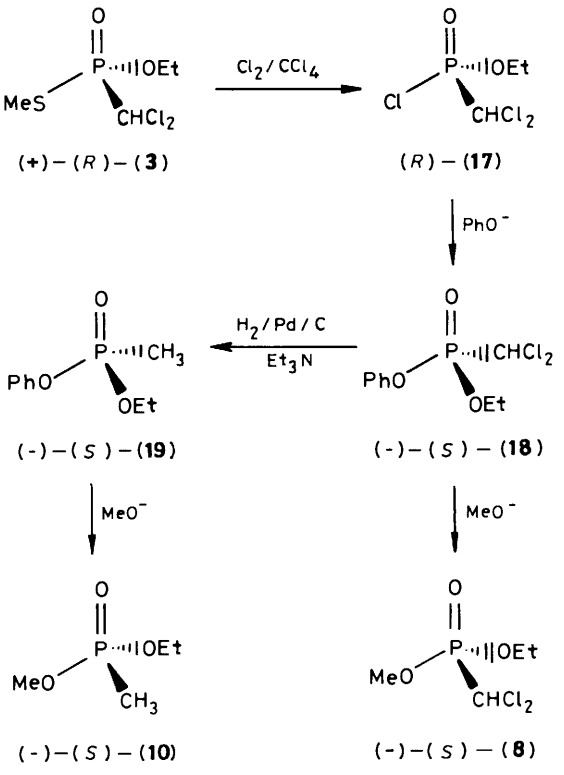
The trichloromethylphosphonate (+)-(*R*)-(**12**) reacts with methoxide to give the already configurationally established (−)-(*R*)-ethyl methyl isopropyl phosphate (**16**).[10] The reaction therefore involves P–C cleavage with inversion of configuration (Scheme 7).



(+)-(*R*)-(**12**) (−)-(*R*)-(**16**)

Scheme 7.

(−)-(*S*)-Ethyl phenyl dichloromethylphosphonate (**18**) was prepared by allowing (+)-(*R*)-(**3**) to react with a solution of chlorine in carbon tetrachloride and then treating the resulting chloridate (**17**), without isolation, with sodium phenoxide (Scheme 8). Hydrogenolysis of (−)-(*S*)-(**18**) gave (−)-(*S*)-(**19**)



(+)-(*R*)-(**3**) (*R*)-(**17**)

(−)-(*S*)-(**19**) (−)-(*S*)-(**18**)

(−)-(*S*)-(**10**) (−)-(*S*)-(**8**)

Scheme 8.

which ^{1}H n.m.r. spectroscopy in the presence of [Eu(hfc)$_3$] showed to be ≥95% a single enantiomer. Thus (−)-(*S*)-(**18**) was also ≥95% enantiomerically pure. The absolute configuration of (**19**) has been assigned previously[11] using the method[3] based on the relative sense of non-equivalence induced in enantiomers by [Eu(hfc)$_3$]. In isolation this method cannot be considered definitive (for example see below), but in this case, since treatment of (−)-(*S*)-(**19**) with methoxide results in the well characterised (−)-(*S*)-(**10**)[10] and since this reaction almost certainly occurs with inversion of configuration, it is likely that (−)-(*S*)-(**19**) has the configuration shown (Scheme 8). The configuration of (−)-(*S*)-(**18**) follows from its relationship to (−)-(*S*)-(**19**) (Scheme 8). This means that either the chlorinolysis of the P–S bond in (+)-(*R*)-(**3**) or the subsequent reaction of (**17**) with phenoxide must occur with retention of configuration. Since some P–S bonds have already been shown to be cleaved by chlorinating reagents with retention of configuration[12,13] it is likely that it is the chlorinolysis which occurs with retention.

Treatment of (−)-(*S*)-(**18**) with methoxide results in ≥95% (−)-(*S*)-(**8**) (Scheme 8). The reaction therefore involves displacement of phenoxide with inversion of configuration.

