Handbook of Organophosphorus Chemistry

edited by

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applications", in which the organophosphorus compound is the final target material for the chemical scientist, and "*en route* applications" in which the chemical scientist uses the organophosphorus compounds as a "tool" for the accomplishment of further chemical or biological purposes.

I wish to thank Dr. Maurits Dekker, Ms. Lisa Honski, and Mr. Eric Stannard for their assistance and patience in bringing this work to completion.

Robert Engel

Contents

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CHAPTER 1

OPTICALLY ACTIVE PHOSPHORUS COMPOUNDS

Tsuneo Imamoto, *Department of Chemistry, Chiba University, Chiba, Japan*

I. Introduction

There have been developed many efficient methods for the synthesis of optically active organophosphorus compounds possessing a chiral center at phosphorus, and a great number of this class of compounds have been prepared. These compounds are highly useful in basic phosphorus stereochemistry, particularly in mechanistic studies on reaction occurring at phosphorus. The utility of these compounds has been recognized in other scientific fields as well. For example, some homochiral bisphosphines exhibit excellent enantioselectivities in catalytic asymmetric reactions, and they are often used in practical asymmetric syntheses. Enantiomers of some chiral phosphorus compounds are known to exhibit a variety of unique biological activities and hence they have a high potential for use as agricultural chemicals.

Academic interests and the practical utility of chiral phosphorus compounds have led to the publication of a number of excellent monographs and reviews.[1-21] Most of these provide a comprehensive discussion regarding a specific use of this class of compounds.

In this Chapter an attempt is made to provide an overview of the synthesis and reactions of optically active phosphorus compounds. The literature survey covers articles appearing until November 1990.

II. Synthesis of Optically Active Organophosphorus Compounds Possessing Chirality at Phosphorus

A. Tricoordinate Phosphorus Compounds

1. Tertiary Phosphines

The reduction of tertiary phosphine oxides is the method most frequently used for the preparation of optically active tertiary

phosphines. The stereospecific reduction of chiral phosphine oxides can be accomplished by the use of silane reducing agents such as $PhSiH_3$,[22] $HSiCl_3$,[23,24] and Si_2Cl_6.[24] The stereospecificity of the reduction depends largely on the structures of the phosphine oxide and the reducing agent. Representative results are shown in Table 1.

Phenylsilane ($PhSiH_3$) appears to be the most useful among these reducing agents. This reagent, which is commercially available, can be handled easily as it is not sensitive to air or moisture, and the reduction with it proceeds in high chemical yield with almost complete retention of configuration.[22,25] Trichlorosilane ($HSiCl_3$) is also a useful reducing agent. Reduction with it in the presence of weakly basic tertiary amines, such as pyridine or diethylaniline, proceeds with retention of configuration. However, the use of more basic amines ($pK_b < 5$) as an additive provides phosphines with inversion of configuration in high stereochemical integrity.[24]

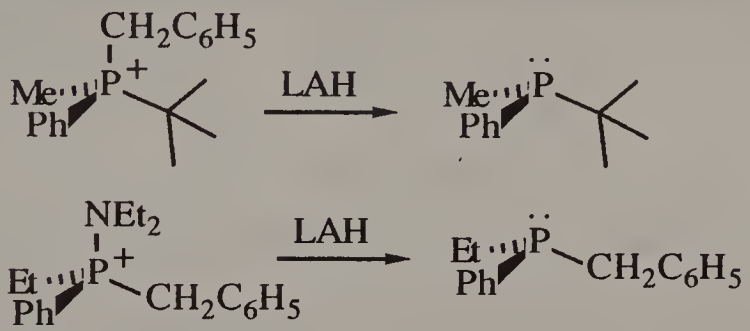
Reduction of acyclic phosphine oxides with hexachlorodisilane ($Cl_3SiSiCl_3$) proceeds rapidly with inversion of configuration. Short reaction times (~ 10 min.) affords products with high optical purity, whereas longer reaction times result in considerable racemization of the products as the reagent itself induces the racemization of phosphines.[24]

The stereospecificity of the deoxygenation of cyclic phosphine oxides depends on the ring size and the reducing agents.[22,26-28] Four-membered phosphine oxides are reduced with almost complete retention of configuration by $HSiCl_3$-NEt_3 or Si_2Cl_6.[26,27] The reduction of five- six- and seven-membered phosphine oxides appears to have nearly the same trend as for the acyclic materials.[22,28]

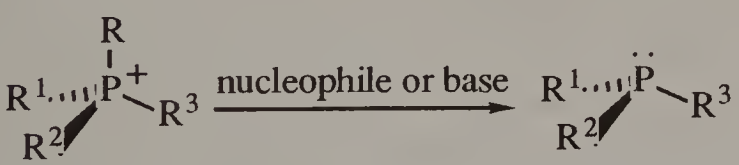
Phosphine sulfides and selenides are reduced by Si_2Cl_6[29] or $LiAlH_4$ (LAH)[30,31] with complete or nearly complete retention of configuration. These results are in contrast to the reduction of the corresponding phosphine oxides, which are reduced by Si_2Cl_6[24] with inversion of configuration while LAH[32] leads to predominantly racemized phosphines.

The electrochemical reduction of optically active phosphonium salts bearing a benzyl group provides phosphines with pre-

dominant retention of configuration.[33-35] Reduction of the quaternary phosphonium salts with LAH affords racemized phosphines in most cases.[36,37] However, quaternary phosphonium salts possessing a sterically hindered group or a dialkylamino group, on treatment with LAH are converted to phosphines with predominant retention of configuration, as shown below.[38,39]

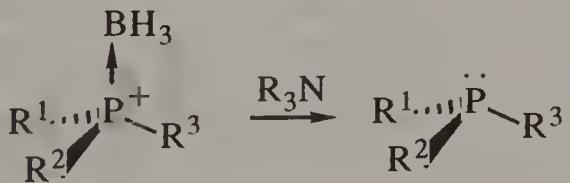


The reaction of tetracoordinate phosphorus compounds with nucleophiles or bases can be employed for the preparation of chiral phosphines with high enantiomeric excess. Some chiral quaternary salts react with nucleophiles such as KCN or EtSNa, or bases such as MeONa or Et_3N, even under mild conditions.[40-43] In most cases, since the nucleophiles or bases attack the substituent and not the phosphorus atom, the released phosphines maintain their stereochemical integrity and net retention of configuration at phosphorus is observed.



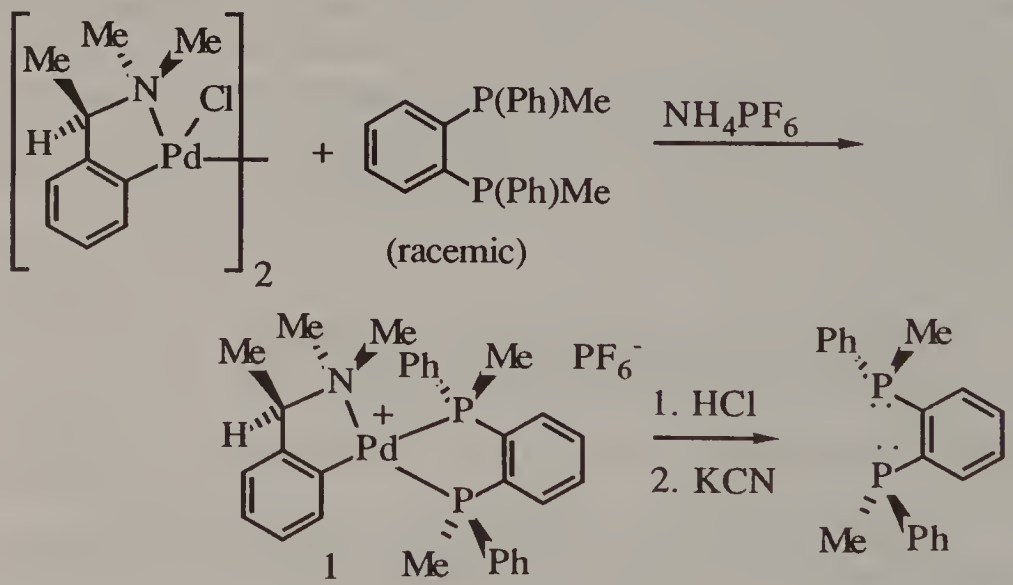
R = $NCCH_2CH_2$-, CH_2=$CHCH_2$-,$HOCH_2$-,CH_3S-, CH_3Se

Optically active phosphine-boranes, adducts of phosphines with borane, react with amines to give phosphines in a completely stereospecific manner.[44-46]



Stereospecific substitution reactions of phosphinous acid derivatives with organolithium reagents has been studied extensively by Mikolajczyk and Chodkiewicz, *et al.*[15,47-51] The displacement reactions proceed with almost complete inversion of configuration. This method, however, is not suitable for the preparation of optically pure phosphines because it is difficult to obtain the starting phosphinates in optically pure form.

Direct resolution of racemic phosphines can be accomplished by the use of asymmetric Pd(II), Pt(II), and Rh(I) complexes.[52-56] A typical example is illustrated in the following scheme.[55] In this case one pure diastereoisomeric Pd(II) complex (1) is readily separated by crystallization, and subsequent decomplexation occurs without any loss of optical activity.

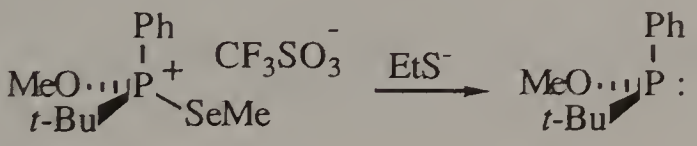


2. Other Tricoordinate Compounds

Optically active phosphinous acid derivatives ($R^1R^2P^*X$) and phosphonous acid derivatives (R^1P^*XY) are prepared by the reaction of alcohols with acid chlorides in the presence of amines. The reactions between racemic phosphinous chlorides and optically active alcohols, such as (-)-menthol or chinchonine, afford a

mixture of diastereoisomeric phosphinites in unequal amounts.[15,48,50,51,57] The reaction of achiral alcohols in the presence of optically active tertiary amines affords optically active phosphinates, although the enantiomeric excesses of the products are only moderate.[47,58]

Preparation of phosphinates or phosphinous acid amides possessing high enantiomeric excess is accomplished from optically active phosphonium salts by cathodic reduction[39] or by the reaction with nucleophiles.[43]



Recently, diastereoisomerically pure oxazaphospholidine[59] and cyclic phosphonites[60,61] have been synthesized by the condensation reactions of bis(diethylamino)phenylphosphine with (-)-ephedrine and of dichlorophenylphosphine with optically active 1,2-diols.

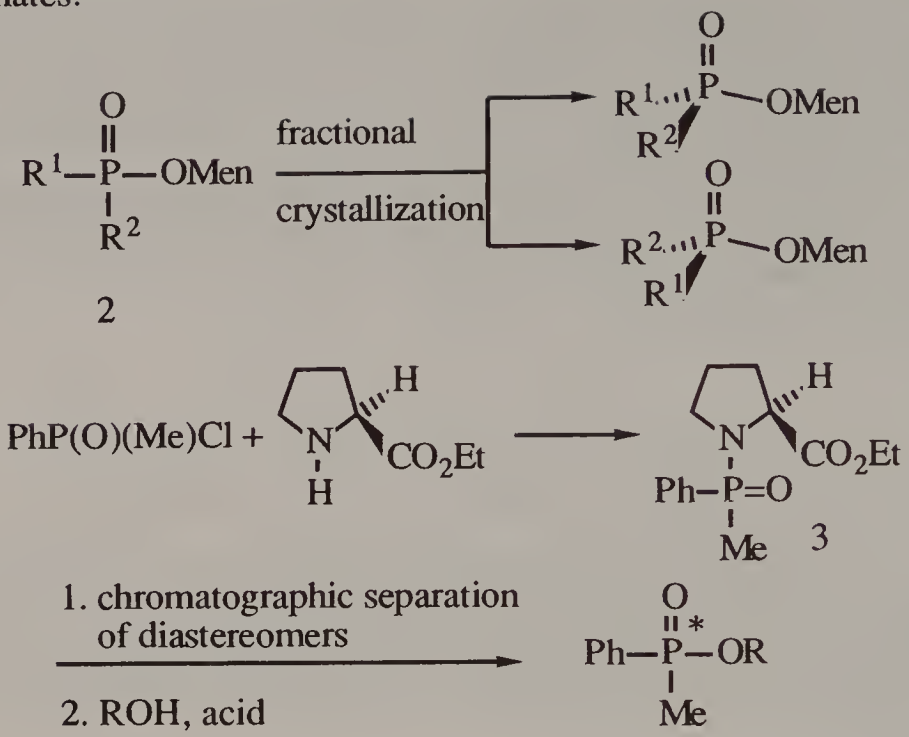
B. Tetracoordinate Phosphorus Compounds

1. Derivatives of Phosphinic and Phosphonic Acids

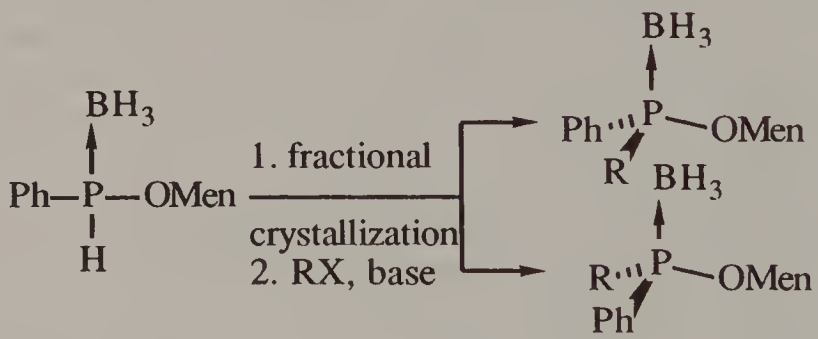
These classes of compounds occupy the central position in organophosphorus stereochemistry, and many efficient preparative methods for them have been described. Diastereomerically pure menthyl phosphinates can be obtained by the Mislow method.[62-64] The starting materials for this synthesis, the unsymmetrically substituted menthyl phosphinates (2) are readily obtained by the reaction of the corresponding phosphinyl chloride and (-)-menthol in the presence of pyridine. The resulting mixtures of diastereomers are subjected to fractional crystallization from hexane to afford each pure or enriched menthyl phosphinate. Separation by chromatography has not been effective in these cases.

