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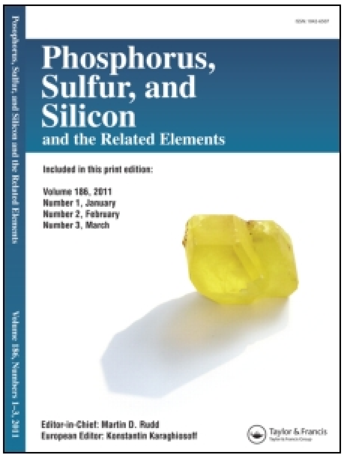

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ASYMMETRIC TETRACOORDINATE PENTACOVALENT ORGANOPHOSPHORUS COMPOUNDS: THEIR RESOLUTION AND DETERMINATION OF ENANTIOMERIC PURITY

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ASYMMETRIC TETRACOORDINATE PENTACOVALENT ORGANOPHOSPHORUS COMPOUNDS: THEIR RESOLUTION AND DETERMINATION OF ENANTIOMERIC PURITY

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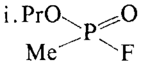
INTRODUCTION

During the last twenty to thirty years there has been considerable interest in the preparation of completely resolved enantiomers of tetracoordinate pentacovalent organophosphorus compounds. This has arisen for three main reasons:

1) The fundamental chemical challenge of preparing enantiomers.

2) Because such enantiomers are essential for many of the mechanistic studies which have contributed to, and will be necessary to validate or otherwise, present ideas about the stereochemical events that occur during reactions of phosphorus.

3) The realization that the interaction of chiral organophosphorus compounds with biological material can be highly stereospecific. For example: the enzyme acetyl cholinesterase is inhibited *in vitro* by the (–)-(S) enantiomer of sarin (**1**) approximately 4200 times faster than by the (+)-(R) enantiomer,[1] the enantiomers of DMPA (**2**) exhibit differences in their phytotoxicities,[2] and the (–) enantiomer of the antitumour agent cyclophosphamide (**3**) is more efficacious against ADJ/PC6 plasma cell tumours in mice and less readily metabolized in human patients than the (+)-enantiomer.[3]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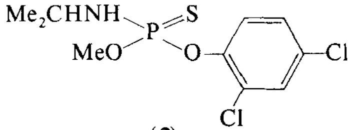
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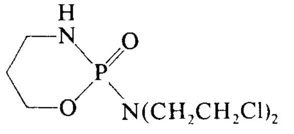
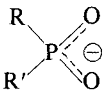

(**3**)

The purpose of this review is to describe recent advances in methods for the preparation of pairs of enantiomers of tetracoordinate pentacovalent organophosphorus compounds and to discuss methods by which their enantiomeric purity may be measured. Classical methods of resolving organophosphorus compounds have been described in detail previously[4–10] and are only mentioned here as background and to enable comparison of the advantages and disadvantages of all the existing methods to be made.

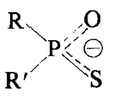
The first successful attempts to obtain optically active compounds containing asymmetric phosphorus atoms were made at the beginning of this century by Meisenheimer and Lichtenstadt[11] who partially resolved ethylmethylphenylphosphine oxide. It was not, however, until the last thirty years that much more significant progress was made. In common with the resolution of other asymmetric centres the method most frequently used in organophosphorus chemistry is the fractional crystallization of diastereomeric isomers. In the case of tetracoordinate pentacovalent compounds, two general classes or types of diastereomeric isomers have successfully been employed: the diastereomeric salt and the covalently bonded diastereomer. These will be considered separately.

DIASTEREOMERIC SALTS

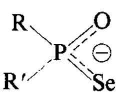
The lack of success of many of the early attempts to resolve various phosphorus based acids was explained by Ephraim[12] who demonstrated that anions such as (**4**) are in fact symmetrical. The diastereomeric salt technique has therefore been essentially limited to the phosphorus acids whose anions are asymmetrical, i.e. the mono-thio and seleno acid anions (**5**) and (**6**). Fortunately, however, these are perhaps the most important compounds in the study of four coordinate phosphorus stereochemistry. This importance stems from their high reactivity and the ambident nature of their anions, which can react either via the sulphur (selenium) or the oxygen.



(**4**)



(**5**)



(**6**)

In 1956 Aaron and Miller[13] succeeded in separating the enantiomers of the first phosphorus thioacid. This was O-ethyl ethylphosphonothioic acid which they resolved by the fractional crystallization of its salts with the alkaloids quinine and brucine. The process was, however, somewhat tedious and over the next few years several improvements in practical procedure were made, although repeated crystallization of thioacid–alkaloid salts was still necessary.[14–16] The route has been found to be applicable to a number of phosphono thioacids[15] although quinine could not be used as resolving base for all thioacids investigated because in some instances only one isomer was obtained with a satisfactory specific rotation.[14, 15] The numbers of phosphino and phosphoro thioacids so far resolved by this route is severely limited (Table I). Perhaps the major advance in this line of research was made in 1967 by Boter and Platenburg[17] who substituted the previously used alkaloids with both optical isomers of α-phenylethylamine. This amine was initially easily resolved itself using D-(+)-tartaric acid[18] and is now readily commercially available. Phosphonothioacid resolutions were generally carried out in dry ether. In

TABLE I

Phosphorus thio and selenoacids resolved by fractional crystallization of diastereomeric salts

R^1	R^2	X	Resolving agent	$[\alpha]_D$ (°)		References
				(+)	(−)	
C_2H_5	C_6H_5	S	Quinine	6.5	6.5[a]	20
CH_3	C_6H_5	S	Quinine	9.25	9.2[a]	21
t-C_4H_9	C_6H_5	S	Quinine	21.4	21.4[b]	22
α-$C_{10}H_7$	C_6H_5	S	Quinine	63.8	64.6[a]	23
t-C_4H_9	C_6H_5	Se	α-Phenylethylamine	25.6	30.0[b]	24
C_2H_5	OC_2H_5	S	Quinine	6.9	7.1[a]	14
CH_3	OCH_3	S	α-Phenylethylamine	6.4	6.4[a]	17
CH_3	OC_2H_5	S	α-Phenylethylamine	8.5	8.5[a]	17
CH_3	OC_3H_7(i)	S	α-Phenylethylamine	7.8	7.7[a]	17
C_2H_5	OCH_3	S	Quinine	4.1	7.0[a]	15
i-C_3H_7	OC_2H_5	S	Quinine	6.5	7.0[a]	15
CH_3	OC_4H_9(*n*)	S	α-Phenylethylamine	7.2	7.2[a]	17
t-C_4H_9	OMe	S	α-Phenylethylamine	13.2	10.5[b]	25
i-C_3H_7	OMe	S	α-Phenylethylamine	4.6	4.2[a]	26
CH_3	OC_3H_7(*n*)	S	α-Phenylethylamine	1.3	1.1[b]	19
CH_3	OC_5H_9(cyclo)	S	α-Phenylethylamine	11.2[d]	11.4[e]	27
CH_3	OC_2H_5	Se	α-Phenylethylamine		16.4[e]	27
C_2H_5	OC_2H_5	Se	Brucine	11.4	17.5[b]	28
n-C_4H_9O	OC_2H_5	S	Cinchonidine	1.0	1.3[f]	29
C_2H_5O	OC_3H_7(i)	S	Quinine	2.1	2.0[f]	29
α-$C_{10}H_7O$	OCH_3	S	(−)-Ephedrine	53.6	57.1[b]	30, 31
CH_3O	SCH_3	S	Strychnine	27.1	27.9[b]	32
CH_3O	NHC_6H_{11}	S	Quinine	38.0	37.0[b]	33
CH_3O	NC_4H_8O	S	Quinine	2.9[g]		34
2,4-$Cl_2C_6H_3O$	NHC_3H_7(i)	S	Quinine	15.9	23.4[g]	35
MeO	$OC_6H_4NO_2$-p	S	Strychnine	18.9	17.4[c]	36

[a] Dicyclohexylamine salt.
[b] Free acid.
[c] Lead salt.
[d] (+)-α-Phenylethylamine salt.
[e] (−)-α-Phenylethylamine salt.
[f] S-methyl ester.
[g] Ammonium salt.