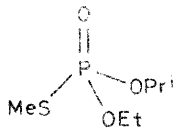
The ^{1}H n.m.r. spectra of all the organophosphorus esters mentioned in this section have been investigated in the presence of [Eu(hfc)$_3$] and, if necessary, authentic racemic ester. In each case, except for (**11**) and (**18**), at least one set of signals is usefully resolved at 60 MHz and, unless otherwise stated above, each sample was shown to be essentially enantiomerically pure. A method has been described previously for relating the absolute configuration of four-co-ordinate phosphoryl esters to the relative sense of the non-equivalence induced in the enantiomers by [Eu(hfc)$_3$].[3,5] The relationship holds for those phosphonates and phosphonothioates mentioned in this paper that contain one or less α-chlorine atoms. However, for those esters containing two or three α-chlorines, the di- or trichloromethyl groups must be given precedence over both OR and SR groups when determining the 'largest' group (this was previously done purely on the basis of the sequence rules) for the method to succeed.

Discussion

In the majority of cases the cleavage of P–S bonds in substitution reactions at acyclic, four-co-ordinate phosphorus esters that also contain at least one P–O bond, occurs with retention of configuration at phosphorus. Thus, treatment of the phosphorothioate (**20**)[5] or the *N*-dialkylphosphoramidothioate (**21**)[14] with alkoxide, the phosphonium salt (**22**) with hydroxide,[15,16] and the phenylphosphonothioate (**23**) with methylmagnesium iodide,[17,18] all result in P–S bond cleavage with retention. The mechanism of the reaction is thought to involve initial attack of the nucleophile opposite alkoxide followed by pseudorotation of the resulting trigonal bipyramidal (tbp) intermediate and apical loss of *S*-alkyl. The competitive P–O bond cleavage with inversion of configuration observed when (**22**) reacts with hydroxide and (**23**) reacts with Grignard reagents is consistent with this mechanism.

One of the exceptions* to the above is the reaction between the methylphosphonothioate (**24**) and alkoxide which results in P–S bond cleavage with predominant inversion of configuration[5] (see above). An attractive explanation for this variation

* Another example of P–S bond fission with predominant inversion of configuration in acyclic systems occurs in phosphoramidothioates such as (**31**) in the presence of alkoxides.[19] In this case P–O bond cleavage is competitive and we now report that this also occurs with inversion of configuration. An elimination mechanism (where OEt and SMe are competitively expelled and this time occurring with inversion) is again a possibility. Alternatively the products may result from competitive nucleophilic attack opposite OEt and SMe. That the tbp formed by attack opposite OEt does not pseudorotate may be because, in basic solution, it is wholly or partially deprotonated, generating the highly apicophobic P–N̄H.



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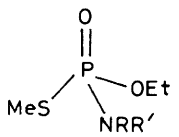
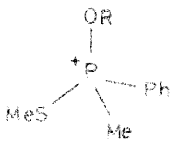


(21) R = Me, R′ = CHMeCHPhOH
(31) R = R′ = H



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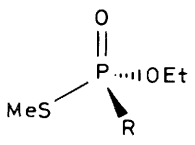
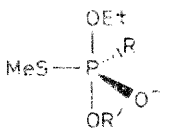
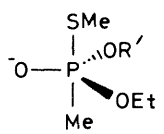


(23) R = Ph
(24) R = Me



(25) R = CH_3
(28) R = CH_2Cl
(29) R = $CHCl_2$



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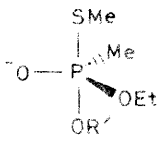

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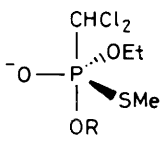