Koizumi, *et al.* have devised another route to chiral phosphinates utilizing the chirality of L-proline ethyl ester.[65] The diastereomeric phosphinamides (3) are separated by column chromatography on silica gel. Acid catalyzed alcoholysis of each diastereomer gives the corresponding alkyl methylphosphinate in a state of high optical purity. This method is applicable for the preparation of optically active phosphotriesters, phosphonates, and thiophos-

phonates.[66-68]

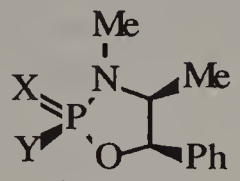


Recently, diastereomerically pure menthyloxyphenylphosphine-boranes have been prepared.[45]



Inch and Hall, *et al.* have established versatile methods for the synthesis of various pentavalent tetracoordinate phosphorus compounds in optically active form.[7,8] Their methods utilize (-)-ephedrine[69-78] and (+)-D-glucose[79-83] as the chiral source. The reactions of these chiral templates with phosphorus halides afford cyclic diastereomers, which are in most cases separated by chromatography and/or fractional crystallization without difficulty. The separated diastereomers, *e.g.* (4)-(7) undergo substitution reactions with nucleophiles in a stereospecific manner with either

retention or inversion, eventually affording a number of optically active phosphorus compounds, such as phosphates or phosphine oxides.



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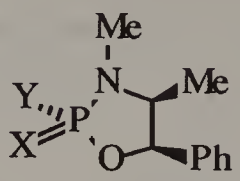

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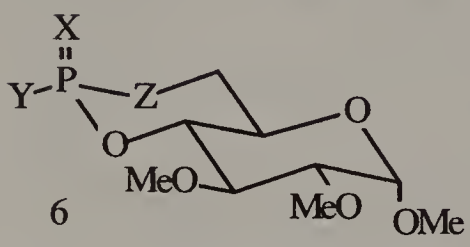
X = O, S, Se; Y = aryl, alkyl, alkoxy, chloro



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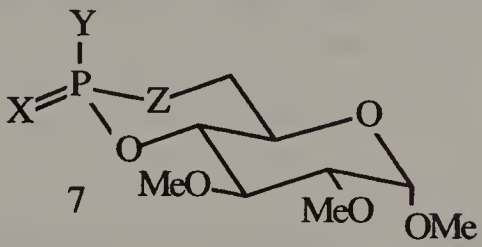

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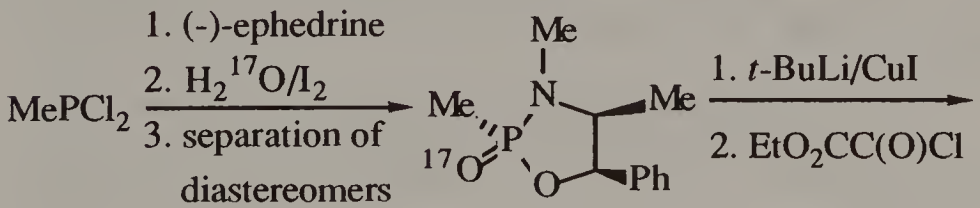
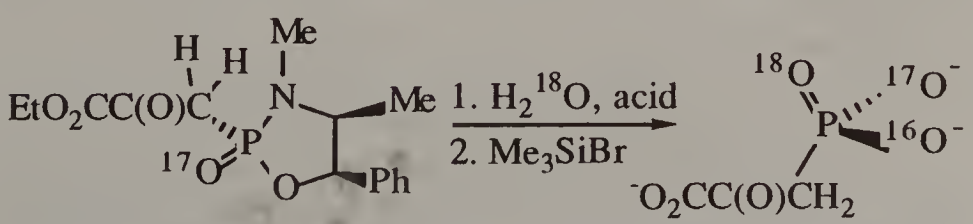
X = O, S; Y = aryl, alkyl, OR, SR, NR_2, halogen; Z = O, S, NMe

Koizumi, *et al.* have developed a similar method by the use of L-proline as the chiral template.[84,85] Each set of diastereomers are readily separated by chromatography and can be used for the synthesis of optically active phosphinates and phosphine oxides.

Utility of these methods, particularly that using ephedrine as a chiral source, has proven successful for the synthesis of a number of important chiral phosphorus compounds. For example, chiral [^{16}O, ^{17}O, ^{18}O] phosphates and thiophosphates have been synthesized using these methods.[86-94] A notable example is shown below.[95,96]





Racemic thioacids or selenoacids form diastereomeric salts

with optically active amines, such as α-phenylethylamine,[97-103] quinine,[104-111] (-)-ephedrine,[112,113] and brucine.[105] The mixtures of diastereomeric salts can be separated by fractional crystallization. In most cases, the separations require tedious work, and in some cases only one of the diastereomers can be separated in optically pure form.[7,10]

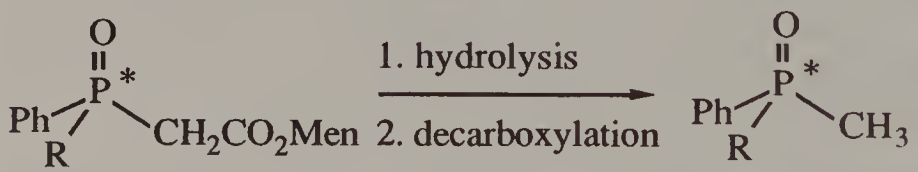
2. Phosphonium Salts

Optically active phosphonium salts are prepared by resolution of the diastereomeric phosphonium dibenzoyltartrates by fractional crystallization.[36,114]

Alkylation of chiral tricoordinated phosphorus compounds also provides chiral quaternary salts. The reactions of phosphine oxides and related compounds with powerful alkylating agents, such as trialkyloxonium tetrafluoroborate or alkyl trifluoromethanesulfonates, provide chiral phosphonium salts.[15,116,117]

3. Phosphine Oxides

New routes to optically active phosphine oxides have been developed by Pietrusiewicz, *et al.*[118-120] The method is illustrated in the scheme shown below.



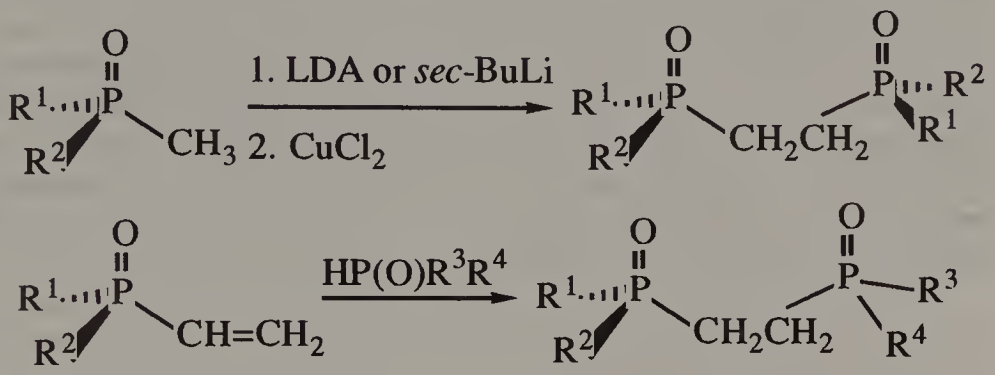
The intermediate menthyl esters of phosphorus-substituted acetic acid are separated by fractional crystallization. This method allows the large scale preparation of optically pure phosphine oxides.

Recently, racemic phosphine oxides and phosphinates have been resolved directly by complex formation with optically active 2,2'-dihydroxy-1,1'-binaphthyl, followed by fractional crystallization.[121]

Phosphine oxides having a functional group have been prepared by the conjugate addition of alcohols or amines to optically active vinyl phosphine oxides.[122-124]

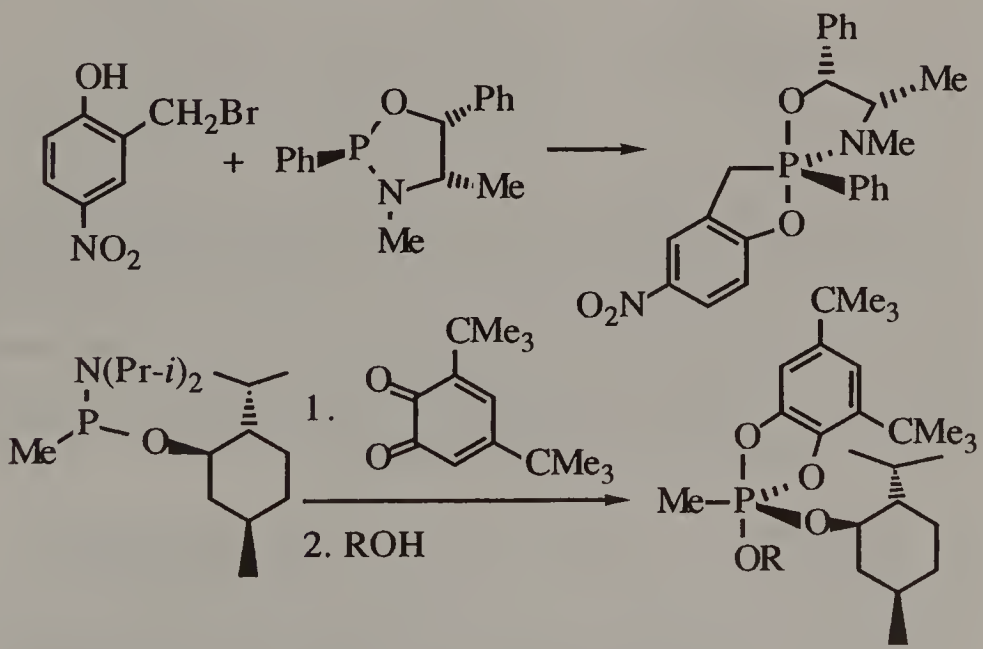
Chiral bis-phosphine oxides, which are useful precursors to bidentate phosphine ligands homochiral at phosphorus, can be synthesized by several methods. Oxidative coupling of chiral

phosphine oxides having a methyl group on phosphorus is a typical method.[125-127] Conjugate addition to chiral vinyl phosphine oxides is another route to chiral bis-phosphine oxides.[122,128,129]



C. Pentacoordinate Phosphorus Compounds

Chiral pentacoordinate phosphorus compounds are known to exist as reaction intermediates.[4,5,8,11,12] However, isolated species are rare.[130-132] Two examples, characterized spectroscopically, are shown below.[131,132]



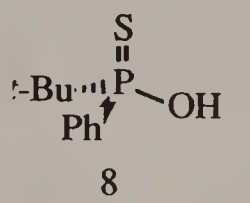
III. Methods of Measurements of Enantiomeric Excesses of Optically Active Organophosphorus Compounds

Several reagents for determining enantiomeric excesses (e.e.)

of chiral phosphorus compounds have been reported. Determination by NMR is the most frequently employed method, and many chiral shift reagents, including lanthanide shift reagents, have been reported.[133-136]

Chiral phosphines react with optically pure 2-phenyl-2-methoxyethyl bromide or its deuterated derivative, 2-phenyl-2-methoxy-1,1-dideuterioethyl bromide, to yield diastereomeric mixtures of phosphonium salts, the relative amounts of which are determined by NMR.[133] Enantiomeric excesses of chiral, chelating diphosphines can be determined by association with a chiral palladium complex noted previously in section II.A.1.[134]

Enantiomeric excess of chiral phosphine oxides can be determined by NMR analysis using optically pure phenyl-*t*-butylphosphinothioic acid (8)[135] or *N*-(3,5-dinitrobenzoyl)-α-phenylethylamine (9).[136] Lanthanide shift reagents such as *tris*-[3-(heptafluoro-*n*-propylhydroxy-methylene)-(+)camphorato]europium (III) [Eu(hfc)] are also often used for determination of e.e. of these compounds.[67,82,137,138]



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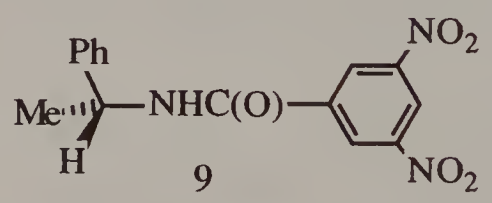

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High-performance liquid chromatography (HPLC) analysis with chiral adsorbants is becoming the most efficient method for the determination of e.e. of phosphorus compounds.[139-143] Racemic mixtures of phosphine oxides, phosphine-boranes, phosphonic acid esters, and related compounds can be resolved by the use of commercially available chiral columns. This techniques is useful for preparing small quantities of pure enantiomers.

