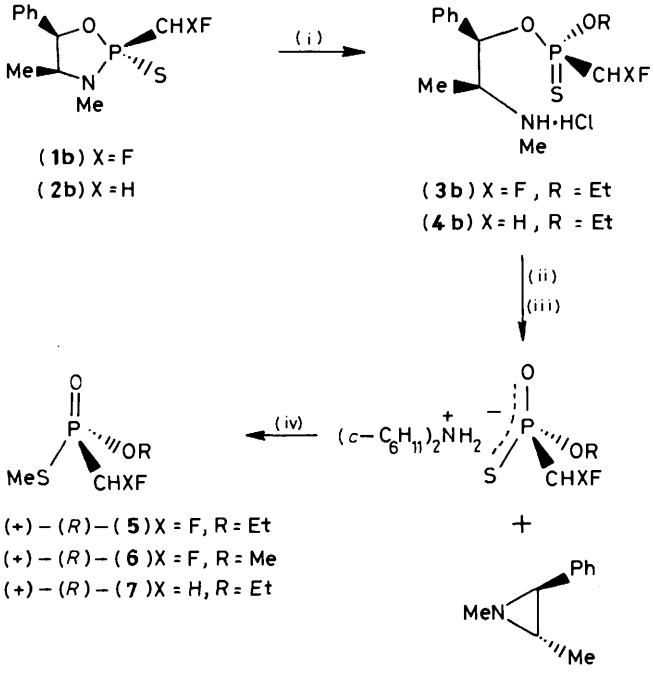
The Preparation and Properties of some Chiral Fluoromethylphosphonates, Phosphonothioates, and Phosphonamidothioates

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

Enantiomerically pure dialkyl di- and mono-fluoromethylphosphonates are prepared by fluorination of the unsubstituted phosphonate anions. The corresponding fluoromethylphosphonothioates and thioic acids are prepared using (−)-ephedrine as a chiral template and the thioic acids are converted, *via* the chloridates, into the phosphoramidothioates. Treatment of *O*-ethyl *S*-methyl difluoromethylphosphonothioate with methoxide results in P–S bond cleavage with retention of configuration. In the corresponding monofluoromethylphosphonothioate and in *S*-methyl *P*-difluoromethyl-*NN*-dimethylphosphonamidothioate the reaction occurs with predominant inversion of configuration. Ethoxide-promoted endocyclic P–N bond cleavage in 2-difluoromethyl-1,3,2-oxazaphospholidine-2-thiones can occur with retention of configuration at phosphorus.

Much of the considerable recent interest in fluoromethylphosphonates[1-13] has been connected with the idea[1,2] that dihydrogen fluoroalkylphosphonates may be good steric and polar analogues of natural dihydrogen alkyl phosphates and as such may be useful in studies of biosynthetic pathways and enzyme-catalysed reactions. One cautionary result has been that the replacement of methyl group protons in methylphosphonothioates by chlorine can affect the stereochemistry of nucleophilic displacements at phosphorus: for example methoxide displaces *S*-alkyl with inversion of configuration at phosphorus in *O*-alkyl *S*-alkyl methylphosphonothioates but with retention of configuration in the corresponding dichloromethylphosphonothioates.[14] In a continuation of these stereochemical studies, results of displacements in fluoroalkylphosphonothioates are reported in this paper. Also, alkoxide-catalysed P–N bond cleavage in 2-difluoromethyl-1,3,2-oxazaphospholidine-2-thiones has been observed to occur with unexpected retention of configuration at phosphorus.

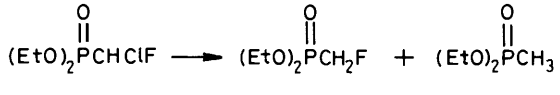


(1a)—(4a) are the phosphorus epimers of (1b)—(4b), respectively

Scheme 1. *Reagents:* (i) H^+, ROH; (ii) Na—MeOH; (iii) dicyclohexylamine; (iv) MeI