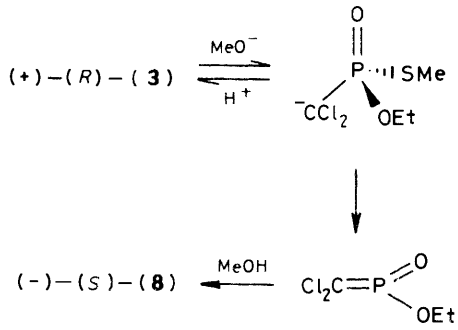
(30)

is that while apical attack opposite alkoxy is kinetically favoured the tbp (**25**) so formed is unlikely to pseudorotate [to (**26**)] because this would involve putting the poorly apicophilic methyl group in an apical position in place of the much more apicophilic alkoxy ligand. The less favourable initial attack of the nucleophile opposite *S*-alkyl to generate tbp (**27**) is therefore able to compete; apical loss of *S*-alkyl from (**27**) results in inversion of configuration. If, in fact, the equilibrium between (**24**) and (**25**) is fast compared to the formation of (**27**) then, since OMe and OEt are similar, one may expect a significant degree of alkoxy exchange and hence the formation of both dimethyl and ethyl methyl methylphosphonate as reaction products. This is not the case; although the products of alkoxide promoted P–O bond cleavage have been observed in the reaction of some other phosphonothioates.[20,21] DeBruin[21] has suggested that in phenylphosphonothioates (**23**) nucleophilic attack opposite *S*-alkyl is the kinetically favoured process (by a factor of 5—10).

Treatment of the chloromethylphosphonothioate (**5**) with methoxide results in P–S bond cleavage with ≈70% inversion (*i.e.* ≈30% retention) of configuration and ≃15% product derived from P–O bond cleavage. This swing towards P–S cleavage with retention may reflect an increase in the apicophilicity of CH_2Cl relative to CH_3 and hence the ease of pseudorotation of the tbp (**28**) compared to that of (**25**). Why in this case P–O bond cleavage is also observed is not apparent. Treatment of the dichloromethylphosphonothioate (**3**) with methoxide results in exclusive P–S bond cleavage with essentially complete retention of configuration. This reflects the situation in phosphorothioates[5] and presumably means that the apicophilicity of $CHCl_2$ and the alkoxy group is sufficiently similar that pseudorotation of (**29**) is now a favourable process and that reaction occurs *via* attack opposite alkoxide and pseudorotation rather than attack opposite *S*-alkyl.

An alternative explanation for the latter result may be that the apical potentiality[14] of $CHCl_2$ in (**3**) is high compared to that of OEt or SMe and hence initial nucleophilic attack occurs opposite it to form a tbp such as (**30**). [Pseudorotation of (**30**) followed by apical P–S bond cleavage results in retention of configuration.] Presumably attack opposite the halogenomethyl group must occur in the CCl_3 containing esters since treatment of both the trichloromethylphosphonothioate (**4**) and the corresponding phosphonate (**12**) with alkoxide results in exclusive P–C bond cleavage with complete inversion of configuration. If nucleophilic attack did occur opposite $CHCl_2$ in (**3**) it is possible that this would also be true in ethyl phenyl dichloromethylphosphonate (**18**) and hence treatment of (**18**) with methoxide would lead to displacement of phenoxide with retention. In fact the reaction occurs with complete inversion of configuration. This does not rule out attack opposite $CHCl_2$ in (**3**) since the lone pairs on sulphur may play a significant role in determining relative apical potentialities, but it does demonstrate that nucleophilic attack opposite $CHCl_2$ ligands is not a general occurrence, as it seems to be for CCl_3 ligands.

As the degree of α-chlorine substitution increases so also does the acidity of any remaining phosphonate protons. A third possible explanation for the change in stereochemical course of the above reactions may therefore be a transition from a substitution mechanism for (**24**) to an elimination mechanism



Scheme 9.

for (**3**) (Scheme 9). That the proton in (**3**) exchanges rapidly with deuterium in D_2O in the presence of a trace of base, but those in (**5**) and (**24**) do not, may support this idea. However, although it cannot be ruled out, such a sequence (Scheme 9) seems unlikely to occur stereospecifically with retention of configuration.