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this solvent (+)-α-phenylethylamine was added to racemic thioacid on a 0.5 : 1 molar basis. In all cases the (+)-acid formed the less soluble salt which was filtered off after crystallization. Since separation of the (+)(+) salt was not quantitative, the remaining (+)-α-phenylethylamine was removed by treatment of the concentrated filtrate with aqueous sodium hydroxide solution, followed by extraction. Subsequent treatment with 0.5 mole equivalents of (—)-α-phenylethylamine resulted in the (—)(—) salt. Until recently this procedure was the most commonly used and general route available; however, as with all methods of its type it suffers from several drawbacks:

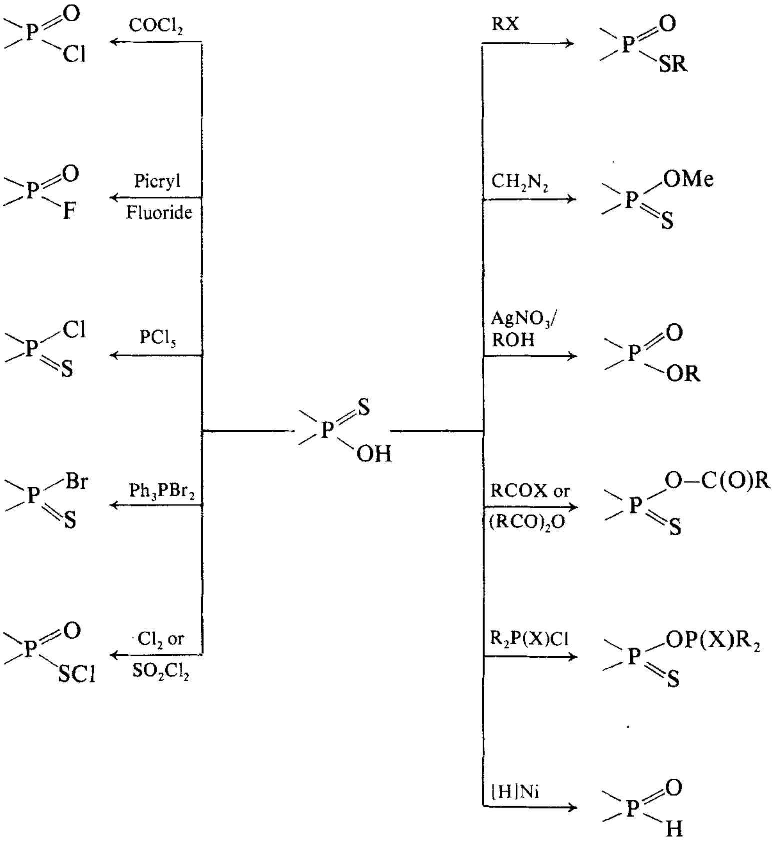
1) The number of asymmetric organophosphorus substrates that form separable crystalline derivatives with α-phenylethylamine is very limited. This is often the case even within a closely related series of compounds.

2) The procedure is often very time consuming. Replacement of alkaloids by α-phenylethylamine has partially overcome this problem since, in several instances, single recrystallization of the salts from ethyl acetate[17] is sufficient to yield products with a constant specific rotation. This is, however, not always the case.[17,19]

3) Preparation of the required racemic thioacids is often not simply achieved.

4) The route gives no information on the absolute stereochemistry of the products.

Most of the phosphorus acids that have been resolved by crystallization of diastereomeric salts are recorded along with their specific rotations and the resolving agent used in Table I. A number of the more important reactions of monothioacids are outlined in *Scheme 1.* The majority are, under suitably controlled conditions, highly stereoselective. Phosphorus thioacids therefore, once resolved, can give rise to a wide range of chiral derivatives.



SCHEME 1[4-10]

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COVALENTLY BONDED ACYCLIC DIASTEREOMERIC ISOMERS

Chiral phosphine oxides have been prepared by a number of indirect routes involving chemical transformations of previously resolved compounds such as quaternary phosphonium salts. For example (Scheme 2) base catalysed hydrolysis of some phosphonium salts occurs with inversion of configuration at phosphorus to form chiral phosphine oxides;[37] the Wittig reaction likewise generates chiral phosphine oxides, but with retention of configuration;[37] some phosphonium salts can be cathodically reduced to chiral phosphines which can then be oxidized.[38] These routes are limited in scope because each reaction must involve at least predominant cleavage of only one of the groups (e.g. R^4) from the phosphonium salt and even when this condition is satisfied the reactions are not always stereospecific.[39]

$$\begin{tikzcd}
\overset{\oplus\ominus}{R^1R^2R^3R^4PX} \arrow[rr, bend left, "NaOH"] \arrow[rr, "nBuLi", "R_2C{=}O"'] \arrow[dr, "2e\ H^+"'] & & R^1R^2R^3P{=}O \\
& R^1R^2R^3P: \arrow[ur, "{[O]}"'] &
\end{tikzcd}$$

SCHEME 2

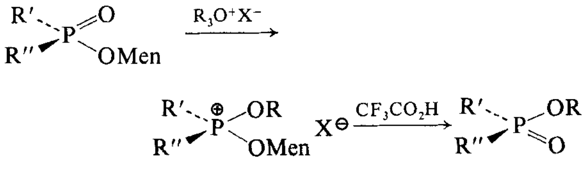
The "simple" covalently bonded diastereomer has probably found its most important role in the direct resolution of phosphine oxides. The route, which was adapted by Mislow[40] from an earlier synthesis of chiral sulphoxides,[41] involves reacting asymmetrical phosphinyl chlorides with (−)-menthol in the presence of pyridine and fractional crystallization of the resulting menthyl phosphinates. Treatment of single diastereomers with alkyl or aryl Grignard reagents leads to phosphine oxides formed with inversion of configuration (Scheme 3). The route is fairly general in its application but it is limited, not only by the recurring need for simply separated diastereomers, but also by the extreme sensitivity of the reaction to the nature of the groups both on phosphorus and the Grignard reagent.

$$R^1R^2P(O)Cl \xrightarrow[\text{pyridine}]{(-)\text{-menthol}}$$

$$R^1R^2P(O)OMen. \xrightarrow{R^3MgX} R^1R^2R^3P{=}O$$

SCHEME 3

De Bruin[42] has developed a convenient method for converting menthyl phosphinates to the more simply substituted alkyl phosphinates whose only chiral centre is at phosphorus. The procedure involves initial alkylation, which occurs on the phosphoryl oxygen, followed by solvolysis of the menthyl group using trifluoroacetic acid (Scheme 4). The conversion involves formal inversion of configuration at phosphorus.