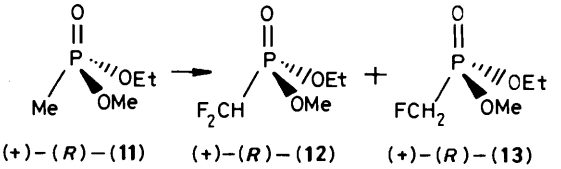
Results

The chiral di- and mono-fluoromethylphosphonothioates (**5**), (**6**) and (**7**) were prepared by the route previously described for the chlorine-containing analogues[14] and other phosphorus esters[15] (Scheme 1). The assignment of configuration to the 1,3,2-oxazaphospholidines (**1a**) and (**2a**) and their phosphorus epimers (**1b**) and (**2b**) is based on a comparison of their $[\alpha]_D$ values and ^1H n.m.r. parameters with those of their analogues.[14,15] On the reasonable assumption that acid-catalysed alcoholysis of (**1b**) and (**2b**) results in P–N bond cleavage with inversion of configuration at phosphorus, and since neither of the last two steps in Scheme 1 involves the cleavage of any bonds to phosphorus, the absolute configurations of (**5**), (**6**), and (**7**) have been assigned as *R*. These assignments are again supported by a comparison of $[\alpha]_D$ values.[14] In the case of the chlorine-containing analogues confirmation of configuration was obtained by hydrogenolysis in the presence of triethylamine which generated the corresponding unsubstituted phosphonothioates of known configuration. Such confirmation has not been possible in the case of (**5**), (**6**), and (**7**) because C–F bonds are not generally cleaved under simple hydrogenolysis conditions. Exceptionally (Scheme 2), treatment of the chlorofluoromethylphosphonate (**8**) with hydrogen/Raney nickel and triethylamine at room temperature results in a mixture of (**9**) and (**10**). Neither (**9**) nor its difluoromethyl analogue reacts under similar conditions.



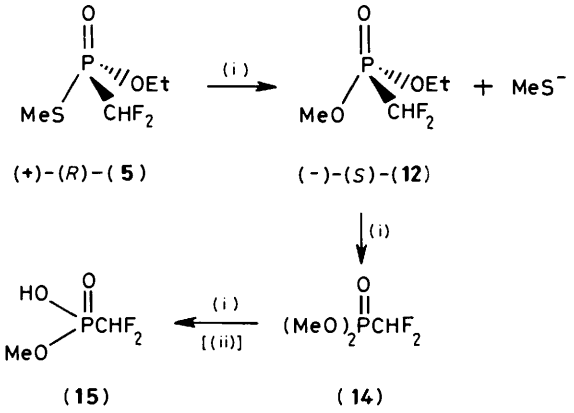
Scheme 2. H_2/Raney nickel, Et_3N

The chiral di- and mono-fluoromethylphosphonates (**12**) and (**13**) were prepared by treatment of ethyl methyl (+)-(*R*)-methylphosphonate[16] (**11**) with n-butyl-lithium and quenching of the resulting anion with fluorine perchlorate. A similar procedure has been used for the fluorination of achiral methanediphosphonate esters.[4] Since the reaction does not involve cleavage of any bonds to phosphorus the absolute configuration of (**12**) and (**13**) can be assigned as *R* (Scheme 3).



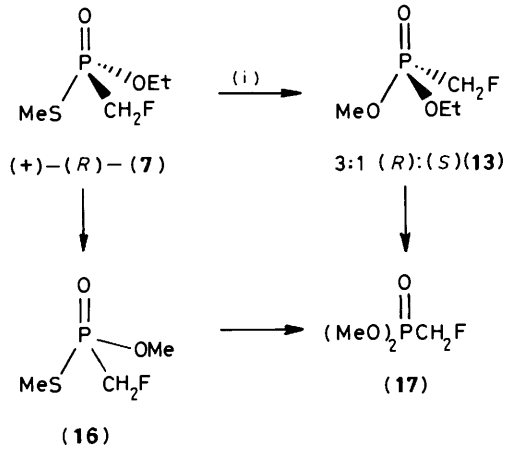
Scheme 3. *Reagents:* Bu^nLi, $FClO_3$

Treatment of the difluoromethylphosphonothioate (+)-(*R*)-(**5**) with a solution (0.1M) of sodium methoxide in methanol results in rapid P–S bond cleavage (complete < 30 s) to give (−)-(*S*)-(**12**) (Scheme 4), which then undergoes ester exchange ($t_{\frac{1}{2}}$ EtO–MeO exchange *ca.* 10 min) to give (**14**) which is then dealkylated to give (**15**) [$t_{\frac{1}{2}}$ *ca.* 100 min. All halogenomethylphosphonates are good alkylating agents but in this case the rate of dealkylation of (**14**) is increased by the presence of MeS^- in the reaction mixture.] Work-up of the reaction mixture after *ca.* 30 s enabled the isolation of essentially enantiomerically pure (−)-(*S*)-(**12**) (compare product from Scheme 3). P–S Bond cleavage in (**5**) therefore occurs with retention of configuration at phosphorus. (The enantiomeric purity of all chiral phosphonyl compounds was established by ^1H n.m.r. spectroscopy in the presence of tris-{3-[heptafluoro(hydroxy)butylidene]-(+)-camphorato}europium(III), $Eu(hfc)_3$[15].)