IV. Reactions of Optically Active Organophosphorus Compounds

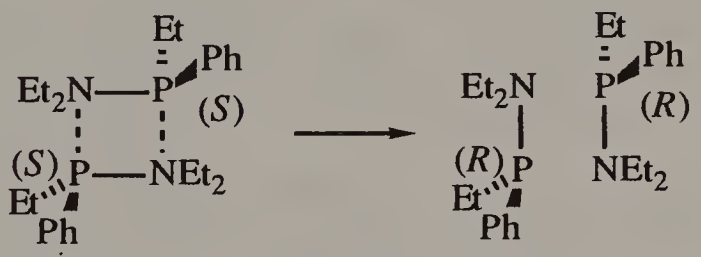
A. Reactions of Tricoordinate Phosphorus Compounds

1. Racemization of Phosphines

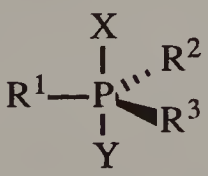
Optically active tertiary phosphines are known to racemize at high temperature.[13] The rates of racemization depend on the

structures of the phosphines. In Table 2 are shown first-order rate constants and half lives of several chiral phosphines.[144] Trialkylphosphines are relatively resistant to racemization, and the rate constant increases with increasing the number of aromatic groups bound to phosphorus. Racemization is also enhanced by the introduction of electron withdrawing groups on an aromatic ring.[144,145]

An optically active phosphinic acid amide, (*R*)-ethylphenylphosphinic acid diethylamide, undergoes spontaneous racemization at 130°, obeying zero-order kinetics.[39] The racemization is believed to proceed *via* four-centered dimeric intermediates, as shown below.



Racemization of phosphines is induced by HBr,[146] $SiCl_4$,[24] ROOR,[147] CCl_3CHO,[148] and halogens.[24,147,149] Racemization of chiral phosphines in the presence of these catalysts may be reasonably explained by assuming the formation of pentacoordinated intermediates. Thus, optically active phosphines react with HBr or $SiCl_4$ to form pentacoordinated intermediates of the type shown below.

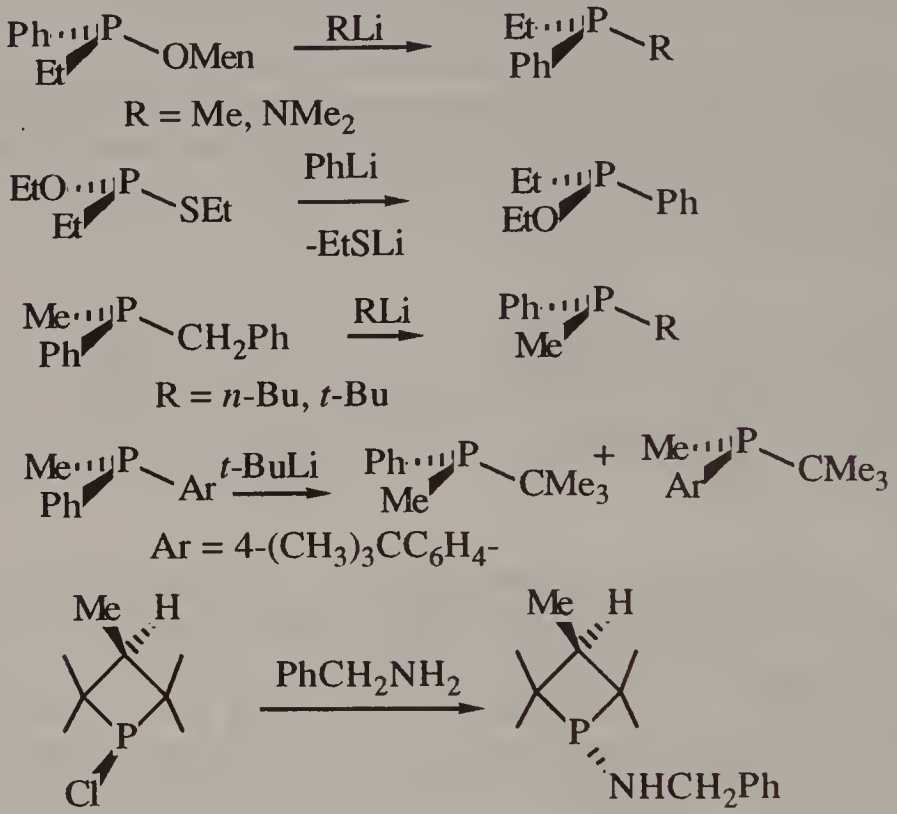


X = H, Y = Br;
X = Cl, Y = $SiCl_3$

At elevated temperatures these species undergo pseudorotation resulting in the formation of racemic mixtures. The racemization by halogen or diethyl peroxide is also explained reasonably by assuming the formation of achiral trigonalbipyramidal intermediates which collapse to parent phosphines with complete racemization.

2. Substitution Reactions at Tertiary Phosphorus

Nucleophilic substitution at tricoordinate phosphorus has been studied extensively by Kyba and Mikolajczyk, *et al.*[15,47-50,150-153] These reactions proceed in almost a completely stereospecific manner with inversion of configuration. Some representative examples are shown below.



It is interesting to note that the substitution reaction of *O*-ethyl *S*-ethyl ethylthiophosphonite with phenyllithium proceeds with inversion of configuration.[15] The result is in sharp contrast to the reaction of the corresponding thiophosphonate which proceeds with retention of configuration. Another notable fact is that the nucleophilic substitution of 1-chloro-2,2,3,4,4-pentamethylphosphetan occurs with inversion of configuration at phosphorus.[152,153] The data indicate that the substitution may best be considered to be a classical $S_N2(P)$-type process.

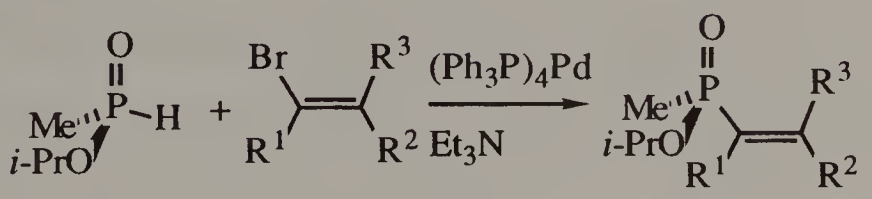
The operability of an $S_N2(P)$ process is suggested also in the substitution reaction of tertiary phosphines. The reaction of optically active 4-*t*-butylphenylmethylphenylphosphine with *t*-butyllithium provides two substitution products with inversion of configuration. This result clearly indicates that the nucleophilic

substitution occurs *via* a process which does not allow even one pseudorotation of any possible hypervalent anion intermediate.[151]

3. Stereochemistry of the Arbuzov Reaction and Related Reactions

The Arbuzov reaction is one of the most versatile pathways for the formation of carbon-phosphorus bonds and is frequently employed in the construction of organophosphorus compounds.[154,155] The reactions of chiral tricoordinate phosphorus compounds with alkyl halides have been studied, and it has been revealed that the reactions proceed with predominant retention of configuration. Almost complete stereospecificity is observed in acyclic systems,[58,156,157] while lower levels occur in cyclic systems.[59-61,158] The lack of complete stereospecificity in the latter systems is mainly ascribed to the steric factor of the ring substituents, unfavorable to the electrophilic attack on the hindered side of P(III) compounds.

Optically active tetracoordinate phosphorus compounds having a P-H bond are highly reactive, and they undergo stereospecific nucleophilic substitution with alkyl halides in the presence of a base to give phosphinates and phosphine oxides.[45,64,156,157,159] The reactions of aryl and vinylic halides also proceed in the presence of Pd(0) species with a high degree of stereospecificity.[160-162]



> 97% e.e.

4. Stereospecific Oxidation of Trivalent Phosphorus Compounds

The stereospecificity of the oxidation of chiral, trivalent phosphorus compounds depends largely on the choice of oxidizing agents and reaction conditions.[31,35,103,147-149,163-166] Oxidation with H_2O_2,[31,167] *t*-BuOOH,[164] *m*-$ClC_6H_4CO_3H$,[166] *t*-$BuOOCOCH_3$,[164] or O_2[103] affords retention products with a high degree of stereochemical integrity. On the contrary, oxidation with HNO_3[31] or Me_2SeO[166] proceeds with inversion of

configuration.

The stereochemical course of the oxidation with BrCN,[149] EtOOEt,[147] $BrCH(CO_2Et)_2$,[147] Cl_3CCHO,[148] or *t*-BuOCl[164] is largely affected by the nature of solvent. Inversion of configuration predominates in solvents containing water, while racemization occurs in aprotic solvents.

B. Nucleophilic Substitution Reactions of Pentavalent Tetracoordinate Organophosphorus Compounds

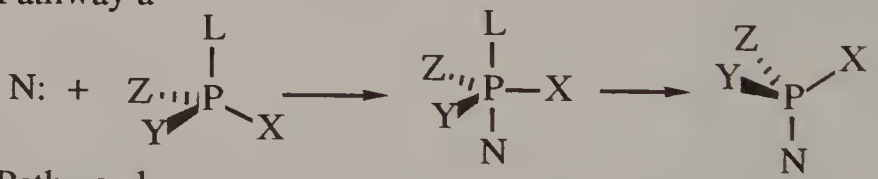
1. General Considerations

The nucleophilic substitution of tetracoordinate phosphorus compounds occupies the central position in the study of stereochemistry at phosphorus, and numerous investigations have been reported thus far. A number of excellent review articles are available.[1-12,18,19]

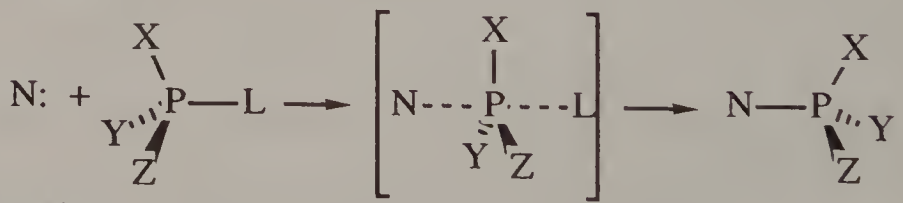
In some systems, the substitutions proceed in a highly stereospecific manner with either retention or inversion of configuration. In other systems, moderate or only marginal stereospecificity is observed. The generally accepted reaction pathways are outlined below.

Inversion:

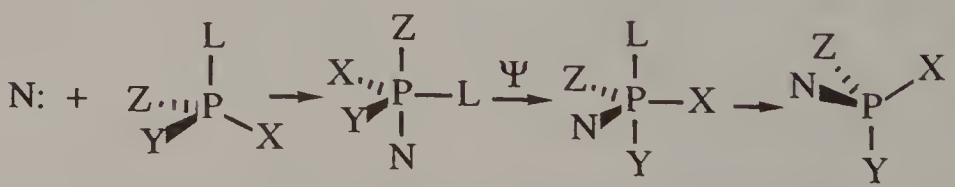
Pathway a -



Pathway b -



Retention:



Inversion of configuration is customarily considered to occur

via pathway a or pathway b. Pathway a is classified as an addition-elimination mechanism which involves a true intermediate. Thus, the nucleophile attacks phosphorus from the side opposite the leaving group to form a trigonalbipyramidal intermediate, and the leaving group departs before ligand reorganization can occur (by Berry pseudorotation or the Ugi turnstile mechanism). Pathway b, which is directly analogous to the S_N2 process at saturated carbon, involves simultaneous bond formation and bond fission within a transition state. It is not easy to distinguish the two pathways experimentally because the difference is not practical but conceptual. The two pathways should be regarded simply as the two extreme cases of the same mechanism depending on the lifetime of the intermediate and the degree of bond formation and bond breaking.