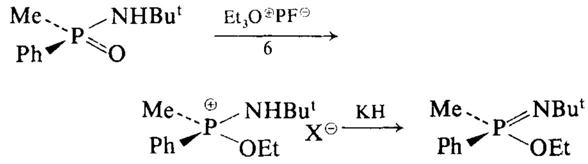
SCHEME 4

Cram[43] has treated both menthyl phosphinates and their cholesteryl analogues with lithium amine salts to generate chiral phosphinamidates. Again the displacement occurs with predominant inversion of configuration (Scheme 5). Phosphinamidates that retain a proton on nitrogen can be converted into chiral phosphinimidates by alkylation on oxygen followed by treatment with potassium hydride (Scheme 6).[44]

$$R^1R^2P(O)OR^3 \xrightarrow{LiNR_2} R^1R^2P(O)NR_2$$

R^3 = (−)-menthyl or cholesteryl

SCHEME 5



SCHEME 6

A recent application of the simple covalent diastereomer provides a practical method for the preparation of chiral dialkyl phenyl phosphates[45] and alkyl phenyl phosphonates.[46]. The route, outlined in Scheme 7 for dialkyl phenyl phosphate, involves the separation by fractional crystallization of the phosphoramidates formed, from the reaction of phenyl phosphoryldichloride and the ethyl ester of L-proline followed by displacement of chloride by alcohol, then their acid catalysed alcoholysis. At present the sequence is limited to phenyl containing phosphates and phosphonates. It is also probable

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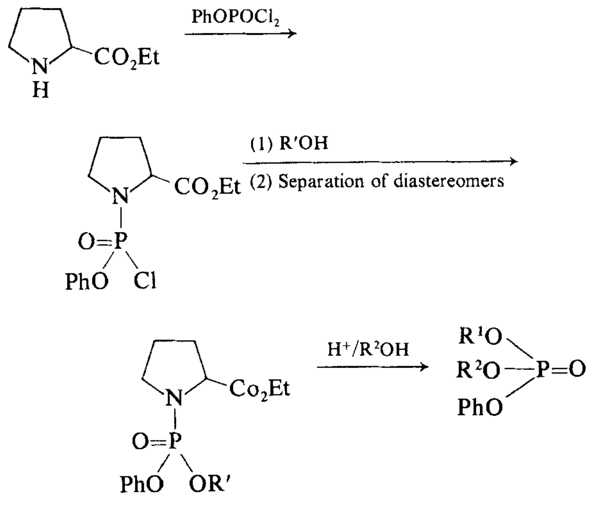
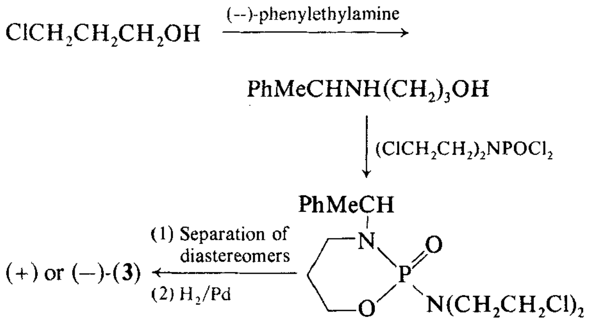


SCHEME 7

that the acid catalysed P–N cleavage step is only stereospecific in the case of simple primary alcohols since nucleophilic competition between more complex alcohols and the acid anion, leading to a loss in stereospecificity, has been shown to be of importance in several related cases.[27,47–49] This synthetic sequence has yet, however, to be fully exploited.

α-Phenylethylamine also finds a use in this category of diastereomers. For example, in the specialized but significant resolution of cyclophosphamide outlined in Scheme 8. Resolution is achieved by fractional crystallization of the cyclic diastereomers of (**7**); ethylbenzene being then removed by catalytic hydrogenation.[50] A similar approach involving coordination of (+)-α-NpPhMeSiCl to the oxazaphosphorinane nitrogen has been successfully adopted by Verkade and his co-workers.[51]



(**7**)

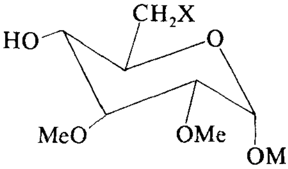
SCHEME 8

COVALENTLY BONDED CYCLIC DIASTEREOMERIC ISOMERS

One of the major disadvantages of any resolution involving the fractional crystallization of diastereomeric isomers is the fact that the difference in physical properties between them is often only very small, thus increasing the difficulty of the separation. The degree of difference in physical properties between geometrical isomers, however, is generally much larger and separation by chromatographic techniques is usually facile. The construction of phosphorus-containing geometrical isomers that are also dia or polystereomers and which are easily separated, has been successfully accomplished by forming cyclic adducts with suitably substituted bifunctional carbohydrates or with the sympathomimetic amines (−)-ephedrine [(1R,2S)-2-methylamino-1-phenylpropan-1-ol] and its isomer (+)-pseudoephedrine [(1S,2S)-2-methylamino-1-phenylpropan-1-ol]. In both cases the two possible geometrical isomers coincide with the two optical isomers at phosphorus (e.g. (**9** ax) and (**9** eq), and (**27a**) and (**27b**)).

Carbohydrates

The use of carbohydrates for the stereoselective synthesis of non-carbohydrate compounds has been reviewed.[52] Their use in the synthesis of non-carbohydrate chiral organophosphorus compounds is demonstrated by the following examples.



(**8**) X = OH
(**11**) X = NHMe

Treatment of the diol (**8**) with methylphosphonic difluoride in the presence of triethylamine afforded the crystalline (R) and (S)-4,6-methylphosphonates (**9** ax) and (**9** eq) which were simply separated by chromatography or crystallization. Compound (**9** ax) was converted into the (S)-4-methylphenylphosphinate (**10**) by heating with phenylmagnesium bromide. Compound (**10**) underwent further reaction when treated under reflux with ethyl magnesium bromide for two days to afford (−)-(S)-ethylmethylphenylphosphine oxide. Similarly (**9** eq) was converted into (+)-(R)-ethylmethylphenylphosphine oxide.[53] Although this particular route is not perhaps the most conventient synthesis of chiral phosphine oxides, it suffers from the same limitations as Mislow's[40] Grignard displacements from menthyl

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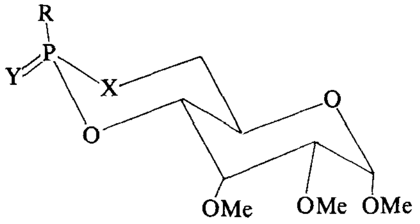
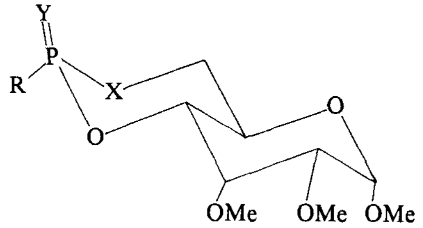
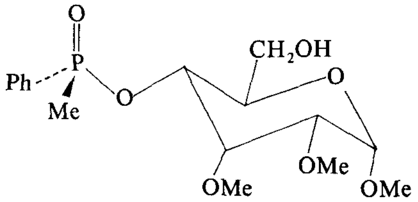


ax



eq

	R	X	Y
(**9**)	Me	O	O
(**12**)	Me	NMe	S
(**13**)	Me	NMe	S
(**14**)	Cl	NMe	O
(**15**)	Cl	NMe	S
(**16**)	OMe	NMe	O
(**17**)	OEt	NMe	O
(**18**)	OPr^n	NMe	O
(**19**)	OMe	NMe	S
(**20**)	OPr^i	NMe	S



(**10**)

phosphinates, it does, however, have a number of important advantages:

1) The relative ease of obtaining pure single isomers of the starting materials.

2) Enantiomeric phosphine oxides can be obtained from the same cyclic precursor by reversing the order of addition of the Grignard reagents.