Experimental

^1H N.m.r. spectra were recorded at 100 MHz with deuteriochloroform as solvent and tetramethylsilane as internal standard except where [Eu(hfc)$_3$] was employed when spectra were recorded at 60 MHz. ^{31}P N.m.r. spectra were measured for the same solutions and shifts are quoted in p.p.m. downfield from phosphonic acid (external). In most cases, although the preparation of only one enantiomer of each compound is described, both enantiomers have been prepared and been shown to have equal and opposite optical rotations. Column chromatography was performed using Merck Kieselgel 60, particle size 0.040—0.063 mm, under a slight positive pressure. Optical rotations were measured in chloroform (path length 1 dm). All organic solutions of reaction products were dried over magnesium sulphate.

(2S,4S,5R)- *and* (2R,4S,5R)-2-*Dichloromethyl*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thiones* (**1a**) *and* (**1b**).—A solution of dichloromethylphosphonothioic dichloride (21.8 g) [22,23] in benzene (50 ml) was slowly added to a solution of (−)-ephedrine (16.5 g) and triethylamine (22 g) in benzene (500 ml). The mixture was stored for 48 h, filtered, and the filtrate was washed with water. Concentration of the organic layer and chromatography of the residue, light petroleum–ether (19:1), gave the *products* (**1a**) (4.0 g, 13%), m.p. 98 °C (from light petroleum), $[\alpha]_D$ −1.9° (*c* 0.5); δ_H 0.79 (d, *J*, 6.4 Hz, CMe), 2.83 (d, *J* 11.2 Hz, NMe), 4.01 (m, 4-H), 5.75 (dd, *J* 6.6 and 5.0 Hz, 5-H), 5.88 (d, *J* 3.8 Hz, $CHCl_2$), and 7.30 (s, Ph); δ_P −86.9 (Found: C, 42.5; H, 4.5; N, 4.6. $C_{11}H_{14}Cl_2NOPS$ requires C, 42.6; H, 4.6; N, 4.5%) and (**1b**) (9.4 g, 31%), m.p. 128 °C (from light petroleum), $[\alpha]_D$ −139° (*c* 1.2); δ_H 0.84 (d, *J* 6.6 Hz, CMe), 2.93 (d, *J* 10.2 Hz, NMe), 3.74 (m, 4-H), 5.77 (dd, *J* 6.0 and <1 Hz, 5-H), 5.80 (d, *J* 2.5 Hz, $CHCl_2$), and 7.30 (m, Ph); δ_P −87.2 (Found: C, 42.6; H, 4.5; N, 4.5%).

Acid Catalysed Ethanolysis of (**1a**) *and* (**1b**).—The appropriate precursor was dissolved in an excess of a dilute solution of anhydrous hydrogen chloride in ethanol. After 15 min the solution was concentrated and the residue crystallised from di-isopropyl ether–benzene. Compound (**1a**) gave a quantitative yield of (**2a**), m.p. 134—135 °C, $[\alpha]_D$ −68.5° (*c* 0.9); δ_H 1.34 (t, *J* 7.0 Hz, OCH_2Me), 1.44 (d, *J* 6.4 Hz, CMe), 2.72 (s, NMe), 6.02 (dd, *J* 10.0 and 2.7 Hz, PhC*H*), and 6.24 (s, $CHCl_2$) (Found: C, 39.7; H, 5.3; N, 3.6. $C_{13}H_{21}Cl_3NO_2PS$ requires C, 39.8; H, 5.4; N, 3.6%); likewise (**1b**) gave (**2b**), m.p. 134 °C, $[\alpha]_D$ −60.2° (*c* 0.9); δ_H 0.95 (t, *J* 7.0 Hz, OCH_2Me), 1.40 (d, *J* 6.4 Hz, CMe), 2.87 (s, NMe), 6.22 (dd, *J* 9.6 and 1.6 Hz, PhC*H*), and 6.98 (d, *J* 2.0 Hz, $CHCl_2$) (Found: C, 39.5; H, 5.3; N, 3.5%).