The reaction with retention of configuration can be reasonably explained using the trigonalbipyramidal concept. When the leaving group is not the most apicophilic of the initially attached ligands, it occupies an equatorial position in the initially formed intermediate. The intermediate undergoes ligand reorganization and the leaving group departs from the apical position resulting in the formation of product with retention of configuration.

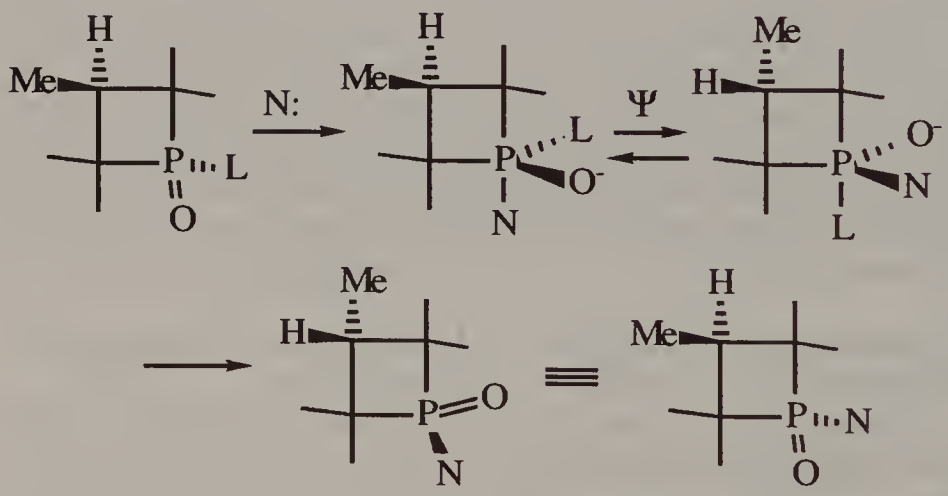
2. Substitution Reactions of Phosphorus Compounds Containing One Potential Leaving Group

Representative examples of substitution reactions of phosphinates, thiophosphinates, and related compounds are listed in Table 3.[14,45,59,62,63,65,168-175] In the acyclic systems (without ring strain) the displacements proceed with inversion of configuration at phosphorus. The reactions of less sterically hindered nucleophiles give products with high stereospecificity, while the reactions of bulky nucleophiles, such as *t*-BuLi, occur with signficiantly lower stereospecificity.

The inversion of configuration is reasonably explained by assuming the formation of a trigonalbipyramidal intermediate. In these systems the leaving group contains an electronegative atom such as oxygen, nitrogen, or sulfur, and hence it is the most apicophilic of the ligands originally attached to phosphorus. The nucleophile approaches a trigonal face of the tetrahedral phosphorus center to form a trigonalbipyramidal intermediate where the leaving group occupies an apical position. Subsequent break-down of the intermediate gives product with inversion of configuration.

On the other hand, nucleophilic displacements on four-mem-

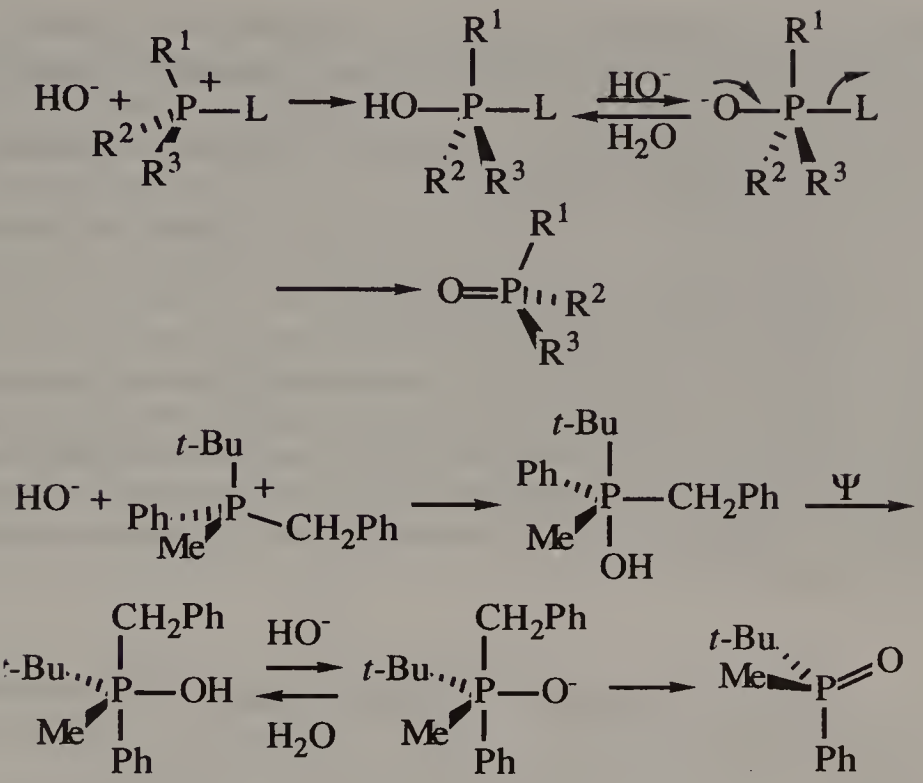
bered ring compounds containing tetracoordinate phosphorus proceed with retention of configuration. The stereochemical results observed in these systems are attributed to the positional requirements of the phosphetan system in the intermediate. As the four-membered ring is forced to span one axial and one equatorial position of the trigonalbipyramid, apical attack of the nucleophile leads to the formation of an intermediate in which the entering nucleophile occupies an apical position and the potential leaving group occupies an equatorial position. The intermediate undergoes pseudorotation to form an alternative trigonalbipyramidal structure, and subsequent departure of the leaving group from an apical position leads to substitution product with retention of configuration at phosphorus.



The stereochemistry of alkaline hydrolysis of phosphonium salts has been extensively studied and many interesting results have been reported thus far.[167,176-180] Representative examples are listed in Table 4.

The hydrolysis of acyclic phosphonium salts containing one potential leaving group proceeds, in most cases, with inversion of configuration. The stereochemical course of the inversion process can be depicted as shown below. There is no need to invoke pseudorotation in order to explain the stereochemistry in normal cases (100% inversion), as shown below.

On the other hand, retention of configuration at phosphorus is observed in the hydrolysis of quaternary phosphonium salts containing a bulky group, such as the *t*-butyl group. A plausible mechanism accounting for this stereochemical result is also shown.



In this latter case the more apicophilic benzyl group occupies an equatorial position and the *t*-butyl group occupies an apical position in the initially formed trigonalbipyramidal intermediate, since the bulky *t*-butyl group retards the formation of the alternative trigonalbipyramidal intermediate in which the benzyl and hydroxyl groups occupy apical positions. The initially formed intermediate undergoes pseudorotation followed by departure of the benzyl group to yield the *t*-butylmethylphenylphosphine oxide with retention of configuration.

Stereochemistry of the alkaline hydrolysis of cyclic phosphonium salts is largely affected by ring size.[181-194] As exemplified in Table 4, hydrolysis of four- and five-membered ring phosphonium salts proceed with complete retention of configuration. Six-membered ring systems are hydrolyzed with partial inversion of configuration. Almost complete inversion is observed in the hydrolysis of seven-membered ring phosphonium salts.

3. Substitution Reactions of Phosphorus Compounds Containing Two or Three Potential Leaving Groups

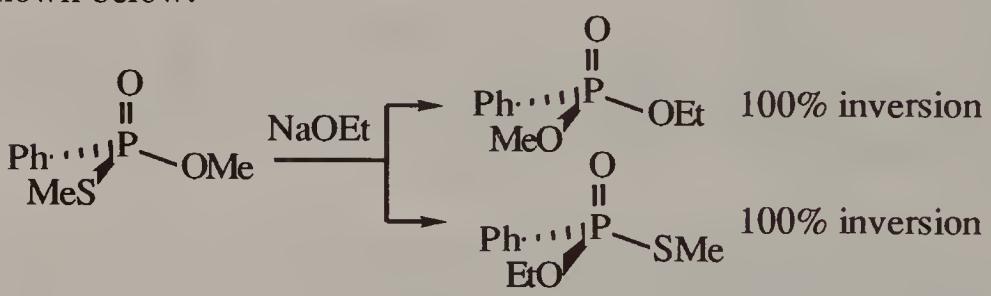
Displacements in tetracoordinate phosphorus containing two potential leaving groups, such as alkoxy, alkylthio, or halogen,

have been studied by a number of researchers.[103,111,171,195-212] The stereochemical results are summarized in Table 5.

The results of Table 5 can be explained reasonably by considering several factors:

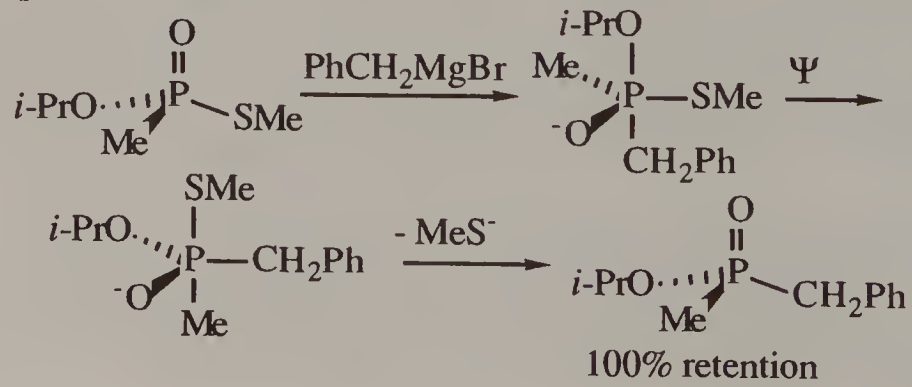
1. apicophilicity of the leaving group, ligands, and entering group;
2. leaving group ability of ligands;
3. ease of pseudorotation of the intermediate.

Inversion of configuration is commonly observed when both the leaving group and the entering group are relatively more apicophilic than the other attached groups, and the reorganization of the trigonalbipyramidal intermediate is energetically blocked by the need for a high-energy reorganization process. A typical example is shown below.[209]



In this reaction competitive displacements of the methylthio and methoxy ligands occur with complete inversion of configuration. Pseudorotation of trigonalbipyramidal intermediates to afford retention products is retarded owing to high energy barriers since the entering ethoxy group is much more apicophilic than phenyl or the oxyanion site.

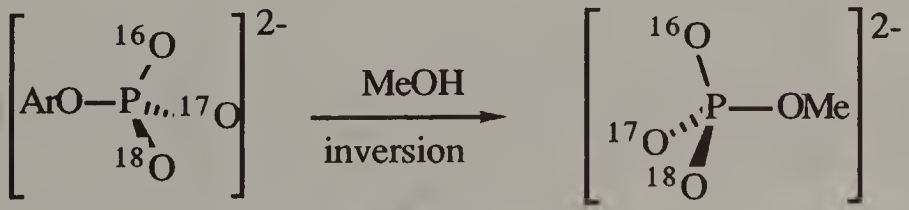
On the other hand, retention of configuration is observed when there is a low energy barrier to pseudorotation. A typical example is shown below.[103]