3) Some conclusions about the absolute configuration of the products can be made[53] because the defined absolute configuration of the carbohydrate portions of the 1,3,2-oxazaphosphorinanes makes it possible to assign the absolute configuration of the phosphorus atom in these molecules. A wide range of physical techniques have been brought to bear in establishing the relationship between the stereochemistry at phosphorus and the variably substituted carbon atoms. For example, nmr and ir spectroscopy, X-ray crystallography, and dipole moment measurements have all been used in conformational and configurational studies.[53] Once the configuration at phosphorus in the cyclic precursors is established, it is possible to make reasonable assumptions about the stereochemical course of the bond cleavage reactions and hence to define the absolute configuration of phosphorus in the acyclic products, e.g. it is probable that both P—O bond cleavage by Grignard reagents in (**9**) and (**10**) occurs with inversion of configuration. This assumption is consistent with the results of experiments in which chiral phosphine oxides of already established configuration were prepared.[53]

A more versatile and practically useful carbohydrate precursor is the amino-sugar (**11**). This was prepared in good yield from the diol (**8**) by successive treatment with *p*-toluene sulphonyl chloride and methylamine.[54] The glucopyranose (R)-4(O),6(N)-NP-dimethylphosphoramidate (**12** ax) was obtained as the major product when (**11**) was treated with methylphosphonic dichloride and triethylamine for a short period.[54] The derivative (**12** ax) was separated from the small amounts of its epimer (**12** eq) by a single crystallization. Similarly, treatment of (**11**) with methylphosphonothioic dichloride gave *ca.* 5:1 ratio of (**13** ax) to (**13** eq) which were separated by simple chromatography and the chloridates (**14** ax) and (**15** ax) were prepared as the only tetrahydro-1,3,2-oxazaphosphorinane products when (**11**) was treated with phosphoric and phosphorothiotic trichloride respectively. Displacement of chloride by alkoxide from both (**14** ax) and (**15** ax) occurs with inversion of configuration giving rise to the single isomers (**16** eq), (**17** eq), (**18** eq), (**19** eq) and (**20** eq). Treatment of single isomers such as (**12** ax), (**18** eq) or (**20** eq) with hot solutions of sodium alkoxides usually led to P—O bond cleavage resulting in the 6-substituted sugars (**21**), (**22**) and (**23**). These, after acetylation of the free 4-hydroxy groups were treated with a solution of hydrogen chloride in either water or methanol. This resulted in P—N bond cleavage and formation of chiral phosphonate (**24**), phosphate (**25**) or phosphorothioacid (which for convenience was isolated as the S-alkyl ester (**26**))[55] (Scheme 9).

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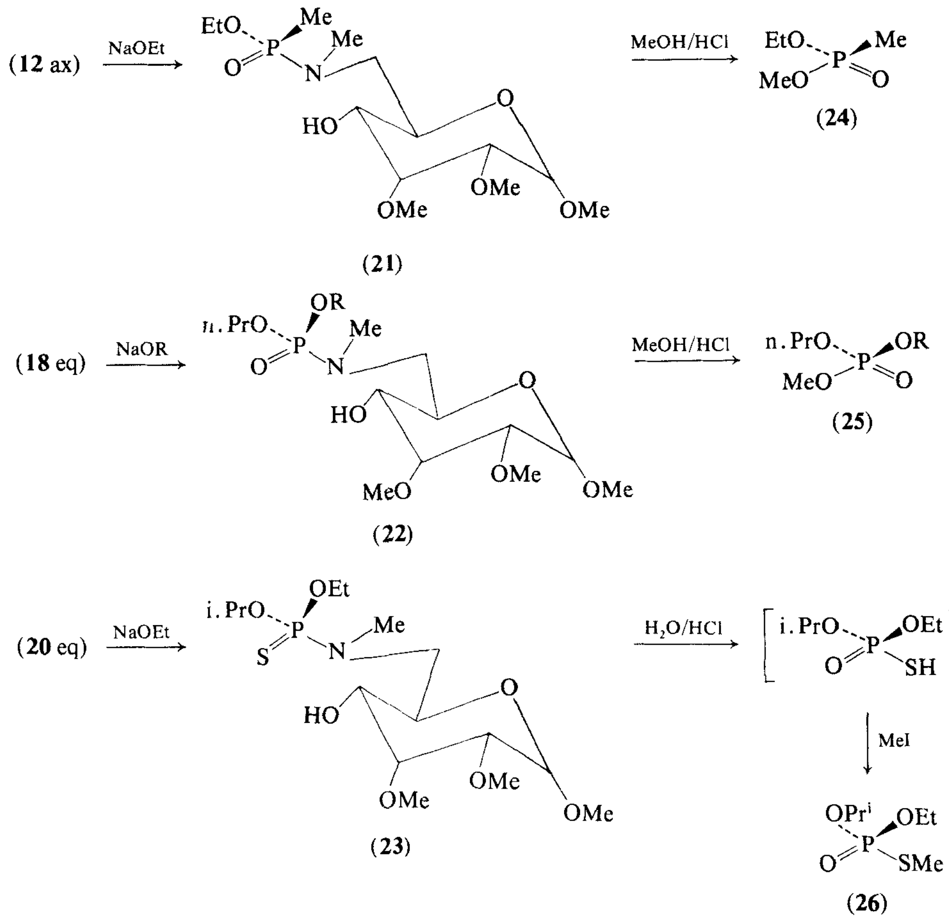

SCHEME 9

Since the absolute configuration of the cyclic sugars is known, and evidence suggests that both the P—O and the P—N bond cleavage occur with inversion of configuration[54] then the absolute stereochemistry of the products can also be assigned (Scheme 9).

Thus carbohydrates have played an important role in the synthesis of a wide range of chiral organophosphorus compounds[53–55] many of which were not previously available. Equally importantly, the synthetic sequence has usually enabled the absolute configuration of the products to be assigned and this will hopefully encourage the development of an effective structure (stereochemical)/activity relationship for many of the previously mentioned applications of chiral organophosphorus compounds. There are, however, a number of drawbacks to this system:

1) Synthesis of suitably substituted carbohydrate 'templates' can be time consuming, and often involves relatively large bulks of material.

2) The reaction of alkoxides with the tetrahydro 1,3,2-oxazaphosphorinanes derived from (**11**) does not always lead to exclusive P—O bond cleavage. For example, treatment of (**13** ax) with sodium methoxide resulted in *ca.* 16% P—N cleavage.[54] Although this does not interfere with the enantiomeric purity of the derived product, it does reduce the yield.

3) It is probable that the hydrogen chloride catalysed P—N bond cleavage is only stereospecific in water or simple primary alcohol solution.[27,47–49]

(—)-*Ephedrine and* (+)-*Pseudoephedrine*

By replacing carbohydrates as the optically active precursors with the readily available (—)-ephedrine (and in some cases (+)-pseudoephedrine) it has been possible to shorten the synthetic sequences with consequent practical advantages.[56–62] (—)-Ephedrine

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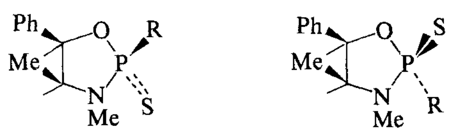
has previously been similarly applied to the preparation of chiral sulphoxides.[63]

(−)-Ephedrine reacts with $RPSCl_2$ (where R = alkyl or chloro) in the presence of triethylamine to form pairs of isomers, e.g. (**27a**) and (**27b**). The ratio of (a) : (b) isomers depends on the nature of the R group and the exact preparative route,[60] but for both (**27**) and (**28**) the resulting isomers are simply separated. (For R = Me either by simple chromatography or crystallization; for R = Cl high yields of the *cis* isomer (**28a**) can be obtained after a single crystallization.) The corresponding seleno adducts can be prepared by a slightly varying procedure.[58,60] Displacement of chloride from (**28**) by alkoxide or amine occurs with retention of configuration at phosphorus[60,62] to form single isomers of the alkoxy or amino adducts, e.g. (**29**) and (**30**).