Scheme 4. *Reagents:* (i) MeO^-; (ii) MeS^-

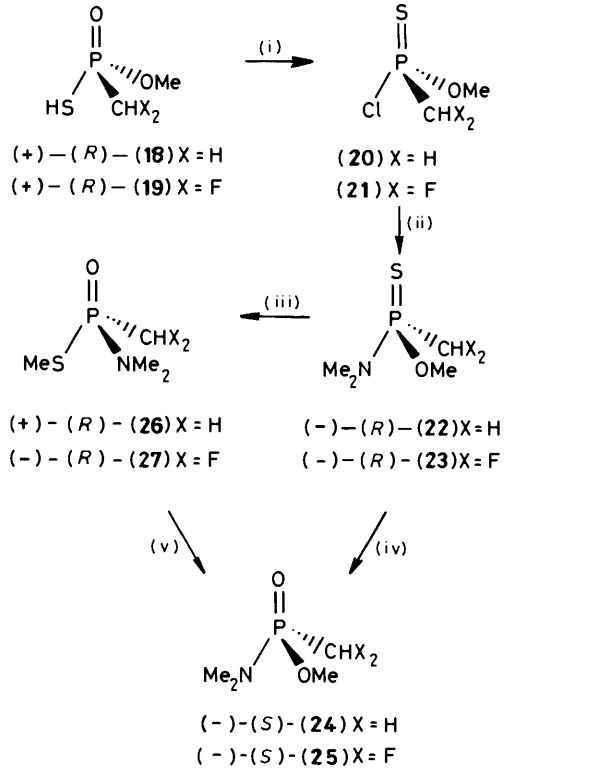
Treatment of the monofluoromethylphosphonothioate (+)-(*R*)-(**7**) with methoxide (0.1M) results in competitive reactions (Scheme 5). The major (80%) product results from P–S bond cleavage and is a 3:1 ratio of (+)-(*R*)-(**13**):(−)-(*S*)-(**13**). P–S Bond cleavage therefore occurs with *ca.* 75% inversion of configuration at phosphorus. The minor product (**16**) was not isolated as it reacted rapidly with more methoxide to give (**17**); however, the intermediacy of (**16**) was clearly demonstrated by ^{31}P n.m.r. spectroscopy. Generation of (**17**) by transesterification of (**13**) occurs at a significantly slower rate.



Scheme 5. *Reagent:* (i) MeO^-

When the base-catalysed methanolysis of (**5**) or (**7**) was carried out in fully deuteriated methanol there was no incorporation of deuterium into any of the phosphorus-containing reaction products (Schemes 4 and 5).

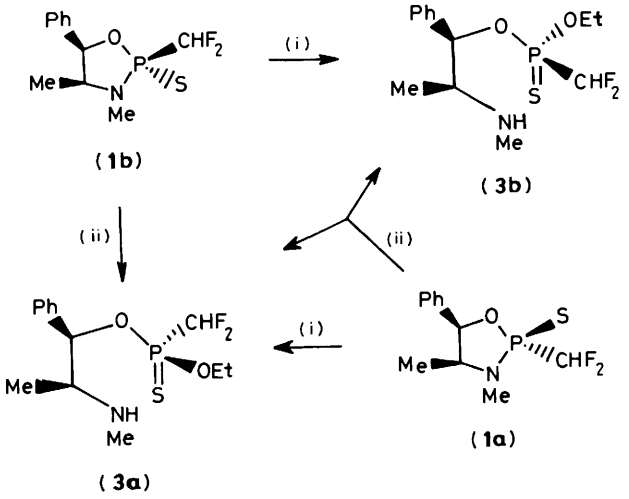
Treatment of the thioacids (+)-(*R*)-(**18**)[17] and (+)-(*R*)-(**19**) with freshly recrystallised PCl_5 gave the chloridates (**20**) and (**21**) which reacted with dimethylamine to give the amidates (**22**) and (**23**) (Scheme 6). Similar reactions have previously been shown to occur with inversion of configuration at phosphorus[18,19] and inversion is assumed for these steps in Scheme 6. Oxidation of (**22**) and (**23**) with *m*-chloroperbenzoic acid (*m*-CPBA) gave the phosphonamidates (**24**) and (**25**). ^1H N.m.r. spectroscopy in the presence of $Eu(hfc)_3$ showed that while (**25**) was essentially enantiomerically pure, (**24**) was a *ca.* 3:1 ratio of enantiomers. Treatment of (**22**) and (**23**) with methyl iodide resulted in the phosphonamidothioates (**26**) and (**27**). Compound (**27**) was enantiomerically pure while (**26**) was a *ca.* 3:1 ratio of enantiomers. Since both (**24**) and (**26**) are *ca.* 3:1 ratios of enantiomers it is likely that so also is (**22**). The loss in enantiomeric purity in the generation of (**22**) is most likely to occur at the chlorination step, although this was not established because P=S-containing esters do not co-ordinate sufficiently well to chiral heavy-metal shift reagents. Since the reaction with methyl iodide does not cleave any bonds to phosphorus and on the assumption that *m*-CPBA oxidation occurs with retention of configuration, the configurations of (**24**), (**25**), (**26**), and (**27**) have been assigned (Scheme 6).



Scheme 6. *Reagents:* (i) PCl_5; (ii) Me_2NH; (iii) MeI; (iv) *m*-CPBA; (v) MeO^-

The reaction between (**26**) (a 3:1 mixture) and sodium methoxide results in (**24**) as the same *ca.* 3:1 mixture of enantiomers as was generated directly from (**22**). The methoxide reaction is therefore approximately stereospecific and occurs with inversion of configuration. Treatment of (**27**) with methoxide gives (**25**) as a *ca.* 3:1 ratio of enantiomers, the major isomer being the same as that generated from (**23**). Since (**27**) was enantiomerically pure, P–S bond cleavage in this case has occurred with ⩾75% inversion of configuration. [It is possible that the configuration of some of the compounds in Scheme 6

has been incorrectly assigned. In particular there must be some doubt as to the stereochemistry of chlorination of (**19**) and the reaction of (**21**) with dimethylamine. It should, however, be noted that the conclusion regarding the stereochemistry of alkoxide-catalysed P–S bond cleavage in (**26**) and (**27**) is independent of the absolute configurations of (**22**) and (**23**) and depends only on the assignment of the stereochemical course of the MeI and *m*-CPBA reactions.]