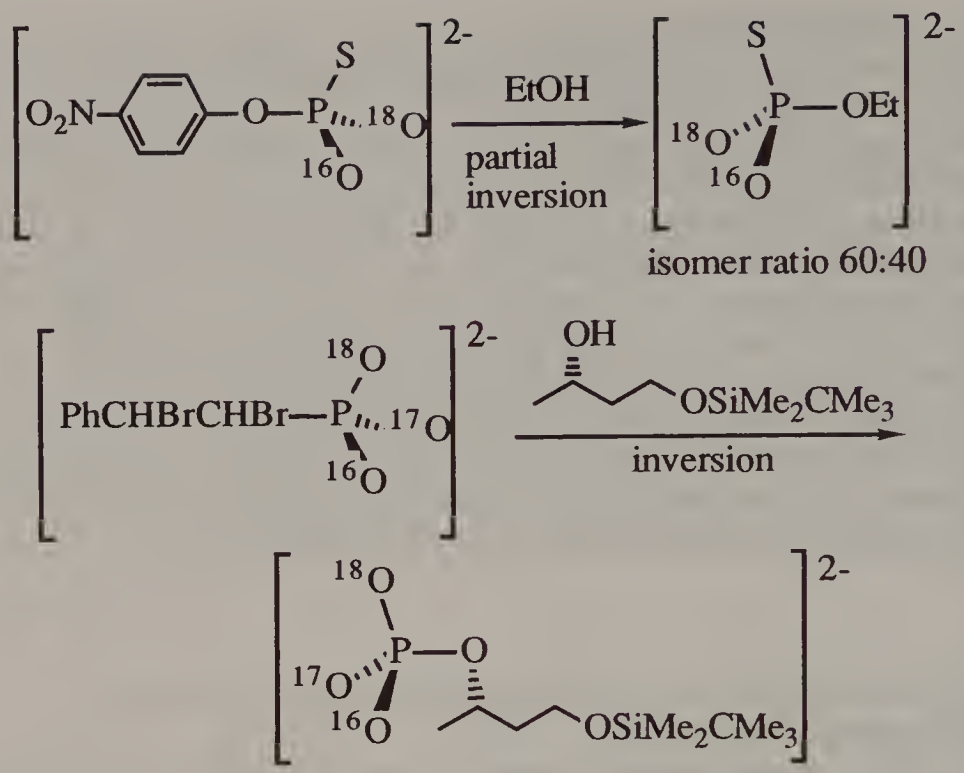
Nucleophilic substitutions of chiral cyclic systems have been studied extensively by Inch and Hall using compounds (4)-(7) noted previously in section II.B.1.[69-83,138,213] These reactions display regiochemical and stereochemical diversity not found in corresponding acyclic systems. The reaction course and stereochemistry are influenced not only by the apicophilicity and the leaving group ability of ligands, but also by ring conformations on directions of attack by nucleophiles and on the geometry of possible transition states and intermediates. In addition, the situations are further complicated in some cases by the fact that the kinetically favored bond-breaking process between phosphorus and the hetero atom does not always give the thermodynamically preferred product. The stereochemical results of these reactions are summarized and discussed in detail by Hall and Inch.[7,8]

4. Solvolysis of Optically Active Phosphate Monoesters and Related Compounds

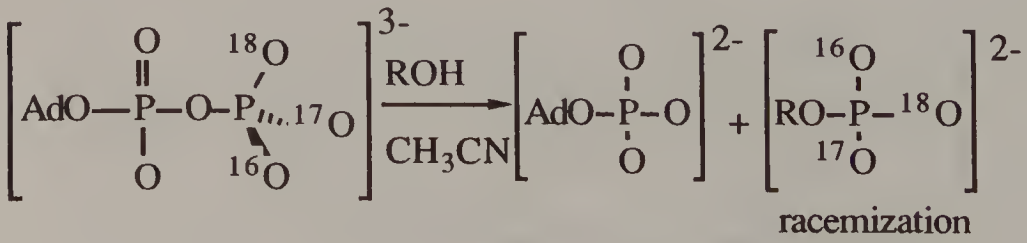
The stereochemical course of nucleophilic displacement reactions of chiral monosubstituted phosphate esters has been studied by several research groups in relation to the elucidation of the mechanism of enzyme-catalyzed phosphoryl-transfer reactions.[89-96,214] Knowles, *et al.* have studied the methanolysis of aryl [(*R*)-^{16}O,^{17}O,^{18}O]phosphate and have demonstrated that the reaction proceeds with inversion of configuration. The same stereochemical course is also observed in the ethanolysis of (*R*)-[^{16}O,^{18}O]thiophosphate and in the Conant-Swan fragmentation reaction. These results imply that metaphosphate is not a free intermediate under these conditions. Thus, the solvolysis is considered to occur by a preassociative mechanism in which there may be some assistance from the incoming nucleophile.

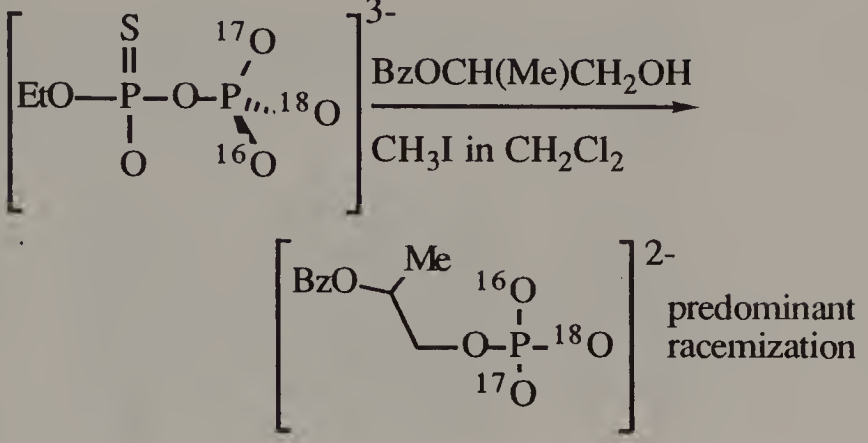


Ar = phenyl, 2,4-dinitrophenyl



On the other hand, alcoholysis of chiral pyrophosphate in an aprotic solvent such as acetonitrile or dichloromethane results in considerable racemization.[92,214] The phosphoryl transfer reactions may involve a relatively "free" metaphosphate intermediate which can be trapped by alcohol from either side.





C. Stereospecific Conversion of P=X to P=Y

Phosphorus pentasulfide, P_4S_{10}, is frequently used for the conversion of the phosphoryl group P(O) into the thiophosphoryl group P(S). The reaction of optically active *O,S*-diethyl ethylphosphonothiolate with this reagent affords *O,S*-diethyl ethylphosphonodithiolate with net retention of configuration.[215,216] In contrast to this stereospecific reaction, that of optically active methylpropylphenylphosphine oxide with P_4S_{10} leads to the racemic methylpropylphenylphosphine sulfide.[215]

Stereospecific conversion of the tertiary phosphine oxides to phosphine sulfides can be accomplished by the use of boron trisulfide (B_2S_3).[217] The reaction occurs with high stereospecificity and net retention of configuration.

Optically active phosphine sulfides and selenides can be stereospecifically converted to the corresponding phosphine oxides. The stereospecificity depends on the oxidizing agents as shown in Table 6.[31,35,48,67,166,218-227]

Table 1. Stereospecific Reduction of Chiral Phosphine Oxides

Reagent	Chiral Phosphine Oxide	Conditions	Stereochemical Result	Reference
$PhSiH_3$	(*n*-C_3H_7)(Ph)(Me)P(O)	neat, 80-100°, 1 hr.	retention (100%)	22
$PhSiH_3$	(R_P)-menthylphenylmethylphosphine oxide	neat, 95°, 4 hr.	retention (~80%)	25
$HSiCl_3$	($PhCH_2$)(Ph)(Me)P(O)	benzene, r.t., 2 hr.	retention (76%)	23
$HSiCl_3$-$PhNMe_2$	($PhCH_2$)(Ph)(Me)P(O)	benzene, ref., 1-2 hr.	retention (58%)	24
$HSiCl_3$-NEt_3	($PhCH_2$)(Ph)(Me)P(O)	benzene, ref., 1-2 hr.	inversion (100%)	24
Si_2Cl_6	($PhCH_2$)(Ph)(Me)P(O)	benzene, 70°, 10 min.	inversion (95%)	24
Si_2Cl_6	(1*S*,3*S*)-2,2,3-trimethyl-1-phenylphosphetan oxide	benzene, r.t., 5 min.	retention (100%)	27

Table 2. First-Order Rate Constants for Thermal Racemization of Phosphines $(R^1)(R^2)(Me)P$ [144]

R^1	R^2	k x 10^5 sec.$^{-1}$	half life (hr.)	relative rate
C_6H_{11}	*n*-C_3H_7	0.0427[a]	450	1.0
C_6H_5	*n*-C_3H_7	3.34[a]	5.76	78.0
C_6H_5	CH_2=$CHCH_2$	1.44[a]	13.4	33.6
C_6H_5	*t*-C_4H_9	1.61[a]	12.0	37.7
C_6H_5	*p*-$CH_3OC_6H_4$	17.0[a]	1.13	397
C_6H_5	*p*-$CH_3C_6H_4$	30.6[a]	0.629	716
C_6H_5	*p*-$CF_3C_6H_4$	145[a]	0.133	3400
C_6H_5	β-$C_{10}H_7$	64.8[b]	0.297	1520

[a] in decalin at 130.0° [b] in benzene at 130.0°

Table 3. Nucleophilic Substitutions of Phosphinates, Thiophosphinates, and Related Compounds

Substrate	Reagent	Product	Stereochemical Result	Reference
MePhP(O)OMen	RMgBr R = Et, *n*-Pr, $PhCH_2$, α-Naph, *o*-Anis	Me(Ph)(R)P(O)	inversion (very high)	62
Ph(β-Naph)P(O)OMen	MeLi	Ph(β-Naph)(Me)P(O)	inversion (95%)	63
Ph(β-Naph)P(O)OMen	*o*-$MeOC_6H_4Li$	Ph(β-Naph)(*o*-MeO-C_6H_4P(O)	inversion (44%)	63
Ph(Me)P(O)OMen	*t*-BuLi	Ph(Me)(*t*-Bu)P(O)	inversion (71%)	179
Ph(Me)P(O)OMen	PhNHLi	Ph(Me)(PhNH)P(O)	inversion (100%)	169
$Ph(Me)P(O)NR^1R^2$	MeOH, acid	Ph(Me)(MeO)P(O)	inversion (96%)	59
Ph(Me)P(O)SMe	*n*-PrMgBr	Ph(Me)(*n*-Pr)P(O)	inversion (not stated)	170
Ph(Me)P(O)SMe	*i*-PrOK	Ph(Me)(*i*-PrO)P(O)	inversion (not stated)	170
$Ph(Me)P(O)NR^1{}_2$	ROH, acid	Ph(Me)P(O)OR	inversion (excellent)	65
Ph(*t*-Bu)P(O)SCN	$R_4{}^+SCN^-$	Ph(*t*-Bu)P(O)NCS	inversion (not stated)	14
$Ph(Me)P(S)OP(O)(OEt)_2$	*p*-$MeC_6H_4O^-$	Ph(Me)P(S)OC_6H_4Me-*p*	inversion (not stated)	173
Ph(*t*-Bu)P(S)OSO_2CF_3	water, 1,4-dioxane	Ph(*t*-Bu)P(S)OH	inversion (not stated)	174
Ph(*t*-Bu)P(S)OSO_2CF_3	$NaBH_4$	Ph(*t*-Bu)P(S)H	inversion (not stated)	174
Ph(*t*-Bu)P(S)OSO_2Me	$AlCl_3$	Ph(*t*-Bu)P(S)Cl	retention (high)	204

$Ph(o\text{-}MeOC_6H_4)P(BH_3)OMen$		inversion (100%)	45
	MeLi	$Ph(o\text{-}MeOC_6H_4)(Me)P(BH_3)$	
$Ph(Me)P(BH_3)OMen$	$p\text{-}MeOC_6H_4Li$	$Ph(Me)(p\text{-}MeOC_6H_4)P(BH_3)$	
		inversion (99%)	175
$Ph(Me)P(BH_3)OMen$	$o\text{-}MeOC_6H_4Li$	$Ph(Me)(o\text{-}MeOC_6H_4)P(BH_3)$	
		inversion (12%)	175
$Ph(R)P(BH_3)NR^1R^2$	MeOH, acid	$Ph(R)(MeO)P(BH_3)$ inversion (100%)	46
R = Me, $o\text{-}MeOC_6H_4$, β-Naph			
(*E*)-2,2,3,4,4-pentamethyl-1-chlorophosphetan oxide		(*E*)-2,2,3,4,4-pentamethyl-1-alkoxyphosphetan oxide	181
	MeONa, EtONa	retention (100%)	182
(*E*)-2,2,3,4,4-pentamethyl--thiomethoxyphosphetan oxide		(*E*)-2,2,3,4,4-pentamethyl-1-dimethylaminophosphetan oxide	
	Me_2NLi	retention (100%)	182

Table 4. Alkaline Hydrolysis of Phosphonium Salts Containing One Potential Leaving Group