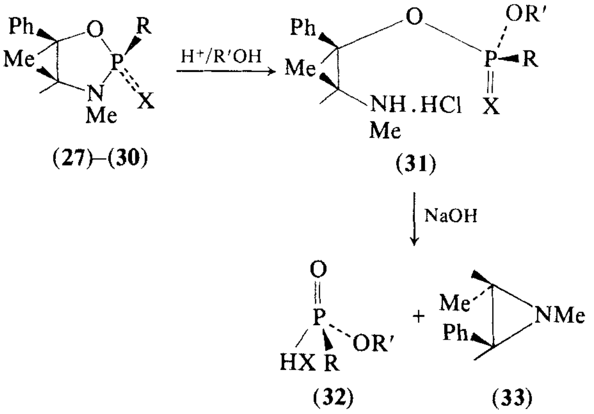


a b

(**27**) R = Me
(**28**) R = Cl
(**29**) R = OR
(**30**) R = NR_2

The assignment of the configurations of the isomeric pairs was initially made on the basis of ^1H nmr studies where it was assumed (particularly for the P=O containing analogues) that protons in a *cis* relationship to the phosphoryl group would be deshielded relative to those in *trans* positions.[56,57,60] Oxidation studies on the sulphur and selenium containing derivatives and comparison of signs and values of the specific rotations supported these results. Recently an X-ray crystallographic study on the major isomer obtained from the reaction of (+)-ephedrine and $PSCl_3$ (the mirror image of (**28a**)) has been published[64] and this confirms the previous assignments.

Treatment of a single cyclic isomer (**27**)–(**30**) (Scheme 10) with a solution of anhydrous hydrogen chloride in alcohol results in essentially exclusive P—N bond cleavage to form (**31**). Addition of a solution of aqueous sodium hydroxide to (**31**) catalyses the attack of the nitrogen lone pair at the benzylic carbon, displacing the phosphorus moiety (**32**) and generating the *trans*-aziridine (**33**). (Although similar cyclic adducts can be prepared and separated when (−)-ephedrine is replaced by (+)-pseudo-ephedrine this base catalysed displacement of phosphate by amine does not occur, presumably for steric reasons.[60]) The phosphorus containing fragment (**32**) is either isolated directly as the acid[61] or as its sulphur or seleno-alkyl ester.[60,62]



X = S or Se, R = Alkyl, alkoxy or alkylamino, R′ = alkyl

SCHEME 10

Since the configuration of the starting materials (**27**)–(**30**) is known and the base catalysed benzylic C—O bond cleavage does not affect the configuration at phosphorus and because the acid catalysed cleavage of the P—N bond can be reasonably assumed to occur with inversion of configuration, then the absolute configurations of the products can be assigned.[51,57–62] Confirmation that P—N cleavage in this system does occur with inversion can be obtained in some cases since the configuration of a number of the chiral products (e.g. phosphonothio-acids) has already been established.[65]

Treatment of a single isomer such as (**27a**) with aryl or alkyl lithium results in preponderant P—O bond cleavage to give (**34**) (Scheme 11). Acetylation of the free OH group in (**34**) gives (**35**) and acid catalysed P—N bond cleavage results in phosphinothioic acids (**36**).[66] Unlike the previous reaction sequence the products are not, however, always optically pure. Although the P—N cleavage is apparently stereospecific (at least in water) the stereospecificity of P—O bond cleavage varies with both the starting material and the reactant.[66] A similar difficulty was encountered by Wudl during attempts to prepare chiral sulphoxides.[63]. Since the configuration of both the starting material (**27a**, **27b** or their (+)-pseudoephedrine analogues) and the product (where R = Ph (**36**)) is known[67] then the

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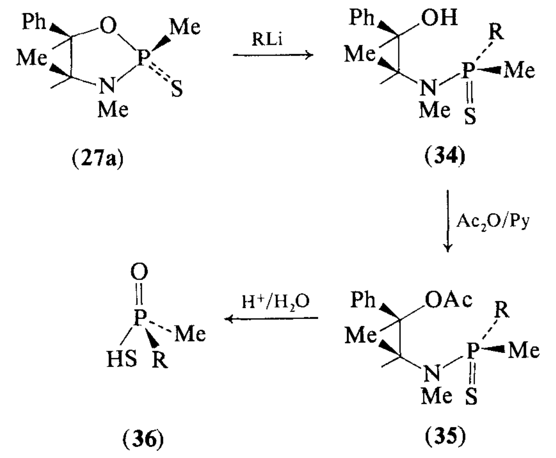
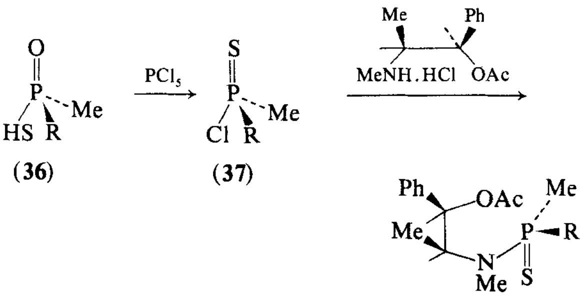


R = Ph, n.Bu, Et

SCHEME 11

overall reaction sequence (Scheme 11) involves inversion of configuration at phosphorus. Thus either the P—O or P—N bond cleavage reaction occurs with retention of configuration. Completion of the reaction sequence (**36**) → (**37**) → (**38**) makes it most likely that P—N cleavage occurs with inversion (since both chlorination of (**36**) with PCl_5[61,68] and displacement of chloride by amine[61] are likely to occur with inversion of configuration and (**38**) has the opposite configuration at phosphorus to (**35**)) and therefore P—O cleavage must occur with retention. This result, although somewhat unexpected, is consistent with the previously observed P—N cleavage by alkoxide with inversion in similar systems.[61]

A simple adaptation of Scheme 10 which involves cleavage of the benzylic C—O bond by catalytic hydrogenation has enabled the preparation of chiral $[^{16}O, ^{17}O, ^{18}O]$ phosphate monoesters.[69] These compounds have also been obtained using a chiral diol derived from (S)-mandelic acid as the template.[70]



SCHEME 12 (**38**)

A list of the compounds resolved using (−)-ephedrine and of those simply derived from such can be found in Table II. It is an interesting observation on the relative simplicity of the scheme that the preparation of several classes of chiral organophosphorus compounds is now no more difficult than preparation of the racemates. There are, however, some limitations such as:

1) For compound (**31**, R = NH_2) it is necessary to use very dilute base or nucleophilic attack at phosphorus by hydroxide resulting in P—O bond cleavage will compete with cleavage of the benzylic C—O bond giving rise to racemic product (Scheme 10).

2) P—O bond cleavage by alkyl lithiums in (**27**) is not always completely stereospecific.[66]

3) At present compounds containing base labile groups cannot be directly resolved and must be prepared from active intermediates such as the thioacids, and these reactions are often not stereospecific. A number of bifunctional carbohydrates and amino acids or their derivatives are potentially useful in this area and some of their applications are currently being assessed.

MISCELLANEOUS ROUTES

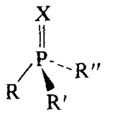
Several other routes have been successfully used to prepare chiral organophosphorus compounds but because they only result in one enantiomer, such as resolution by stereoselective enzyme inhibition[71] or in only partially resolved material, such as stereospecific inclusion in cycloamyloses[72] and various forms of asymmetric induction, they will not be considered here.