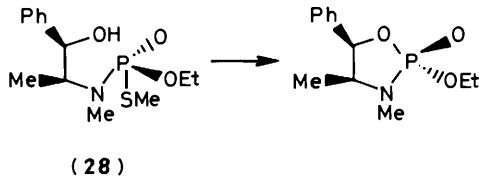
Scheme 7. *Reagents:* (i) H^+, EtOH; (ii) EtO^-

Treatment of the 1,3,2-oxazaphospholidine (**1b**) with ethoxide results in P–N bond cleavage to give (**3a**) (Scheme 7). This product has the opposite configuration at phosphorus to that formed when (**1b**) reacts with a dilute solution of anhydrous hydrogen chloride in ethanol, compound (**3b**). Whilst (**1a**) undergoes stereospecific acid-catalysed ethanolysis to give (**3a**), the base-catalysed reaction is not stereospecific and results in a mixture of (**3a**) and (**3b**). Similar results are obtained for the corresponding 2-dichloromethyl-1,3,2-oxazaphospholidines. In this instance it can be shown that it is the acid-catalysed reaction that occurs with inversion and the base-catalysed reaction with retention of configuration, by converting the initial products to *O*-alkyl *S*-alkyl dichloromethylphosphonothioates[14] and then hydrogenolysing these esters to the unsubstituted phosphonothioates of already established configuration.[14] By analogy, and on consideration of other results reported in this paper, the 2-difluoromethyl-1,3,2-oxazaphospholidines react in the same way.

Discussion

The results obtained for the stereochemical course of P–S bond cleavage by attack of methoxide at phosphorus are essentially the same in dialkyl fluoromethylphosphonothioates as in the corresponding chloromethyl analogues,[14] *i.e.* retention of configuration for the difluoro derivative and preponderant inversion of configuration plus competing P–O bond cleavage in the monofluoro derivatives. Thus analogous mechanisms are possible and these have been discussed previously.[14] However, because in the dichloro derivatives in $NaOCD_3$–CD_3OD deuterium exchange of the α-proton occurred more rapidly than P–S bond cleavage, it was not possible to exclude unequivocally substitution by an elimination–addition mechanism. In the difluoro derivative (**5**) no deuterium exchange of the α-proton occurred, thus excluding the possibility of substitution by the latter mechanism.

The influence of the difluoromethyl group depends on the nature of the other groups attached to phosphorus. For example (Scheme 6), transformation of the difluoro derivative (−)-(*R*)-(**27**) to (−)-(*S*)-(**25**) is less stereoselective (70% inversion) than the corresponding conversion of the methylphosphonamidate (+)-(*R*)-(**26**) into (−)-(*S*)-(**24**) which goes stereospecifically with inversion. In other words the stereochemistry is not changed completely from inversion to retention as it is when *O*-alkyl *S*-alkyl methylphosphonothioates are compared with the corresponding difluoro derivatives. A complete switch of stereochemistry would not have been unexpected if the analogy of phosphonothioates and phosphorothioates had been followed. Thus *O*-alkyl *S*-alkyl methylphosphonothioates and the corresponding phosphonamidothioates [*e.g.* (**26**)] undergo displacement of *S*-alkyl with inversion of configuration and *O*-alkyl *O*-alkyl *S*-alkyl phosphorothioates and at least one phosphoramidothioate[20] [(**28**), Scheme 8] lose *S*-alkyl with retention of configuration. Since this latter reaction is intramolecular, however, it may not be truly representative.



Scheme 8. *Reagent:* RO^-

Perhaps the most unexpected result was that in 0.1 M ethoxide the 2-difluoromethyl-1,3,2-oxazaphospholidine derivative (**1b**) derived from (−)-ephedrine undergoes P–N bond cleavage with retention of configuration. In all other ring-opening reactions of 1,3,2-oxazaphospholidines in base P–N bond cleavage, where it occurs, has been with inversion of configuration.[21] Mechanistically the options are (assuming apical attack to form a trigonal bipyramid) for initial attack opposite the endocyclic oxygen or for initial attack, despite the unfavourable ring strain, opposite the CHF_2 group. The latter form of attack seems most unlikely since even where chlorine is the exocyclic group it is displaced with retention of configuration following initial attack opposite an endocyclic heteroatom. Thus the probability is for attack opposite endocyclic oxygen. This raises the question why a CHF_2 group should switch the direction of nucleophilic attack from nitrogen to oxygen. There is obviously no simple answer since the reaction depends greatly on reaction conditions as is illustrated by the fact that increasing the ethoxide concentration or replacing (**1b**) with its phosphorus epimer (**1a**) results in P–N bond cleavage with mixed stereochemistry. Similar reactions have been observed with the dichloro analogues. It is reasonable to suggest as a consequence of these results that the dihalogenomethyl group does not have the highest apical potentiality in acyclic derivatives but simply has a strong influence on the apical potentiality of other groups. Leaving-group ability is not altered (^{31}P n.m.r. monitoring did not reveal any reaction intermediates).