(+)-(R)-*Ethyl* S-*Methyl Dichloromethylphosphonothioate* (**3**).—A solution of sodium (0.7 g) in methanol (70 ml) was slowly added to a solution of (**2b**) (5 g) in methanol (20 ml). After 1 h the mixture was poured into an excess of water and extracted with chloroform. The aqueous layer was made acidic and again extracted with chloroform. This extract was concentrated and the residue dissolved in light petroleum–ether. On addition of dicyclohexylamine (2.5 g), (+)-(R)-*ethyl dichloromethylphosphonothioic acid* crystallised from solution as its dicyclohexylamine salt (4.5 g, 90%), m.p. 161 °C (from light petroleum), $[\alpha]_D$ +10.6° (*c* 1.8) (Found: C, 46.0; H, 7.75; N, 3.7. $C_{15}H_{30}Cl_2NO_2PS$ requires C, 46.1; H, 7.75; N, 3.6%). A solution of this salt in benzene and an excess of methyl iodide was boiled under reflux for 1 h; the mixture was then allowed to cool, washed with water, and concentrated. The residue was distilled, b.p. 100 °C (bath) at 1 mmHg, to give (+)-(*R*)-(**3**) (2.2 g, 86%), $[\alpha]_D$ +47.6° (*c* 1.3); δ_H 1.40 (t, OCH_2Me), 2.51 (d, *J* 13.2 Hz, SMe), 4.32 (m, OCH_2Me) and 5.79 (d, *J* 1.4 Hz, $CHCl_2$). Addition of [Eu(hfc)$_3$] shows the sample to be essentially enantiomerically pure. Addition of racemic (**3**) shows that the SMe signal in (+)-(*R*)-(**3**) resonates at highfield relative to that for the (−)-(*S*) enantiomer.

(+)-(R)-*Ethyl* S-*Methyl Chloromethylphosphonothioate* (**5**).—A mixture of (+)-(*R*)-(**3**) (1 g), 10% palladium on charcoal (0.25 g), triethylamine (5 ml), and ethyl acetate (75 ml) was stirred under an atmosphere of hydrogen for 3 h, and then filtered and the filtrate concentrated. The residue was dissolved in chloroform and washed with water. Concentration of the organic layer and chromatography of the residue, benzene–acetone–methanol (12:1:1), gave (+)-(*R*)-(**5**) (0.5 g, 73%), $[\alpha]_D$ +62° (*c* 0.6); δ_H 1.38 (t, OCH_2Me), 2.39 (d, *J* 12.9 Hz, SMe), 3.69 (d, *J* 7.8 Hz, CH_2Cl), and 4.24 (m, OCH_2Me). Addition of [Eu(hfc)$_3$] shows the sample to be essentially enantiomerically pure. Addition of racemic (**5**) shows that the SMe in (+)-(*R*)-(**5**) resonates at lowfield and the OCH_2Me signal at highfield relative to those in (−)-(*S*)-(**5**).

(+)-(R)-*Ethyl* S-*Methyl Trichloromethylphosphonothioate* (**4**).—A solution (1.6 M) of Bu^{n}Li in hexane (2.5 ml) was slowly added to a solution of (+)-(*R*)-(**3**) (0.9 g) in tetrahydrofuran (20 ml) cooled to −100 °C. After 15 min an excess of carbon tetrachloride was added, and the mixture allowed to warm to room temperature; it was then partioned between water and chloroform. Concentration of the organic layer and chromatography of the residue, benzene–acetone (9:1) gave (+)-(*R*)-(**4**) (0.12 g, 12%), $[\alpha]_D$ +32° (*c* 1.2); δ_H 1.45 (t, OCH_2Me), 2.56 (d, *J* 14.1 Hz, SMe), and 4.41 (m, OCH_2Me).