DETERMINATION OF ENANTIOMERIC PURITY AND OBSERVATIONS ON ABSOLUTE CONFIGURATION

For optically active organophosphorus compounds to fulfil their role as an effective probe into the mechanistic pathway of chemical and biological reactions, an accurate method for determination of the enantiomeric purity of both reactants and reaction products must be available. In some cases comparison of optical rotations is sufficient, but a number of difficulties often arise, particularly for compounds with low specific rotations (e.g. trialkyl phosphates[61]) and those for which no standards are

TABLE II

Absolute configuration, rotation and magnetic non-equivalence data for organophosphorus compounds resolved using (−)-ephedrine as a template and their derivatives [60–62, 66, 69]



R	R′	R″	X	Configuration	$[\alpha]_D$ (°)[a]	Sense of magnetic non-equivalence[b]
SH	OEt	OMe	O	R	+ 1.5	—
SH	OMe	OEt	O	S	− 1.4	—
SH	OEt	OPr^{i}	O	S	− 5.1	—
SH	OPr^{i}	OEt	O	R	+ 5.0	—
SMe	OEt	OMe	O	R	+ 1.0	*h*(OMe)
SMe	OMe	OEt	O	S	− 0.9	*l*(OMe)
SMe	OEt	OPr^{i}	O	S	+ 3.4	*h*(SMe)
SMe	OPr^{i}	OEt	O	R	− 3.5	*l*(SMe)
SMe	OPr^{i}	OMe	O	R	− 3.0	*h*(OMe) *l*(SMe)
SMe	OMe	OPr^{i}	O	S	+ 3.1	*l*(OMe) *h*(SMe)
SMe	Me	OEt	O	R	+85.5	*l*(SMe) *l*(PMe) *h*(POCH$_2$*Me*)
SMe	OEt	Me	O	S	−87.5	*h*(SMe) *h*(PMe) *l*(POCH$_2$*Me*)
SMe	Me	R^{3}	O	R	+70	*l*(SMe) *l*(PMe)
SMe	R^{3}	Me	O	S	−69	*h*(SMe) *h*(PMe)
SCH$_2$CH$_2$N(i-Pr)$_2$	Me	R^{3}	O	R	+32	*l*(PMe)
SCH$_2$CH$_2$N(i-Pr)$_2$	R^{3}	Me	O	S	−31	*h*(PMe)
SeMe	Me	OEt	O	R	+81	*l*(PMe) *l*(PSeMe) *h*(POCl$_2$*Me*)
SeMe	OEt	Me	O	S	−80	*h*(PMe) *h*(PSeMe) *l*(POCH$_2$*Me*)
SeMe	OPr^{i}	OMe	O	R	− 5.3	*h*(OMe) *l*(PSeMe)
SeMe	OMe	OPr^{i}	O	S		*l*(OMe) *h*(PSeMe)
OMe	OEt	Me	O	R	+ 1.9	*h*(OMe)
OMe	Me	OEt	O	S	− 1.9	*l*(OMe)
OMe	OEt	OPr^{i}	O	R	− 0.2	*h*(OMe)
OMe	OPr^{i}	OEt	O	S	+ 0.2	*l*(OMe)
Cl	OMe	OEt	S	R	+ 6.4	
Cl	OEt	OMe	S	S	− 6.4	
OPr^{i}	OEt	OMe	S	S	− 0.7	
OPr^{i}	OMe	OEt	S	R	+ 0.7	
NMe$_2$	OMe	OEt	S	R	+ 2.2	
NMe$_2$	OPr^{i}	OEt	S	S	+ 1.0	
NH$_2$	OMe	OEt	S	R	+ 2.9	
NH$_2$	OPr^{i}	OEt	S	S	− 1.5	
SMe	OEt	NH$_2$	O	S	−40	*h*(SMe)
SMe	NH$_2$	OEt	O	R	+40	*l*(SMe)
SMe	NH$_2$	OMe	O	R	+24	*l*(SMe) *h*(OMe)
SMe	NMe$_2$	OMe	O	R	+36	
SMe	NHMe	OMe	O	R	+24	*l*(SMe) *l*(OMe)
SMe	NHR^{4}	OMe	O	R	−22	
SMe	R^{5}	OMe	O	R	+46	
SMe	R^{5}	OEt	O	R	+38	
SMe	NMe$_2$	OEt	O	R	+32	
Cl	SMe	OMe	O	R		*l*(SMe) *h*(OMe)
Cl	OMe	NMe$_2$	O	S	−33	*l*(OMe) *h*(NMe$_2$)
Cl	OMe	R^{5}	O	S	−35	*l*(OMe)
Cl	OEt	R^{5}	O	S	−26	
OMe	OEt	NMe$_2$	O	R	− 1.5	
OEt	OMe	NMe$_2$	O	S	+ 0.9	
OEt	OMe	NHMe	O	S		*h*(OMe)
OMe	OEt	NH$_2$	O	R	+ 2.5	*h*(OMe)
OEt	OMe	NH$_2$	O	S		*l*(OMe)
OPr^{i}	OMe	NHMe	O	S		*h*(OMe)
OEt	R^{5}	OMe	O	R	+ 1.6	*l*(OMe)[c]
OEt	OMe	R^{5}	O	S	− 1.6	*h*(OMe)[c]
NH$_2$	NMe$_2$	OMe	O	S	−28	*l*(OMe) *h*(NMe$_2$)
Cl	OEt	OMe	O	R		*h*(OMe)

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TABLE II. *continued*

R	R′	R″	X	Configuration	$[\alpha]_D$ (°)[a]	Sense of magnetic non-equivalence[b]
Cl	OMe	OEt	O	S		*l*(OMe)
F	OEt	OMe	O	R		*h*(OMe)
F	OMe	OEt	O	S		*l*(OMe)
OPh	OEt	OMe	O	R	+ 2.8[d]	*h*(OMe)
SH	Ph	Me	O	R	+19.5[e]	
SH	n-Bu	Me	O	R	− 3.6[f]	

[a] Solutions in chloroform.

[b] The sense of non-equivalence is deemed *h* for that enantiomer in which the relevant signal undergoes the least change in chemical shift on addition of $Eu(hfc)_3$ (100 mg) to a solution of mixed enantiomers (30–40 mg) in deuteriochloroform (0.5 ml) at 60 MHz.

[c] Spectra run at 60°C.

[d] Value calculated from a 4 : 1 mixture of enantiomers.

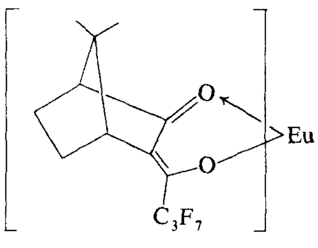
[e] 94% major enantiomer.

[f] ~90% major enantiomer.

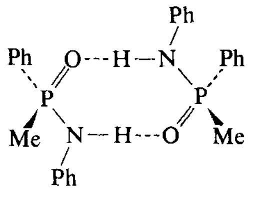
R^3 = cyclopentyloxy, R^4 = (−)-α-phenylethyl, R^5 = morpholino.

available. A number of workers have recently demonstrated the applicability of more convenient nmr procedures.

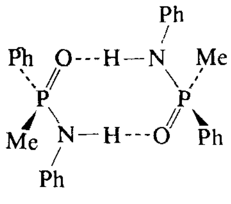
Enantiomers exhibit identical nmr spectra but diastereomers, whether covalently bonded or in equilibrium have distinctive spectra. Thus the enantiomeric purity of Mislow's[40] (−)-menthyl phosphinates can be directly established by simple ^1H nmr spectroscopy. Likewise the purity of diastereomeric salts such as those formed from phosphorus thioacids and (−)-phenylethylamine can be determined.[73,74] Both cases are limited to similar types of compound. Of more general application is the approach adopted by Pirkle[75,76] and co-workers who have developed a method based on the chemical shift non-equivalence of enantiomers induced by optically active solvents such as (+) or (−)-2,2,2-trifluoro-1-phenylethanol. This technique is unfortunately limited to polar solvent-solute interactions because non-equivalence results from such diastereomeric solute-solvent effects. Observed shift differences are also usually fairly small. Another successful approach utilizes the chiral shift reagent *tris*-[3-(heptafluoro-*n*-propylhydroxy-methylene)-(+)-camphorato]europium (111), $Eu(hfc)_3$ (**39**), to determine the enantiomeric composition of a range of phosphorus compounds containing a phosphoryl oxygen ($P{=}O$).[55,60] The observed enantiomeric shift differences for at least one set of protons are usually much larger than those observed in chiral solvents, thus allowing the presence of less than 5% of a minor enantiomer to be simply and accurately determined. This method is as yet limited to $P{=}O$ containing phosphorus compounds since the phosphoryl sulphur in $P{=}S$ is not a sufficiently good Lewis base to establish a complexed/uncomplexed equilibrium with this shift reagent. Recently Harger [77,78] has demonstrated that for some classes of asymmetric organophosphorus compounds it is not necessary for any foreign optically active additive to be introduced in order to observe nmr non-equivalence of enantiomers. Both phosphinic amides and phosphinothioic acids are known to form hydrogen bonded dimers in non-polar solvents such as chloroform.[77,78] Nmr of solutions of such compounds containing an excess of one enantiomer can give rise to two sets of signals proportional to the relative amounts of each isomer. These signals are rationalized in terms of short-lived diastereomeric dimers such as (**40**) and (**41**) in which associated molecules have, respectively, the same and opposite configurations at phosphorus. The major enantiomer in a mixture will on average be associated with partners of the same configuration, whereas the minor