Experimental

^1H N.m.r. spectra were recorded at 100 MHz (JEOL MH100) with deuteriochloroform as solvent and tetramethylsilane as internal standard. ^{31}P N.m.r. spectra were measured for the same solutions on a JEOL FY 40a instrument at 24.15 Hz and shifts are quoted in p.p.m. downfield from phosphoric acid. Enantiomeric purity was measured by ^1H n.m.r. spectroscopy at 60 MHz using the shift reagent $Eu(hfc)_3$; the guidelines for relating sense of magnetic non-equivalence to absolute

configuration used previously[16] did not give consistent results for chlorine[14] or the fluorine-containing derivatives. Most reactions were first monitored by ^{31}P n.m.r. spectroscopy in the appropriate solvent then products were isolated in reactions as described below. Column chromatography was performed over 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. Light petroleum refers to the fraction boiling in the range 60—80 °C.

Mono- and di-fluoromethylphosphonothioic dichlorides were prepared by converting diethyl mono- and di-fluoromethylphosphonates[4,8,22] into the diacids by acid hydrolysis,[12] followed by chlorination with phosphorus pentachloride[12] and oxygen–sulphur exchange using phosphorus pentasulphide.[23]

(2R,4S,5R)- *and* (2S,4S,5R)-2-*Fluoromethyl*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (**2a** *and* **b**).—A solution of fluoromethylphosphonothioic dichloride (4.4 g) in benzene (50 ml) was added slowly to a solution of (−)-ephedrine (4.4 g) and triethylamine (5.5 g) in benzene (100 ml). The mixture was stored overnight, filtered, and the filtrate was concentrated. Chromatography of the residue with light petroleum–ether (5:1) gave the *products* (**2a**) (1.8 g, 26%), m.p. 69 °C (from light petroleum); $[\alpha]_D$ −26° (*c* 1.0); δ_H 0.82 (d, *J* 6.4 Hz, CMe), 2.73 (d, *J* 11.7 Hz, NMe), 3.83 (m, 4-H), 4.79 (d, J_{HF} 46.5 Hz, CH_2F), 5.65 (dd, *J* 6.2 and 4.5 Hz, 5-H), and 7.32 (s, Ph); δ_P −91.3 p.p.m. (J_{PF} 56 Hz) (Found: C, 50.9; H, 5.9; N, 5.4. $C_{11}H_{15}FNOPS$ requires C, 50.9; H, 5.8; N, 5.4%) and (**2b**) (3.6 g, 52%), m.p. 97 °C (from light petroleum); $[\alpha]_D$ −157° (*c* 1.2); δ_H 0.79 (d, *J* 6.5 Hz, CMe), 2.84 (d, *J* 10.5 Hz, NMe), 3.71 (m, 4-H), 4.66 (ddd, $J_{HH'}$ 13.5, J_{PH} 3.4, and J_{FH} 46.8 Hz, CHF), 4.89 (ddd, $J_{PH'}$ 1.0 and $J_{FH'}$ 46.8 Hz, CH′F), 5.74 (d, *J* 6.2 Hz, 5-H), and 7.29 (s, Ph); δ_P −90.8 p.p.m. (J_{PF} 57.4 Hz) (Found: C, 50.6; H, 5.8; N, 5.5%).

(2R,4S,5R)- *and* (2S,4S,5R)-2-*Difluoromethyl*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholidine*-2-*thione* (**1a** *and* **b**).—The above procedure, but substituting difluoromethylphosphonothioic dichloride, gave *compound* (**1a**) (20%), m.p. 38 °C (from light petroleum; $[\alpha]_D$ −1.0° (*c* 0.9); δ_H 0.79 (d, *J* 6.5 Hz, CMe), 2.77 (d, *J* 11.3 Hz, NMe), 3.87 (m, 4-H), 5.65 (dd, *J* 6.0 and 4.5 Hz, 5-H), 5.97 (ddd, J_{HF} 51.0, $J_{HF'}$ 50.0, and J_{HP} 33.5 Hz, CHF_2), and 7.32 (s, Ph); δ_P (EtOH) −78.9 p.p.m. (dd, $J_{PF} = J_{PF'}$ = 83.0 Hz) (Found: C, 47.6; H, 5.1; N, 5.0. $C_{11}H_{14}F_2NOPS$ requires C, 47.6; H, 5.1; N, 5.0%) and *compound* (**1b**) (48%), m.p. 98 °C (from light petroleum); $[\alpha]_D$ −176° (*c* 1.6); δ_H 0.81 (d, *J* 6.5 Hz, CMe), 2.90 (d, *J* 10.0 Hz, NMe), 3.75 (m, 4-H), 5.78 (d, *J* 6.2 Hz, 5-H), 6.02 (ddd, J_{HF} 51.5, $J_{HF'}$ 50.0, and J_{PH} 34.5, CHF_2), and 7.32 (m, Ph); δ_P (EtOH) −78.8 p.p.m. (dd, J_{PF} 85.5 and $J_{PF'}$ 89.1 Hz) (Found: C, 47.8; H, 5.0; N, 4.9%).