Substrate	Reagent	Product	Stereochemical Result	Reference
$[Ph(Me)(Me_3CCH_2PCH_2Ph]^+Br^-$	NaOH	$Ph(Me)(Me_3CCH_2)P(O)$	inversion (100%)	177
$[Ph(Me)(c\text{-}C_6H_{11})PCH_2Ph]^+Br^-$	NaOH	$Ph(c\text{-}C_6H_{11})(Me)P(O)$	inversion (100%)	177
$[Ph(Me)(p\text{-}MeC_6H_4)PCH_2Ph]^+Br^-$	NaOH	$Ph(Me)(p\text{-}MeC_6H_4)P(O)$	inversion (58%)	177
$[Ph(Me)(\alpha\text{-Naph})PCH_2Ph]^+Br^-$	NaOH	Ph(Me)(α-Naph)P(O)	inversion (28%)	177
$[Ph(Me)(t\text{-Bu})PCH_2Ph]^+Br^-$	NaOH H_2O	Ph(Me)(*t*-Bu)P(O)	inversion (19%)	178
$[Ph(Me)(t\text{-Bu})PCH_2Ph]^+Br^-$	NaOH aq. EtOH	Ph(Me)(*t*-Bu)P(O)	inversion (35%)	178
$[Ph(Me)(t\text{-Bu})P(\alpha\text{-Naph})]^+Br^-$	NaOH H_2O	Ph(Me)(*t*-Bu)P(O)	retention (64%)	178
$[Ph(Me)(t\text{-Bu})P(\alpha\text{-Naph})]^+Br^-$	NaOH aq. EtOH	Ph(Me)(*t*-Bu)P(O)	retention (91%)	178
$[Ph(Me)(\beta\text{-Naph})POEt]^+NO_3^-$	NaOH	Ph(Me)(β-Naph)P(O)	inversion (100%)	29
$[Ph(Me)(t\text{-Bu})POEt]^+SbCl_6^-$	NaOH	Ph(Me)(*t*-Bu)P(O)	inversion (100%)	179
$[Ph(Me)(n\text{-Pr})PSEt]^+SbCl_6^-$	NaOH	Ph(Me)(*n*-Pr)P(O)	inversion (100%)	29

$[Ph(Me)(n\text{-}Pr)P(NMeC_6H_4NO_2\text{-}p)]^+$

I^-	NaOH	Ph(Me)(*n*-Pr)P(O)	inversion (100%)	35
cis-2,2,3,4,4-pentamethyl-1-phenyl-1-ethoxyphosphatanium hexachloroantimonate	NaOH	*cis*-2,2,3,4,4-pentamentyl-1-phenyl phosphatan oxide	retention (100%)	183
trans-2,2,3,4,4-pentamethyl-1-phenyl-1-ethoxyphosphatanium hexachloroantimonate	NaOH	*trans*-2,2,3,4,4-pentamethyl-1-phenyl phosphatan oxide	retention (100%)	183
cis-1,2,2,3,4,4-hexamethyl-1-benzyl phosphatanium bromide	NaOH	*cis*-1,2,2,3,4,4-hexamethyl-		184
		phosphatan oxide	retention (100%)	185
cis-2,2,3,4,4-pentamethyl-1-phenyl-1-benzylphosphatanium bromide	NaOH	*cis*-2,2,3,4,4-pentamethyl-1-phenyl		184
		phosphatan oxide	retention (100%)	185
cis-1,3-dimethyl-1-benzyl-phospholanium bromide	NaOH	*cis*-1,3-dimethylphospholane		183
		oxide	retention (100%)	190
				192
trans-1,3-dimethyl-1-benzyl-phospholanium bromide	NaOH	*trans*-1,3-dimethylphospholane		183
		oxide	retention (100%)	190
				192
cis-1-phenyl-4-methyl-1-benzyl-phosphorinanium bromide	NaOH	48% *cis*- and 52% *trans*-1-phenyl-4-methyl-phosphorinan oxide		193
trans-1-phenyl-4-methyl-1-benzyl-phosphorinanium bromide	NaOH	22% *cis*- and 78% *trans*-1-phenyl-4-methyl-phosphorinan oxide		193
cis-1-phenyl-4-methyl-1-benzyl-phosphepanium bromide	NaOH	*trans*-1-phenyl-4-methyl-phosphepan oxide	inversion (100%)	191

Table 5. Substitution Reactions of Acyclic Phosphonic Acid Derivatives and Related Compounds

Substrate	Reagent	Product	Stereochemical Result	Reference
Me(*i*-PrO)P(O)Cl	PhMgBr	Me(*i*-PrO)P(O)Ph	inversion (100%)	171
Me(*i*-PrO)P(O)F	PhMgBr	Me(*i*-PrO)P(O)Ph	inversion (>47%)	171
t-Bu(MeO)P(O)SCN	$R_4N^+SCN^-$	*t*-Bu(MeO)P(O)NCS	inversion (not stated)	14
Me(*i*-PrO)P(O)SH	PCl_5	Me(*i*-PrO)P(S)Cl	inversion (high)	208
Ph(MenO)P(O)SMe	MeMgI	Ph(MenO)P(O)Me	retention (>95%)	203
Me(*i*-PrO)P(O)SMe	$PhCH_2MgCl$	Me(*i*-PrO)P(O)CH_2Ph	retention (100%)	103
Me(*i*-PrO)P(O)S$(CH_2)_2$-O$(CH_2)_2$OEt	PhMgBr	Me(*i*-PrO)P(O)Ph	inversion (57-75%)	103
Me(*i*-PrO)P(O)S$(CH_2)_2$-O$(CH_2)_2$OEt	*n*-PrMgBr	Me(*i*-PrO)P(O)(*n*-Pr)	retention (~50%)	103
Ph(MeO)P(O)SMe	NaOEt	Ph(MeO)P(O)OEt Ph(MeS)P(O)OEt	inversion (100%) inversion (100%)	209
Me(*i*-PrO)P(S)Cl	EtSK	Me(*i*-PrO)P(S)SEt	inversion (100%)	215
Me(*i*-PrO)P(S)Cl	NaOMe	Me(*i*-PrO)P(S)OMe	inversion (high)	208
Ph(R_2N)P(S)Cl	NH_3	Ph(R_2N)P(S)NH_2	inversion (high)	67
Ph(R_2N)P(S)Cl	MeOH-Et_3N	Ph(R_2N)P(S)OMe	inversion (high)	67
Me(*i*-PrO)P(S)SPr-*i*	KOH	Me(*i*-PrO)P(O)SK	racemization	216

$Ph(OMe)P(S)NR_2$	aq. acid	Ph(MeO)P(S)OH	inversion (high)	67
$[Ph(Me)P(OMen)SMe]^+SbCl_6^-$	NaOH	Ph(Me)P(O)OMen	retention (100%)	111
$[Ph(Me)P(OMe)SMe]^+SbCl_6^-$		Ph(Me)P(O)SMe	inversion	200
	NaOH	Ph(Me)P(O)OMe	retention	
$[Ph(Me)P(OEt)OMen]^+SbCl_6^-$	NaOH	Ph(Me)P(O)OEt	inversion (88%)	210

Table 6. Conversion of P=S or P=Se to P=O

Substrate	Reagent	Product	Stereochemical Result	Reference
Ph(Me)(MenO)P(S)	*m*-$ClC_6H_4CO_3H$	Ph(Me)(MenO)P(O)	retention (95%)	218
Ph(Me)(MenO)P(S)	CF_3CO_3H	Ph(Me)(MenO)P(O)	inversion (58%)	218
Ph(Et)MenO)P(S)	$Me_2S(O)/I_2$	Ph(Et)MenO)P(O)	inversion (98%)	48
Ph(Et)(MenO)P(S)	H_2O_2/EtOH	Ph(Et)(MenO)P(O)	retention (86%)	48
Me(MeO)(MenO)P(S)	*m*-$ClC_6H_4CO_3H$	Me(MeO)(MenO)P(O)	retention (not stated)	221
Ph(MeO)(R_2N)P(S)	*m*-$ClC_6H_4CO_3H$	Ph(MeO)(R_2N)P(O)	retention (>98%)	67
Ph(*t*-Bu)(MeO)P(S)	H_2O_2	Ph(*t*-Bu)(MeO)P(O)	retention (not stated)	111
Ph(Me)(*n*-Pr)P(S)	$KMnO_4$	Ph(Me)(*n*-Pr)P(O)	retention (100%)	35
Ph(Me)(*n*-Pr)P(S)	H_2O_2/Me_2CO	Ph(Me)(*n*-Pr)P(O)	inversion (43%)	225
Ph(Me)(*n*-Pr)P(S)	$Me_2S(O)/I_2$	Ph(Me)(*n*-Pr)P(O)	inversion (100%)	219
Ph(Me)(*n*-Pr)P(S)	$Me_2S(O)/H_2SO_4$	Ph(Me)(*n*-Pr)P(O)	inversion (100%)	220
Ph(Me)(*n*-Pr)P(S)	$Me_2Se(O)$	Ph(Me)(*n*-Pr)P(O)	inversion (86%)	166
Ph(Me)(*n*-Pr)P(S)	cyclohexene oxide/ CF_3CO_2H	Ph(Me)(*n*-Pr)P(O)	retention (not stated)	223
Ph(Me)(*n*-Pr)P(S)	$(CF_3CO)_2O$	Ph(Me)(*n*-Pr)P(O)	racemization	227

Table 6. - (continued)

4-methyl-1-methoxy-1,3,2 dioxaphosphrin sulfide	$(CF_3CO)_2O$	4-methyl-1-methoxy-1,3,2 dioxaphosphorin oxide	retention (not stated)	222
4-methyl-1-methoxy-1,3,2 dioxaphosphrin sulfide	HNO_3	4-methyl-1-methoxy-1,3,2 dioxaphosphorin oxide	retention (high)	224
4-methyl-1-methoxy-1,3,2 dioxaphosphrin sulfide	N_2O_4	4-methyl-1-methoxy-1,3,2 dioxaphosphorin oxide	retention (high)	224
4-methyl-1-methoxy-1,3,2 dioxaphosphrin sulfide	O_3	4-methyl-1-methoxy-1,3,2 dioxaphosphorin oxide	retention (100%)	226
Ph(Me)(*n*-Pr)P(Se)	$Me_sS(O)/I_2$	Ph(Me)(*n*-Pr)P(O)	inversion (83%)	219
Ph(Me)(*n*-Pr)P(Se)	$KMnO_4$	Ph(Me)(*n*-Pr)P(O)	retention (high)	31
Ph(Me)(*n*-Pr)P(Se)	HNO_3	Ph(Me)(*n*-Pr)P(O)	inversion (high)	31
Ph(Me)(*n*-Pr)P(Se)	N_2O_4	Ph(Me)(*n*-Pr)P(O)	inversion (low)	31
Ph(Me)(*n*-Pr)P(Se)	H_2O_2/Me_2CO	Ph(Me)(*n*-Pr)P(O)	inversion (52%)	225
Ph(Me)(*n*-Pr)P(Se)	H_2O_2/EtOH	Ph(Me)(*n*-Pr)P(O)	retention (36%)	225

Table 6. - (continued)

Ph(Me)(*n*-Pr)P(Se)	$Me_2Se(O)$	Ph(Me)(*n*-Pr)P(O)	inversion (100%)	166
Ph(Me)(*n*-Pr)P(Se)	$(CF_3CO)_2O$	Ph(Me)(*n*-Pr)P(O)	inversion (20%)	227
4-methyl-1-methoxy-1,3,2 dioxaphosphorin selenide	$Me_2Se(O)$	4-methyl-1-methoxy-1,3,2 dioxaphosphorin oxide	retention	166
4-methyl-1-methoxy-1,3,2 dioxaphosphorin selenide	$(CF_3CO)_2O$	4-methyl-1-methoxy-1,3,2 dioxaphosphorin oxide	inversion (86%, 75%)	227

V. Bibliography

1. Gallagher, M.J., and Jenkins, I.D. (1968). Stereochemical aspects of phosphorus chemistry, *Topics in Stereochemistry, Vol. 3*, (Eliel, E.L., and Allinger,N.L., eds.), Wiley, New York, pp. 1-96.
2. Smith, D.J.H. Phosphines, phosphonium salts, and halogenophosphines, *Comprehensive Organic Chemistry, Vol. 2*, Pergamon, London, Chapter 10.2.
3. Edmundson, R.S. Phosphorus acid derivatives, *Comprehensive Organic Chemistry, Vol. 2*, Pergamon, London, Chapter 10.3.
4. Smith, D.J.H. Penta-coordinate phosphorus compounds, *Comprehensive Organic Chemistry, Vol. 2*, Pergamon, London, Chapter 10.4.
5. Luckenbach, R. (1973). *Dynamic Stereochemistry of Penta-Coordinated Phosphorus and Related Elements*, Georg Thieme Publishers, Stuttgart.
6. Emsley, J., and Hall, D. (1976). *The Chemistry of Phosphorus*, Harper & Row, London.
7. Hall, C.R., and Inch, T.D. (1979). Asymmetric tetracoordinate pentacovalent organophosphorus compounds: their resolution and determination of enantiomeric purity, *Phosphorus Sulfur*, *7*: 171.
8. Hall, C.R., and Inch, T.D. (1980). Phosphorus stereochemistry, *Tetrahedron*, *36*: 2059.
9. Kagan, H.B., and Sasaki, M.(1990). Optically active phosphines: preparation, uses and chiroptical properties, *The Chemistry of Organophosphorus Compounds, Vol. 1*, (Hartley, F.R., ed.) Wiley, New York, Chapter 3.
10. Valentine, D. (1984). Preparation of the enantiomers of compounds containing chiral phosphorus centers, *Asymmetric Synthesis, Vol 4*, (Morrison, J.D., and Scott, J.W., eds.), Academic Press, New York, Chapter 3.
11. Mislow, K. (1970). Role of pseudorotation in the stereochemistry of nucleophilic displacement reactions, *Acc. Chem. Res.*, *3*: 321.
12. Zon, G., and Mislow, K. (1971). Studies in phosphorus stereochemistry, *Fortsch. Chem. Forsch.*, *19*: 61.
13. Rauk, A., Allen, L.C., and Mislow, K. (1970). Pyramidal inversion, *Angew. Chem., Int. Ed. Eng.*, *9*: 400.
14. Michalski, J., and Lopusinski, A. (1988). Organophosphorus thiocyanidates >P(O)SCN and their structural analogues.