Hydrogenolysis of Halogenomethylphosphonothioates and Halogenomethylphosphonates.—The appropriate halogenomethylphosphonothioate (+)-(*R*)-(**3**), (+)-(*R*)-(**4**), or (+)-(*R*)-(**5**) was stirred with a suspension of 10% Pd/C, in an excess of triethylamine and ethyl acetate under an atmosphere of hydrogen for 50 h and then processed by conventional methods. In each case the product was enantiomerically pure (+)-(*R*)-ethyl *S*-methyl methylphosphonothioate (**6**), $[\alpha]_D$ +88° (*c* 0.3).[5]

A similar procedure starting with (−)-(*S*)-(**8**) gave (−)-(*S*)-(**10**)[5] as ≥95% a single enantiomer and a 7:3 ratio of (*R*):(*S*)-(**9**) gave a similar ratio of (*R*):(*S*)-(**10**).

Likewise (−)-(*S*)-(**18**) gave (—)-(*S*)-(**19**)[11] $[\alpha]_D$ −12.1° (*c* 0.7) as ≥95% a single enantiomer. In the presence of [Eu(hfc)$_3$] the PMe resonates at highfield and the $POCH_2Me$ at lowfield in (−)-(*S*)-(**19**) relative to those in the (+)-(*R*) enantiomer.

(+)-(R)-*Ethyl Isopropyl Trichloromethylphosphonate* (**12**).—A solution (1.6 M) of Bu^{n}Li in hexane (3.8 ml) was slowly added to a solution of (−)-(*R*)-(**13**) (1 g),[5] $[\alpha]_D$ −1.2° (*c* 1.1), in tetrahydrofuran (20 ml) cooled to −78 °C. After 15 min an excess of carbon tetrachloride was added and the mixture was allowed to warm to room temperature; it was then partioned between water and chloroform. Concentration of the organic layer and chromatography of the residue, benzene–acetone (10:1) gave (+)-(*R*)-(**12**) (0.35 g, 21%), $[\alpha]_D$ +1.75° (*c* 2.0); δ_H 1.41 (dt 7.0 and 1 Hz, OCH_2Me), 1.44 (d, $CHMe_2$), 4.40 (m, OCH_2Me), and 5.00 (m, $CHMe_2$). Addition of [Eu(hfc)$_3$] and racemic (**12**) shows that the OCH_2Me in (+)-(*R*)-(**12**) resonates at lowfield relative to that for the (−)-(*S*) enantiomer.

A similar procedure starting with (*R*)-(**11**) also gave (+)-(*R*)-(**12**).

(−)-(S)-*Ethyl Phenyl Dichloromethylphosphonate* (**18**).—A solution of chlorine (0.8 g) in carbon tetrachloride (10 ml) was slowly added to an ice-cooled solution of (+)-(*R*)-(**3**) (1.1 g) in carbon tetrachloride (5 ml). After 10 min the solution was concentrated and the residue dissolved in cold acetonitrile (25 ml). Sodium phenate (0.57 g) was added in one portion. After 15 min the mixture was poured into water and extracted with chloroform. Concentration of the organic layer and chromatography of the residue, light petroleum–ether (3:2) gave (−)-(*S*)-(**18**) (0.65 g, 49%), $[\alpha]_D$ −8.6° (*c* 3.2); δ_H 1.37 (dt, OCH_2Me), 4.40 (m, OCH_2Me), 5.76 (d, *J* 1.6 Hz, $CHCl_2$), and 7.24 (m, Ph), which is ≥95% one enantiomer (see hydrogenolysis expts).