Acid-catalysed Ethanolysis of the 1,3,2-*Oxazaphospholidines* (**1a** *and* **b**) *and* (**2a** *and* **b**).—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 benzene. Compound (**2a**) gave a quantitative yield of *compound* (**4a**), m.p. 125 °C, $[\alpha]_D$ −57° (*c* 0.8); δ_H 1.27 (d, *J* 6.7 Hz, CMe), 1.29 (t, *J* 7.0 Hz, CH_2Me), 2.78 (s, NMe), 3.60 (m, 4-H), 4.20 (m, OCH_2), 4.50 (ddd, $J_{HH'}$ 12.8, J_{HF} 45.6, and J_{HP} 0.9 Hz, CHF), 4.64 (dd, $J_{H'F}$ 45.6 and $J_{H'P}$ 0 Hz, CH′F), 5.92 (dd, *J* 11.0 and 3.4 Hz, 5-H), and 7.38 (m, Ph) (Found: C, 45.8; H, 6.4; N, 4.1. $C_{13}H_{22}ClFNO_2PS$ requires C, 45.7; H, 6.5; N, 4.1%). Similarly, compound (**2b**) gave the product (**4b**), $[\alpha]_D$ −99.3 (*c* 0.7); δ_H 0.93 (t, CH_2Me), 1.26 (d, *J* 6.6 Hz, CMe), 2.82 (s, NMe), 3.57 (m, OCH_2), 3.91 (m, 4-H), 5.10 (dd, $J_{HH'}$ 12.2, J_{HF} 45.2, and J_{HP} O Hz, CHF), 5.22 (ddd, $J_{H'F}$ 45.2, $J_{H'P}$, 3.0, CH′F), 6.04 (dd, *J* 10.6 and 3.0 Hz, 5-H), and 7.41 (s, Ph). Compound (**1a**) gave *compound* (**3a**), m.p. 107—109 °C; $[\alpha]_D$ −71° (*c* 1.0); δ_H 1.29 (t, *J* 7.0 Hz, CH_2Me), 1.45 (d, *J* 6.7 Hz, CMe), 2.77 (s, NMe), 6.00 (dt, J_{HF} 50 and J_{HP} 33 Hz, CHF_2), 6.19 (dd, *J* 11.0 and 3.0 Hz, 5-H), and 7.40 (m, Ph) (Found: C, 43.7; H, 6.0; N, 4.1. $C_{13}H_{21}ClF_2NO_2PS$ requires C, 43.4; H, 5.9; N, 3.9%). Similarly, compound (**1b**) gave the *product* (**3b**), m.p. 128 °C; $[\alpha]_D$ −84° (*c* 1.0); δ_H 1.01 (t, *J* 7.2 Hz, CH_2Me), 1.41 (d, *J* 6.6 Hz, CMe), 2.83 (s, NMe), 6.19 (dd, *J* 9.8 and 2.2 Hz, 5-H), 6.72 (dt, J_{HF} 48 and J_{HP} 32.5 Hz, CHF_2), and 7.39 (m, Ph) (Found: C, 43.6; H, 5.9; N, 3.9%).

O-*Ethyl* S-*Methyl* (+)-(R)-*Fluoromethylphosphonothioate* (**7**).—A solution of sodium (0.15 g) in methanol (15 ml) was slowly added to a solution of (**4b**) (1 g) in methanol (5 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. On addition of dicyclohexylamine (0.5 g), O-*ethyl hydrogen* (+)-(R)-*fluoromethylphosphonothioate* crystallised from solution as its *dicyclohexylamine salt* (0.55 g, 42%), m.p. 135—136 °C (from light petroleum); $[\alpha]_D$ +11.2° (*c* 1.7) (Found: C, 53.0; H, 9.1; N, 4.1. $C_{15}H_{31}FNO_2PS$ requires C, 53.1; H, 9.2; N, 4.1%). A solution of this salt in benzene and an excess of methyl iodide was boiled under reflux for 1 h, allowed to cool, washed with water, and concentrated. The residue was distilled, b.p. 110 °C (bath) at 40 mmHg, to give (+)-(*R*)-(**7**) (0.22 g, 88%), $[\alpha]_D$ +74° (*c* 1.6); δ_H 1.39 (t, CH_2Me), 2.36 (dd, J_{PH} 12.8 and J_{FH} 0.7 Hz, SMe), 4.24 (m, CH_2Me), and 4.76 (dd, J_{FH} 46.0 and J_{PH} 2.1 Hz, CH_2F); δ_P −45.5 p.p.m. (d, J_{PF} 66 Hz).