Mechanism of thiocyanidate-isothiocyanidate isomerisation, *Reviews on Heteroatom Chemistry, Vol. 1*, (Oae, S., Ohno, A., and Furukawa, N., eds.), Myu, Tokyo, pp. 95-114.
15. Mikolajczyk, M. (1980). Optically active trivalent phosphorus acid esters: synthesis, chirality at phosphorus and some transformations, *Pure Appl. Chem.*, *52*: 959.
16. Bentrude, W.G. (1982). Phosphoranyl radicals: their structure, formation, and reactions, *Acc. Chem. Res.*, *15*: 117.
17. Bentrude, W.G. (1983). Phosphoranyl radicals, *Reactive Intermediates, Vol. 3*, (Abramovitch, R.A., ed.), Plenum, New York, pp. 199-298.
18. Westheimer, F.H. (1968). Pseudo-rotation in the hydrolysis of phosphate esters, *Acc. Chem. Res.*, *1*: 70.
19. Frey, P.A. (1982). Stereochemistry of enzymatic reactions of phosphates, *Tetrahedron*, *38*: 1541.
20. Stec, W.J. (1988). New opportunities in bioorganic phosphorus chemistry, *Reviews on Heteroatom Chemistry, Vol. 1*, (Oae, S., Ohno, A., and Furukawa, N., eds.), Myu, Tokyo, pp. 367-389.
21. Fest, C., and Schmidt, K.J. (1982). *The Chemistry of Organophosphorus Pesticides*, Springer, Berlin.
22. Marsi, K.L. (1974). Phenylsilane reduction of phosphine oxides with complete stereospecificity, *J. Org. Chem.*, *39*: 265.
23. Horner, L., and Balzer, W.D. (1965). Phosphororganische Verbindungen. IXL. Zum sterischen Verlauf der Desoxygenierung von tertiaren Phosphinoxyden zu tertiaren Phosphinen mit Trichlorsilan, *Tetrahedron Lett.*: 1157.
24. Nauman, K., Zon, G., and Mislow, K. (1969). The use of hexachlorodisilane as a reducing agent. Stereospecific deoxygenation of acyclic phosphine oxides, *J. Am. Chem. Soc.*, *91*: 7012.
25. Valentine, D., Blount, J.F., and Toth, K. (1980). Synthesis of phosphines having chiral organic groups ligated to chiral phosphorus, *J. Org. Chem.*, *45*: 3691.
26. Cremer, S.E., and Chorvat, R.J. (1967). Synthesis of substituted phosphetanes and related derivatives, *J. Org. Chem.*, *32*: 4066.
27. DeBruin, K.E., Zon, G., Naumann, K., and Mislow, K. (1969). Stereochemistry of nucleophilic displacement at phosphorus in some phosphetanium salts, *J. Am. Chem.*

Soc., *91*: 7027.
28. Egan, W., Chauviere, G., and Mislow, K. (1970). Nucleophilic displacements on a phospholane: a case of inversion of configuration, *J. Chem. Soc., Chem. Commun.*: 733.
29. Zon, G., DeBruin, K.E., Naumann, K., and Mislow, K. (1969). The stereospecific desulfurization of acyclic phosphine sulfides with hexachlorodisilane and the alkaline hydrolysis of monoalkoxy- and monoalkylmercaptophosphonium salts. Stereochemistry and mechanism, *J. Am. Chem. Soc.*, *91*: 7023.
30. Luckenbach, R. (1971). Stereospezifische Desulfurierung eines optisch aktiven Phosphinsulfids mit $LiAlH_4$, *Tetrahedron Lett.*: 2177.
31. Stec, W., Okruszek, A., and Michalski, J. (1971). Optically active selenoxomethylphenylpropylphosphoranes and their transformations, *Angew. Chem., Int. Ed. Eng.*, *10*: 494.
32. Henson, P.D., Naumann, K., and Mislow, K. (1969). Stereomutation of phosphine oxides by lithium aluminum hydride, *J. Am. Chem. Soc.*, *91*: 5645.
33. Horner, L., Winkler, H., Rapp, A., Mentrup, A., Hoffmann, H., and Beck, P. (1961). Phosphororganische Verbindungen. Optisch aktive tertiare Phosphine aus Optisch aktiven quartaren Phosphoniumsalzen, *Tetrahedron Lett.*: 161.
34. Horner, L., and Mentrup, A. (1961). Reduktiver Abbau quartarer Phosphoniumsalze an der Blei- bzw. Quecksilberkathode, *Ann.*, *646*: 65.
35. Horner, L. (1964). Darstellung und Eigenschaften optisch aktiver, tertiarer Phosphine, *Pure Appl. Chem.*, *9*: 225.
36. McEwen, W.E., Kumli, K.F., Blade-Font, A., Zanger, M., and VanderWerf, C.A. (1964). Mechanisms of substitution reactions at phosphorus. X. The Wittig reaction and the decomposition of quaternary phosphonium hydroxides, *J. Am. Chem. Soc.*, *86*: 2378.
37. Horner, L., and Ernst, M. (1970). Notiz zur Stereochemie der hydrogenolytischen Spaltung quarterer Arsonium- und Phosphoniumsalze mit $LiAlH_4$, *Ber.*, *103*: 318.
38. Luckenbach, R. (1973). Stereochemistry of the reduction of chiral quaternary phosphonium salts and *tertiary* phosphine oxide with a *tert*-butyl group to *tertiary* phosphines using lithium aluminum hydride, *Phosphorus*, *3*: 77.
39. Horner, L., and Jordan, M. (1980). Phosphororganische

Verbindungen. 92. Zur Stereochemie und zum chemischen Verhalten optisch aktiver Amidophosphoniumsalze und optisch aktiver Phosphinigsaureamide, *Phosphorus Sulfur*, *8*: 225.

40. Young, D.P., McEwen, W.E., Velex, D.C., Johnson, J.W., and VanderWerf, C.A. (1964). Reactions of optically active methyl-*n*-butylbenzylphosphine with cyclohexene episulfide and with sulfur, *Tetrahedron Lett.*: 359.
41. Horner, L., and Luckenbach, R. (1971). Phosphororganische Verbindungen. 70. Zum sterischen Verlauf der Cyanolysis und der Alkalispaltung optisch aktiver Phosphoniumsalze mit einer Alkylgruppe, *Phosphorus*, *1*: 73.
42. Wittig, G., Braun, H., and Cristau, H.-J. (1971). Darstellung und Racematspaltung chiraler Triarylphosphine, *Ann.*, *751*: 17.
43. Omelanczuk, J., and Mikolajczuk, M. (1979). Optically active trivalent phosphorus compounds. 2. Reactivity of alkylthio- and alkylselenophosphonium salts. The first stereospecific synthesis of a chiral phosphinite, *J. Am. Chem. Soc.*, *101*: 7292.
44. Imamoto, T., Kusumoto, T., Suzuki, N., and Sato, K. (1985). Phosphine oxides and $LiAlH_4$-$NaBH_4$-$CeCl_3$: synthesis and reactions of phosphine-boranes, *J. Am. Chem. Soc.*, *107*: 5301.
45. Imamoto, T., Oshiki, T., Onozawa, T., Kusumoto, T., and Sato, K. (1990). Synthesis and reactions of phosphine-boranes. Synthesis of new bidentate ligands with homochiral phosphine centers *via* optically pure phosphine-boranes, *J. Am. Chem. Soc.*, *112*: 5244.
46. Juge, S., Stephan, M., Laffitte, J.A., and Genet, J.P. (1990). Efficient asymmetric synthesis of optically pure tertiary mono and diphosphine ligands, *Tetrahedron Lett.*, *31*: 6357.
47. Omelanczuk, J., and Mikolajczyk, M. (1976). Stereochemistry of nucleophilic substitution at the optically active trivalent phosphorus atom, *J. Chem. Soc., Chem. Commun.*: 1025.
48. Mikolajczyk, M., Omelanczuk, J., and Perlikowska, W. (1979). Optically active trivalent phosphorus compounds. I. Diastereoisomeric *O*-menthyl ethylphenylphosphinites: synthesis, chirality at phosphorus and stereochemistry of nucleophilic displacement reaction, *Tetrahedron*, *35*: 1531.

49. Omelanczuk, J., Perlikowska, W., and Mikolajczyk, M. (1980). Stereospecific synthesis of diastereoisomerically pure (-)-(R_P)-*O*-menthyl methylphenylphosphinite and ethylphenylphosphinite: key intermediates in synthesis of chiral tertiary phosphines, *J. Chem. Soc., Chem. Commun.*: 24.
50. Chodkiewicz, W., Jore, D., and Wodzki, W. (1979). Optically active phosphines: new synthetic approach, *Tetrahedron Lett.*: 1069.
51. Chodkiewicz, W., and Guillerm, D. (1979). Stereoselective synthesis of phosphinite complexes. New route to chiral phosphines, *Tetrahedron Lett.*: 3573.
52. Chan, T.H. (1968). Optical resolution of phosphines by asymmetric platinum(II) complexes, *J. Chem. Soc., Chem. Commun.*: 895.
53. Otsuka, S., Nakamura, A., Kano, T., and Tani, K. (1971). Partial resolution of racemic tertiary phosphines with an asymmetric palladium complex, *J. Am. Chem. Soc., 93*: 4301.
54. Tani, K., Brown, L.D., Ahmed, J., Ibers, J.A., Yokota, M., Nakamura, A., and Otsuka, S. (1977). Chiral metal complexes. 4. Resolution of racemic tertiary phosphines with chiral palladium(II) complexes. The chemistry of diastereoisomeric phosphine Pd(II) species in solution, and the absolute configuration of [(*S*)-isopropyl-*tert*-butylphenylphosphine]-[(*R*)-*N*,*N*-dimethyl-α-(2-naphthyl)ethylamine-3*C*,*N*]chloropalladium(II) determined by X-ray diffraction, *J. Am. Chem. Soc., 99*: 7876.
55. Roberts, N.K., and Wild, S.B. (1979). Resolutions using metal complexes. Synthesis, separation into diastereoisomers, and resolution of *o*-phenylenebis(methylphenylphosphine) using palladium complexes containing optically active *ortho*-metalated dimethyl(α-methylbenzyl)amines, *J. Am. Chem. Soc., 101*: 6254.
56. Yoshikuni, T., and Bailar, J.C. (1982). Asymmetric hydrogenation: chiral bis(phosphine)rhodium catalysts with phenyl group derivatives, *Inorg. Chem., 21*: 2129.
57. Chodkiewicz, W. (1980). Stereoselectivite de la formation directe d'esters phosphineux de chinchonine acces aux phosphines chirales, *J. Organomet. Chem., 194*: C25.
58. Mikolajczyk, M., and Drabowicz, J. (1975). Optically active trivalent phosphorus acid esters: an approach by asymmetric

synthesis, *J. Chem. Soc., Chem. Commun.*: 382.
59. Juge, S., and Genet, J.P. (1989). Asymmetric synthesis of phosphinates, phosphine oxides and phosphines by Michaelis-Arbuzov rearrangement of chiral oxazaphospholidine, *Tetrahedron Lett.*, *30*: 2783.
60. Segi, M., Nakamura, Y., Nakajima, T., and Suga, S. (1983). Preparation of optically active phosphine oxides by regioselective cleavage of cyclic phenylphosphonite with alkyl halides, *Chem. Lett.*: 913.
61. Kato, T., Kobayashi, K., Masuda, S., Segi, M., Nakajima, T., and Suga, S. (1987). Asymmetric synthesis of phosphine oxides with the Arbuzov reaction, *Chem. Lett.*: 1915.
62. Korpiun, O., Lewis, R.A., Chickos, J., and Mislow, K. (1968). Synthesis and absolute configuration of optically active phosphine oxides and phosphinates, *J. Am. Chem. Soc.*, *90*: 4842.
63. Lewis, R.A., and Mislow, K. (1969). Direct configurational correlation of trialkyl- and triarylphosphine oxides, *J. Am. Chem. Soc.*, *91*: 7009.
64. Farnham, W.B., Murray, R.K., and Mislow, K. (1970). Stereospecific alkylation of menthyl phenylphosphinate, *J. Am. Chem. Soc.*, *92*: 5809.
65. Koizumi, T., Amitani, H., and Yoshii, E. (1979). A new synthesis of chiral alkyl methylphenylphosphinates, *Synthesis*: 110.
66. Koizumi, T., Kobayashi, Y., Amitani, H., and Yoshii, E. (1977). A practical method of preparing optically active dialkyl phenyl phosphates, *J. Org. Chem.*, *42*: 3459.
67. Koizumi, T., Takagi, H., and Yoshii, E. (1980). Chiral phenylphosphonic esters, their preparation *via* ethyl *N*-[chloro(phenyl)thiophosphoryl] L-prolinate and their absolute configurations, *Chem. Lett.*: 1403.
68. Koizumi, T., Amitani, H., and Yoshii, E. (1978). A new method of preparing optically active alkyl phenyl phosphonates, *Tetrahedron Lett.*: 3741.
69. Hall, C.R., and Inch, T.D. (1976). The preparation and stereochemistry of some phosphorus-selenoates. The stereochemistry of displacement of *S*-alkyl and *Se*-alkyl groups from phosphorus, *Tetrahedron Lett.*: 3645.
70. Cooper, D.B., Hall, C.R., Harrison, J.M., and Inch, T.D. (1977). (1,3,2-Oxazaphospholidines from (-)-ephedrine. Intermediates for the stereospecific synthesis of optically

active dialkyl alkylphosphono-thioates and -selenoates, trialkyl phosphoro-thioates and -selenoates, dialkyl methylphosphonates, and trialky phosphates, *J. Chem. Soc., Perkin Trans. I*: 1969.