(**39**)



(**40**)



(**41**)

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enantiomer will tend to be paired with those of the opposite configuration, thus giving rise to two sets of signals. This phenomenon is apparently not as limited as was previously thought since not only can chiral phosphinothioic acids induce non-equivalence in the enantiomers of phosphinic amides[78] which contain both hydrogen bond donor (N–H) and acceptor (P=O) groups, but also in some compounds containing only hydrogen bond acceptor groups (P=O) such as methyl methylphenylphosphinate.[79] In the latter case the precise geometry of the asymmetric "dimers" is unclear but it seems probable that hydrogen bonding between the phosphoryl group of the ester and the thioic acid is responsible. To date all published examples of this technique include a phenyl group in both partners in "dimer" formation. This seems to be necessary in order for the induced shift differences to be practically large.

A number of attempts have been made to relate the sense of magnetic non-equivalence induced in enantiomers to the absolute configuration at phosphorus. Both Pirkle[76] for diastereomeric solvates and Mikolajczyk and co-workers[73] for thioic acid/α-phenylethylamine salts have shown that within single classes of compounds the observed nmr signals (i.e. whether one enantiomer resonates at high or low field relative to the other) appear to correspond to the absolute configuration at phosphorus. It has been pointed out, however, that there are possible difficulties in the general application of this technique.[80]

After the investigation of the interaction of a large number of classes of P=O containing organophosphorus compounds of known absolute configuration with the chiral shift reagent Eu(hfc)$_3$ we have concluded[60–62] that there is some sort of relation between the observed sense of magnetic non-equivalence and the absolute configuration at phosphorus. Without far more detail about the nature of the complexes formed between shift reagent and substrate it is not possible to propose any model to explain these observations. It is possible, however, to put forward a simple generalization which is consistent with the vast majority of our data (some of which is recorded in Table II) and which allows the assignment of absolute configuration, provided at least that the signals for one set of protons can be resolved. The generalization is that when viewing the molecule along the O=P bond from oxygen to phosphorus:

1) Where splitting of the resonance due to the largest (Sequence Rule) group is observed, the enantiomer with the lower field signal has the *R* configuration.

2) The group in a clockwise relation to the largest group always has a high field shift (if any).

3) The group in an anti-clockwise relation to the largest group always has a low field shift (if any).

Thus for a phosphoryl (P=O) containing compound where only any one group (X) of signals is resolved; if X is the largest group the enantiomer with the lower field signal has the *R* configuration, if X is not the largest group then its relation to the largest group (clockwise or anti-clockwise) and hence the absolute configuration can easily be determined. If more than one group of signals is resolved the same set of rules apply. The only compounds in Table II to disobey these results are MeO(MeS)P(O)NHMe and MeO(EtO)P(O)NC$_4$H$_8$O, and in the latter case it can be reasonably argued that in fact morpholino is the "largest" group. Care should, however, be taken in applying them to new compounds or classes of compound.

Other methods of determining enantiomeric compositions not involving the use of nmr include the recent observation by Luckenbach and Horner[81] of a second small peak in the differential scanning calorimetry (DSC) thermogram of some phosphonium salts after adding as little as 1% of the racemate to a previously optically pure sample. This technique, originally applied by Fouquey and Jacques[82] to carboxylic acids, potentially offers an accurate method for determining the enantiomeric composition of some classes of solid organophosphorus compounds.

Where two enantiomers inhibit an enzyme such as acetyl cholinesterase at significantly different rates or where such enzymes, once inhibited by pairs of enantiomers, age at different rates it is possible to use the rate(s) of these reactions to obtain a minimum value of the enantiomeric purity.[83]

Circular Dichroism (CD) studies have been used to confirm the validity of configurational assignments made by other methods[84] to phosphonothioic acids. Brewster's asymmetry rules[85] have also been successfully applied in these cases.

Fukuto and co-workers[86] have determined the absolute configurations of (S)-(–)-O-ethyl-S-p-bromophenyl ethylphosphonodithioate and (S)-(–)-α-phenylethylammonium O-ethyl ethylphosphonothioate by X-ray crystallography.