Base Catalysed Alcoholysis of Halogenomethylphosphonothioates and Halogenomethylphosphonates: General Procedure.—A solution of the appropriate precursor (0.1 g) in methanol (4 ml) was mixed rapidly with a solution (0.4 M) of sodium in methanol (6 ml). When the yield of the primary product(s) was judged (^{31}P n.m.r.) to be at a maximum (2—15 min) the mixture was poured into water and extracted with chloroform. Concentration of the organic layer and chromatography of the

residue, benzene–acetone–methanol (8:1:1 or 12:1:1), gave the product.

Compound (+)-(*R*)-(**4**) gave (+)-(*R*)-(**7**)[5] (85%) as ≥95% a single enantiomer: (+)-(*R*)-(12) gave (—)-(*R*)-(16)[5] (88%) as ≥ 95% a single enantiomer: (+)-(*R*)-(**3**) gave (−)-(*S*)-(**8**) (80%), $[\alpha]_D$ −2.2° (*c* 2.7); δ_H 1.39 (dt, *J* 7.0 and 0.7 Hz, OCH_2Me), 3.93 (d, *J* 10.5 Hz, OMe), 4.33 (m, OCH_2Me), and 5.79 (d, *J* 2.0 Hz, $CHCl_2$); δ_P −11.6, as essentially a single enantiomer. Addition of [Eu(hfc)$_3$] and racemic (**8**) shows that in (−)-(*S*)-(**8**) the OMe resonates at highfield and the $POCH_2Me$ at lowfield relative to the (+)-(*R*) enantiomer: (+)-(*R*)-(**3**) when treated with Pr^iO^-/Pr^iOH gave (*R*)-(**11**) (80%), δ_H 1.34 (dt, *J* 7.0 and 0.7 Hz, OCH_2Me), 1.35 (d, *J* 6.1 Hz, $CHMe_2$), 4.27 (m, OCH_2Me), 4.86 (m, $CHMe_2$), and 5.75 (d, *J* 1.8 Hz, $CHCl_2$). Addition of [Eu(hfc)$_3$] does not usefully resolve any of the signals (60 or 100 MHz) but chlorination gave (+)-(*R*)-(**12**) as ≥80% a single enantiomer: (+)-(*R*)-(**5**) gave a mixture of dimethyl chloromethylphosphonate (**15**) (15%) and (*R*)-(**14**) (70%), δ_H 1.36 (t, OCH_2Me), 3.57 (d, *J* 10.3 Hz, CH_2Cl), 3.84 (d, *J* 10.7 Hz, OMe), and 4.21 (m, OCH_2Me). Addition of [Eu(hfc)$_3$] showed the sample to be a 7:3 ratio of (*R*):(*S*) enantiomers. In the (*R*) enantiomer the OMe resonates at highfield and the CH_2Cl at lowfield relative to those of the (*S*) enantiomer: (−)-(*S*)-(**18**) gave (−)-(*S*)-(**8**) (92%). Addition of [Eu(hfc)$_3$] showed the sample to be ≥95% a single enantiomer.

Basic Ethanolysis of (+)-(R)-O,S-*Dimethyl Phosphoramidothioate* (**31**).—A solution (0.04 M) of sodium ethoxide in ethanol (6 ml) was added to a solution of (+)-(*R*)-(**31**),[19] $[\alpha]_D$ +51° (*c* 0.8) (0.4 g) in ethanol (20 ml). After 30 min an excess of solid carbon dioxide was added. The mixture was filtered, and the filtrate concentrated. Chromatography of the residue, benzene–acetone (3:2), gave *O*-ethyl *S*-methyl phosphoramidothioate (0.12 g, 28%) as a 5:2 mixture of the *S*:*R* enantiomers,[12] $[\alpha]_D$ −18° (*c* 1.2); *O*,*O*-diethyl phosphoramidate (0.1 g, 23%) and (−)-(*S*) *O*-ethyl *O*-methyl phosphoramidate (0.06 g, 15%) as ≥95% a single enantiomer, $[\alpha]_D$ −3.0° (*c* 0.6).[12]

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