In a similar manner the appropriate precursors gave O-*ethyl hydrogen* (+)-(R)-*difluoromethylphosphonothioate dicyclohexylamine salt*, m.p. 160 °C (from light petroleum); $[\alpha]_D$ +3.4° (*c* 0.6) (Found: C, 50.3; H, 8.3; N, 4.1. $C_{15}H_{30}F_2NO_2PS$ requires C, 50.4; H, 8.5; N, 3.9%) which on *S*-methylation gave (+)-(*R*)-(**5**), $[\alpha]_D$ +55.5° (*c* 1.5); δ_H 1.40 (t, CH_2Me), 2.42 (d, *J* 13.0 Hz, SMe), 4.28 (m, CH_2Me), and 5.90 (dt, J_{FH} 48 and J_{PH} 28 Hz, CHF_2). Addition of Eu(hfc)$_3$ and racemic ester showed that both the SMe and CH_2Me groups resonate at high field in (+)-(*R*)-(**5**) compared with (−)-(*S*)-(**5**); also obtained was O-*methyl hydrogen difluoromethylphosphonothioate* (**19**) as its *dicyclohexylamine salt*, m.p. 173 °C (from light petroleum–benzene); $[\alpha]_D$ +2.2° (*c* 0.5) (Found: C, 49.1; H, 8.3; N, 4.2. $C_{14}H_{28}F_2NO_2PS$ requires C, 49.0; H, 8.2; N, 4.1%).

Diethyl Fluoromethylphosphonate (**9**).—A mixture of diethyl chlorofluoromethylphosphonate[10] (**8**) (25 g) (prepared from sodium diethyl phosphite and dichlorofluoromethane[8,22]), triethylamine (20 ml), Raney nickel (5 g), ethanol (100 ml), and water (100 ml) was stirred under hydrogen for 30 h, then filtered, and the filtrate was washed with chloroform. The chloroform layer was concentrated. Chromatography of the residue with benzene–acetone (3:1) gave *compound* (**9**) (9 g, 43%), δ_H 1.36 (t, CH_2Me), 4.20 (m, CH_2Me) and 4.68 (dd, J_{FH} 45.6 and J_{PH} 4.8 Hz, CH_2F); δ_P −17.16 p.p.m. (d, J_{PF} 62.3 Hz), and diethyl methylphosphonate (**10**) (6 g, 32%).

Fluorination of Ethyl Methyl (+)-(R)-*Methylphosphonate* (**11**).—A solution of n-butyl-lithium (1.6M; 8.8 ml) in hexane was added slowly to a solution of (+)-(*R*)-(**11**) (2 g) in toluene (40 ml) at −78 °C. After 10 min an excess of fluorine perchlorate was bubbled into the mixture. After a further 30 min the solution was degassed with nitrogen, allowed to warm to room temperature, and concentrated. Chromatography of the residue with benzene–acetone (7:3) gave the difluoromethylphosphonate (+)-(*R*)-(**12**) (0.16 g, 7%), $[\alpha]_D$ +1.2° (*c* 1.7); δ_H 1.40 (t, CH_2Me), 3.88 (d, *J* 10.6 Hz, OMe), 4.29 (m, CH_2Me), and 5.97 (dt, J_{FH} 49 and J_{PH} 26 Hz, CHF_2); δ_P −5.6

p.p.m. (t, J_{PF} 92 Hz). Addition of $Eu(hfc)_3$ and racemic ester showed that in (+)-(*R*)-(**12**) the OMe resonate at low field and the CH_2Me at high field when compared with (−)-(*S*)-(**12**); further chromatography gave the fluoromethylphosphonate (+)-(*R*)-(**13**) (0.71 g, 28%), $[\alpha]_D$ +2.3° (*c* 1.3); δ_H 1.35 (t, CH_2Me), 3.82 (d, *J* 10.7 Hz, OMe), 4.19 (m, CH_2Me), and 4.67 (dd, J_{FH} 45.5 and J_{PH} 4.7 Hz, CH_2F); δ_P −18.0 p.p.m. (d, J_{PF} 62.3 Hz). Addition of $Eu(hfc)_3$ and racemic ester showed that in (+)-(*R*)-(**13**) the OMe resonate at high field when compared with (−)-(*S*)-(**13**).

O-*Methyl* (−)-(R)-N,N-*Dimethyl*-P-*methylphosphonamidothioate* (**22**).—Freshly crystallised phosphorus pentachloride (5 g) was added in portions to an ice-cooled solution of *O*-methyl hydrogen (+)-(*R*)-methylphosphonothioate[17] (**18**) (3 g) in carbon tetrachloride (25 ml). After the addition was complete the mixture was allowed to warm to room temperature and the solvent and $POCl_3$ were removed under reduced pressure. The residue was dissolved in cold benzene (35 ml) and an excess of dimethylamine was added. After 1 h the mixture was filtered, then concentrated. Chromatography of the residue with light petroleum–ether (9:1) gave (−)-(*R*)-(**22**) (2 g, 63%), $[\alpha]_D$ −42.0° (*c* 0.7), probably as a 3:1 mixture of *R*:*S* enantiomers (see below).