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REFERENCES

1. H. L. Boter, A. J. J. Ooms, G. R. van der Berg and C. van Dijk, *Rec. Trav. Chim.* **85**, 147 (1966).
2. T. W. Holmsen, *Weed Sci.* **17**, 187 (1969).
3. P. J. Cox, P. B. Farmer, M. Jarman, M. Jones, W. J. Stec and P. Kinas, *Biochem. Pharmacol.* **25**, 993 (1976); P. J. Cox, P. B. Farmer, A. B. Foster, E. D. Gilby and M. Jarman, *Cancer Tr. Rep.* **60**, 483 (1976).
4. G. Kamai and G. M. Usacheva, *Russian Chem. Rev.* **35**, 601 (1966).
5. L. Horner, *Pure Appl. Chem.* **9**, 225 (1964).
6. J. Michalski, *Bull. Soc. Chim. Fr.* 1109 (1967).
7. M. Mikolajczyk, *Wiadomosci Chem.* **21**, 205 (1967).
8. H. Christol and H. J. Cristau, *Ann. Chim.* **6**, 179 (1971).
9. H. Christol and H. J. Cristau, *Ann. Chim.* **6**, 191 (1971).
10. M. Mikolajczyk and M. Leitloff, *Russian Chem. Rev.* **44**, 670 (1975).
11. J. Meisenheimer and L. Lichtenstadt, *Ber. btsch. Chem. Ges.* **44**, 356 (1911).
12. F. Ephraim, *Ber. btsch. Chem. Ges.* **44**, 631 (1911).
13. H. S. Aaron and J. I. Miller, *J. Amer. Chem. Soc.* **78**. 3538 (1956).
14. H. S. Aaron, T. M. Shryne and J. I. Miller, *J. Amer. Chem. Soc.* **80**, 107 (1958).
15. H. S. Aaron, J. Braun, T. M. Shyrne, H. F. Frack, G. E. Smith, R. T. Uyeda and J. I. Miller, *J. Amer. Chem. Soc.* **82**, 596 (1960).
16. J. Michalski and A. Ratajczak, *Roczniki Chem.* **36**, 911 (1962).
17. H. L. Boter and D. H. J. M. Platenburg, *Rec. Trav. Chim.* **86**, 399 (1967).
18. W. Theilacker and H. G. Winkler, *Chem. Ber.* **87**, 690 (1954).
19. M. Leitloff, Doctoral Thesis, Technical University (Politechnika), Lodz, 1973; C. R. Hall, unpublished observations.
20. H. Green and R. F. Hudson, *J. Chem. Soc.* 540 (1963).
21. H. P. Benschop and G. R. van den Burg, *Rec. Trav. Chim.* **87**, 362 (1968).
22. N. J. DeAth, K. Ellis, D. J. H. Smith and S. Trippett, *Chem. Comm.* 714 (1971).
23. V. A. Chauzov and I. F. Lutsenko, *Z. Obs. Khim.* **43**, 69 (1973).
24. B. Krawiecka, Z. Skrypczynski and J. Michalski, *Phosphorus* **3**, 177 (1973).
25. B. Krawiecka and J. Michalski, *Bull. Acad. Polon. Sci.*, Ser. sci. chim. **19**, 373 (1971).
26. M. Mikolajczyk and J. Omelanczuk, *Phosphorus* **3**, 47 (1973).
27. C. R. Hall and N. H. Nicholson, unpublished results.
28. I. A. Nuretdinov, N. A. Buina, E. V. Bayandina and F. G. Sibgatulina, *Izv. Akad. Nauk SSSR* 483 (1974).
29. J. Michalski, A. Ratajczak and Z. Tulimowski, *Bull. Acad. Polon, Sci.*, Ser. sci, chim. **11**, 237 (1963).
30. C. Donninger and D. H. Hutson, *Tetrahedron Lett.* 4871 (1968).
31. D. A. A. Akintonwa, *Tetrahedron* **34**, 959 (1978).
32. H. Teichmann and Phi Trong Lam, *Z. Chem.* **9**, 310 (1969).
33. N. K. Hamer, *J. Chem. Soc.* 2731 (1965).
34. A. F. Gerrard and N. K. Hamer, *J. Chem. Soc.* (B) 1122 (1967).
35. J. N. Seiber and H. Tolkmith, *Tetrahedron* **25**, 381 (1969).
36. G. Hilgetag and G. Lehman, *Angew. Chem.* **69**, 506 (1957).
37. A. Blade Font, C. A. Van der Werf and W. E. McEwen, *J. Amer. Chem. Soc.* **82**, 2396 (1960); L. Horner and H. Winkler, *Tetrahedron Lett.* 3265 (1964).
38. L. Horner, H. Fuchs, H. Winkler and A. Rapp, *Tetrahedron Lett.* 965 (1963).
39. R. Luckenbach, *Phosphorus* **1**, 223 (1972).
40. O. Korpium, R. A. Lewis, J. Chickos and K. Mislow, *J. Amer. Chem. Soc.* **90**, 4842 (1968).
41. K. K. Anderson, *Tetrahedron Lett.* 93 (1962).
42. K. E. DeBruin and E. D. Perrin, *J. Org. Chem.* **40**, 1523 (1975).
43. A. Nudelman and D. J. Cram, *J. Org. Chem.* **36**, 335 (1971).
44. K. E. DeBruin and L. L. Thomas, *Chem. Comm.* 33 (1977).
45. T. Koizumi, Y. Kobayashi, H. Amitani and E. Yoshii , *J. Org. Chem.* **42**, 3459 (1977).
46. T. Koizumi, H. Amitani and E. Yoshii, *Tetrahedron Lett.* 3741 (1978).
47. T. Koizumi, Y. Kobayashi and E. Yoshii, *Chem. Comm.* 678 (1974).
48. C. R. Hall and T. D. Inch, *Tetrahedron Lett.* 3765 (1977).
49. M. J. P. Harger, *J. C. S. Perkin I* 2057 (1977).
50. R. Kinas, K. Pankiewicz and W. J. Stec, *Bull. Acad. Polon. Sci.*, Ser. sci. Chim. **23**, 981 (1975).
51. T. Kawashima, R. D. Kroshefsky, R. A. Kok and J. G. Verkade, *J. Org. Chem.* **43**, 1111 (1978).
52. T. D. Inch, *Adv. Carbohydrate Chem. Biochem.* **27**, 191 (1972).
53. D. B. Cooper, T. D. Inch and G. J. Lewis, *J. C. S. Perkin I* 1043 (1974) and references therein.
54. J. M. Harrison, T. D. Inch and G. J. Lewis, *J. C. S. Perkin I* 1892 (1975).
55. C. R. Hall, T. D. Inch, G. J. Lewis and R. A. Chittenden, *Chem. Comm.* 720 (1975).
56. D. B. Cooper, J. M. Harrison and T. D. Inch. *Tetrahedron Lett.* 2697 (1974).
57. D. B. Cooper, C. R. Hall and T. D. Inch, *Chem. Comm.* 721 (1975).
58. C. R. Hall and T. D. Inch, *Tetrahedron Lett.* 3645 (1976).
59. C. R. Hall and T. D. Inch, *Tetrahedron Lett.* 3761 (1977).
60. D. B. Cooper, C. R. Hall, J. M. Harrison and T. D. Inch, *J. C. S. Perkin I* 1969 (1977).
61. C. R. Hall and T. D. Inch, *J. C. S. Perkin I* in press.
62. C. R. Hall and T. D. Inch, *J. C. S. Perkin I* in press.
63. F. Wudl and T. B. K. Lee, *J. Amer. Chem. Soc.* **95**, 6349 (1973).
64. T. Prange, C. Pascard, J. Devillers and J. Navech, *Bull. Soc. Chim.* (France) 185 (1977).
65. M. Mikolajczyk, J. Omelanczuk and M. Para, *Tetrahedron* **28**, 3855 (1972).
66. C. R. Hall, T. D. Inch and I. W. Lawston, *Tetrahedron Lett.* in press.
67. H. P. Benschop, G. R. van den Berg and H. L. Boter, *Rec. Trav. Chim.* **87**, 387 (1968).
68. R. Luckenbach and H. H. Bechtolsheimer, *Z. Naturforsch Sect. B* **32**, 584 (1977).
69. S. J. Abbott, S. R. Jones, S. A. Weinman and J. R. Knowles, *J. Amer. Chem. Soc.* **100**, 2558 (1978).
70. P. M. Cullis and G. Lowe, *Chem. Comm.* 512 (1978).
71. N. P. B. Dudman and B. Zerner, *J. Amer. Chem. Soc.* **95**, 3019 (1973).
72. H. P. Benschop and G. R. van den Berg, *Chem. Comm.* 1431 (1970).
73. M. Mikolajczyk, M. Para, A. Ejchart and J. Jurczak, *Chem. Comm.* 654 (1970).

74. M. Mikolajczyk and J. Omelanczuk, *Tetrahedron Lett.* 1539 (1972).
75. W. H. Pirkle, *J. Amer. Chem. Soc.* **88**, 1837 (1966).
76. W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.* **91**. 5150 (1969).
77. M. J. P. Harger, *J. C. S. Perkin II* 1882 (1977).
78. M. J. P. Harger, *J. C. S. Perkin II* 326 (1978).
79. M. J. P. Harger, *Tetrahedron Lett.* 2927 (1978).
80. W. H. Pirkle, *Chem. Comm.* 1525 (1970).
81. R. Luckenbach and L. Horner, *Thermochimica Acta* **11**, 216 (1975).
82. C. Fouquey and J. Jacques, *Tetrahedron* **23**, 4009 (1967).
83. L. P. A. De Jong and C. van Dijk, *Biochem. Biophys. Acta* **268**, 680 (1972) and references therein.
84. M. Mikolajczyk, M. Para, J. Omelanczuk, M. Kajtar and G. Snatzke, *Tetrahedron* **28**, 4357 (1972).
85. J. H. Brewster, *J. Amer. Chem. Soc.* **81**. 5475 (1959).
86. R. Allahyari, P. W. Lee, G. H. Y. Lin, R. M. Wing and T. R. Fakuto, *J. Agric. Food Chem.* **25**, 471 (1977).

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