A similar procedure starting with the *O*-methyl hydrogen (+)-(*R*)-difluoromethylphosphonothioate (**19**) gave (−)-(*R*)-(**23**) (42%), $[\alpha]_D$ −81.5° (*c* 1.5); δ_H 2.86 (d, *J* 9.8 Hz, NMe_2), 3.70 (d, *J* 12.8 Hz, OMe), and 5.89 (dt, J_{PH} 30 and J_{FH} 50 Hz, CHF_2); δ_P −72.9 p.p.m. (dd, J_{PF} 80.6 and J_{PF}, 89.1 Hz).

O-*Methyl* (−)-(S)-NN-*Dimethyl*-P-*methylphosphonamidate* (**24**).—*m*-Chloroperbenzoic acid (1.2 g) was added in portions to an ice-cooled solution of (−)-(*R*)-(**22**) (1 g) in methylene dichloride (30 ml). After 15 min the mixture was filtered and the solution washed with dil. aqueous sodium carbonate. Concentration of the organic layer and chromatography of the residue with benzene–acetone–methanol (8:1:1) gave (−)-(*S*)-(**24**) (0.35 g, 39%), $[\alpha]_D$ −27.2° (*c* 0.1). The ^1H n.m.r. spectrum in the presence of $Eu(hfc)_3$ showed that this sample was a 3:1 ratio of *S*:*R* enantiomers. The NMe_2 and OMe signals due to the (−)-(*S*) enantiomer resonated at high field, and the PMe signal at low field, relative to the corresponding signals in the (+)-(*R*) enantiomer.

A similar procedure starting with (−)-(*R*)-(**23**) gave (−)-(*S*)-(**25**) (45%), $[\alpha]_D$ −35° (*c* 2.4); δ_H 2.80 (d, *J* 9 Hz, NMe_2), 3.77 (d, *J* 10.5 Hz, OMe), and 5.90 (dt, J_{PH} 26 and J_{FH} 48 Hz, CHF_2). Addition of $Eu(hfc)_3$ and racemic ester showed that in (−)-(*S*)-(**25**) both the NMe_2 and OMe signals resonate at low field when compared with those in the (+)-(*R*) enantiomer.

S-*Methyl* (+)-(R)-NN-*Dimethyl*-P-*methylphosphonamidothioate* (**26**).—A solution of (−)-(*R*)-(**22**) (3 g) in methyl iodide (25 ml) was heated in a sealed tube at 110 °C for 10 h, then was cooled and concentrated. Chromatography of the residue with benzene–acetone–methanol (16:3:1) gave (+)-(*R*)-(**26**) (1.7 g, 57%), $[\alpha]_D$ +23.2° (*c* 0.9). The ^1H n.m.r. spectrum in the presence of $Eu(hfc)_3$ showed that this sample was a 3:1 ratio of *R*:*S* enantiomers. Both the NMe_2 and PMe signals in the (+)-(*R*) enantiomer resonate at high field relative to those in the (−)-(*S*) enantiomer.

A similar procedure starting with (−)-(*R*)-(**23**) gave (−)-(*R*)-(**27**) (25%), $[\alpha]_D$ −1.2° (*c* 1.0); δ_H 2.38 (d, *J* 12.2 Hz, SMe), 2.82 (d, *J* 10 Hz NMe_2), and 5.98 (dt, J_{PH} 32 and J_{FH} 44 Hz, CHF_2). Addition of $Eu(hfc)_3$ and racemic ester showed that in (−)-(*R*)-(**27**) both the NMe_2 and SMe signals resonate at low field when compared with those in the (+)-(*S*) enantiomer.

Base-catalysed Methanolyses.—General procedure. A solution of the appropriate precursor (0.1 g) in methanol (6 ml) was mixed rapidly with a solution (0.4M) of sodium in methanol (2 ml). When the yield of the primary product(s) was judged (^{31}P n.m.r.) to be at a maximum (0.5—15 min) the mixture was poured into water and extracted with chloroform. Concentration of the organic layer and chromatography of the residue with benzene–acetone–methanol (8:1:1) gave the product. Thus, (+)-(*R*)-(**5**) gave (−)-(*S*)-(**12**) (80%), $[\alpha]_D$ −1.3° (*c* 1.7); (+)-(*R*)-(**7**) gave (+)-(*R*)-(**13**) (80%). The ^1H n.m.r. spectrum in the presence of $Eu(hfc)_3$ showed that this sample was a 3:1 mixture of *R*:*S* enantiomers; (−)-(*R*)-(**27**) gave (−)-(*S*)-(**25**) (70%) as a 3:1 ratio of *S*:*R* enantiomers; (+)-(*R*)-(**26**) (3:1 *R*:*S*) gave (−)-(*S*)-(**24**) (81%), $[\alpha]_D$ −26.3° as a 3:1 ratio of *S*:*R* enantiomers; (**1b**) with ethoxide gave (**3a**) (98%) and (**1a**) gave a 1:1 mixture of (**3a**):(**3b**).

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