71. Hall, C.R., and Inch, T.D. (1979). Preparation of some chiral alkyl alkyl phosphorothioates and stereochemical studies of their conversion into other chiral organophosphates, *J. Chem. Soc., Perkin Trans. I*: 1104.
72. Hall, C.R., and Inch, T.D. (1979). Chiral *O,S*-dialkyl phosphoramidothioates: their preparation, absolute configuration, and stereochemistry of their reactions in acid and base, *J. Chem. Soc., Perkin Trans. I*: 1646.
73. Hall, C.R., and Inch, T.D. (1981). Stereochemistry of alkaline hydrolysis of 1,3,2-oxazaphospholidine-2-thiones and related reactions, *J. Chem. Soc., Perkin Trans. I*: 2368.
74. Hall, C.R., and Williams, N.E. (1980). The preparation of and some reactions of 1,3,2-thiazaphospholidine-2-ones, *Tetrahedron Lett., 21*: 4959.
75. Hall, C.R., and Williams, N.E. (1981). 1,3,2-Thiazaphospholidin-2-ones derived from ephedrine. Preparation and stereochemistry of ring-opened reactions, *J. Chem. Soc., Perkin Trans. I*: 2746.
76. Hall, C.R., Inch, T.D., and Williams, N.E. (1982). 1,3,2-Oxazaphospholidine-2-thiones from (+)-norephedrins: stereospecific ring opening, possibly by an elimination-addition mechanism, *J. Chem. Soc., Perkin Trans. I*: 639.
77. Hall, C.R., Inch, T.D., and Williams, N.E. (1983). The stereochemical course of substitution reactions at halomethylphosphonates, *Phosphorus Sulfur, 18*: 213.
78. Hall, C.R., Inch, T.D., Peacock, G., Pottage, C., and Williams, N.E. (1984). Chiral mono-, di-, and tri-chloromethylphosphonates and phosphonothioates: preparation, absolute configuration, and the stereochemical course of their reaction with methoxide, *J. Chem. Soc., Perkin Trans. I*: 669.
79. Cooper, D.B., Inch, T.D., and Lewis, G.J. (1974). Use of carbohydrate derivatives for studies of phosphorus stereochemistry. Part I. Stereochemistry of 1,3,2-dioxaphosphorinan-2-ones and synthesis of optically active phosphine oxides, *J. Chem. Soc., Perkin Trans. I*: 1043.
80. Harrison, J.M., Inch, T.D., and Lewis, G.J. (1974). Use of carbohydrate derivatives for studies of phosphorus stereo-

chemistry. Part III. Stereochemical course of nucleophilic displacements of 2-substituents in 1,3,2-dioxaphosphorinan-2-ones and related compounds, *J. Chem. Soc., Perkin Trans. I*: 1053.

81. Inch, T.D., Lewis, G.J., Wilkinson, R.G., and Watts, P. (1975). Differences in mechanisms of nucleophilic substitution at phosphorus in *S*-alkyl alkylphosphonothioates and *S*-alkyl phosphorothioates, *J. Chem. Soc., Chem. Commun.*: 500.
82. Hall, C.R., Inch, T.D., Lewis, G.J., and Chittenden, R.A. (1975). Stereospecific synthesis from carbohydrate precursors of (*R*)- and (*S*)-ethyl isopropyl methyl phosphate and other optically active neutral phosphorus esters, *J. Chem. Soc., Chem. Commun.*: 720.
83. Hall, C.R., Inch, T.D., and Lawston, I.W. (1979). Ring opening of 1,3,2-oxazaphospholidine-2-thiones with alkyl lithiums; synthesis of chiral phosphinothioic acids, *Tetrahedron Lett.*: 2729.
84. Koizumi, T., Yanada, R., Takagi, H., Hirai, H., and Yoshii, E. (1981). Stereochemistry of the base-catalyzed methanolysis of 2-phenyl-tetrahydropyrrolo-1,3,2-oxazaphospholes, *Tetrahedron Lett.*, *22*: 477.
85. Koizumi, T., Yanada, R., Takagi, H., Hirai, H., and Yoshii, E. (1981). Grignard reaction of 2-phenyl-tetrahydropyrrolo-1,3,2-oxazaphospholes. Observation of stereospecific inversion of configuration, *Tetrahedron Lett.*, *22*: 571.
86. Jones, S.R., Kindman, L.A., and Knowles, J.R. (1978). Stereochemistry of phosphoryl group transfer using a chiral [oxygen-16, -17, -18] phosphate. Stereochemical course of alkaline phosphatase, *Nature*, *275*: 564.
87. Abbott, S.J., Jones, S.R., Weinman, S.A., and Knowles, J.R. (1978). Chiral [^{16}O, ^{17}O, ^{18}O] phosphate monoesters. 1. Asymmetric synthesis and stereochemical analysis of [1(*R*)-^{16}O, ^{17}O, ^{18}O]phospho-(*S*)-propane-1,2-diol, *J. Am. Chem. Soc.*, *100*: 2558.
88. Cullis, P.M., and Lowe, G. (1981). Synthesis of chiral [^{16}O, ^{17}O, ^{18}O]phosphate esters, *J. Chem. Soc., Perkin Trans. I*: 2317.
89. Buchwald, S.L., Friedman, J.M., and Knowles, J.R. (1984). Stereochemistry of nucleophilic displacement on two phosphoric monoesters and a phosphoguanidine: the role of metaphosphate, *J. Am. Chem. Soc.*, *106*: 4911.

90. Jarvest, R.L., Lowe, G., and Potter, B.V.L. (1981). Analysis of the chirality of [^{16}O, ^{17}O, ^{18}O]phosphate esters by ^{31}P nuclear magnetic resonance spectroscopy, *J. Chem. Soc., Perkin Trans. I*: 3186.
91. Calvo, K.C. (1985). The Conant-Swan fragmentation reaction: stereochemistry of phosphate ester formation, *J. Am. Chem. Soc.*, *107*: 3690.
92. Cullis, P.M., and Rous, A.J. (1985). Stereochemical course of phosphoryl transfer reactions of P^1,P^1-disusbstituted pyrophosphate in aprotic solvent. A model for the enzyme-catalyzed "dissociative" phosphoryl transfer, *J. Am. Chem. Soc.*, *107*: 6721.
93. Cullis, P.M., Iagrossi, A., and Rous, A.J. (1986). Thiophosphoryl-transfer reactions: a general synthesis and configurational analysis of *O*-substituted [^{16}O, ^{18}O]thiophosphates, *J. Am. Chem. Soc.*, *108*: 7869.
94. Cullis, P.M., and Iagrossi, A. (1986). Thiophosphoryl-transfer reactions: stereochemical course of solvolysis of *p*-nitrophenyl thiophosphate in protic solvent and the possible role of thiometaphosphate, *J. Am. Chem. Soc.*, *108*: 7870.
95. Freeman, S., Seidel, H.M., Schwalbe, C.H., and Knowles, J.R. (1989). Phosphonate biosynthesis: the stereochemical course of phosphoenolpyruvate phosphomutase, *J. Am. Chem. Soc.*, *111*: 9233.
96. Seidel, H.M., Freeman, S., Schwalbe, C.H., and Knowles, J.R. (1990). Phosphonate biosynthesis: the stereochemical course of phosphoenolpyruvate mutase, *J. Am. Chem. Soc.*, *112*: 8149.
97. Boter, H.L., and Platenburg, D.H.J.M. (1967). Organophosphorus compounds. V. The resolution of *O*-alkyl hydrogen methylphosphonothioates with (+)- and (-)-α-phenylethylamine, *Rec. Trav. Chim. Pays-Bas*, *86*: 399.
98. Krawiecka, B., and Michalski, J. (1971). Organophosphorus compounds. CLIV. Synthesis, resolution, and some optically active derivatives of *O*-methyl *tert*-butylphosphonothioic acid, *Bull. Acad. Pol. Ser. Sci. Chim.*, *19*: 377.
99. Mikolajczyk, M., and Omelanczuk, J. (1973). Configuration of the optically active phosphorus thioacids. III. Synthesis and optical resolution of *O*-methyl isopropylphosphonothioic acid, *Phosphorus*, *3*: 47.
100. Harger, M.J.P. (1978). Chemical shift non-equivalence of

enantiomers in the proton magnetic resonance spectra of partly resolved phosphinothioic acids, *J. Chem. Soc., Perkin Trans. II*: 326.

101. Hall, C.R., and Inch, T.D. (1979). Asymmetric tetracoordinate pentacovalent organophosphorus compounds: their resolution and determination of enantiomeric purity, *Phosphorus Sulfur*, *7*: 171.
102. Moriyama, M., and Bentrude, W.G. (1982). A convenient preparation of an optically active trialkylphosphine, (+)-(*S*)-*n*-propylmethylbenzylphosphine, from (-)-(*S*)-methyl *O*-isopropyl methylphosphonothioate, *Tetrahedron Lett.*, *23*: 4547.
103. Moriyama, M., and Bentrude, W.G. (1983). Optically active phosphines. Facile preparation of the optically active *n*-propylmethylbenzyl- and methylphenylbenzylphosphine oxides as precursors to the corresponding tertiary phosphines, *J. Am. Chem. Soc.*, *105*: 4727.
104. Aaron, H.S., Shryne, T.M., and Miller, J.I. (1958). The stereochemistry of asymmetric phosphorus compounds. I. The resolution of *O*-ethyl ethylphosphonothioic acid, *J. Am. Chem. Soc.*, *80*: 107.
105. Aaron, H.S., Braun, J., Shryne, T.M., Frack, H.F., Smith, G.E., Uyeda, R.T., and Miller, J.I. (1960). The stereochemistry of asymmetric phosphorus compounds. III. The resolution of a series of *O*-alkyl alkylphosphonothioic acids, *J. Am. Chem. Soc.*, *82*: 596.
106. Green, M., and Hudson, R.F. (1963). Optically active phosphorus compounds. Part II. The configurational change accompanying transesterification, *J. Chem. Soc.*: 540.
107. Hamer, N.K. (1965). Studies in phosphorylation. Part XXVII. Nucleophilic displacements on methyl hydrogen *N*-cyclohexylphosphoramidothioate, *J. Chem. Soc.*: 2731.
108. Gerrard, A.F., and Hamer, N.K. (1967). Mechanism of the rapid alkaline hydrolysis of a phosphoramidothioate ester, *J. Chem. Soc. B*: 1122.
109. Benschop, H.P., and Van den Berg, G.R. (1968). Organophosphorus compounds. VI. The complete resolution of methylphenylphosphinothioic acid, *Rec. Trav. Chim. Pays-Bas*, *87*: 362.
110. Seiber, J.N., and Tolkmith, H. (1969). Optically active organophosphoramides. *O*-2,4-Dichlorophenyl *O*-methyl isopropylphosphoramidothioate and some related

compounds, *Tetrahedron*, *25*: 381.
111. De'ath, N.J., Ellis, K., Smith, D.J.H., and Trippett, S. (1971). Alkaline hydrolysis of alkoxy(methylthio)phosphonium salts with retention of configuration at phosphorus, *J. Chem. Soc., Chem. Commun.*: 714.
112. Donninger, C., and Hutson, D.H. (1968). The stereochemistry of enzymatic reactions at phosphorus. I. Resolution of methyl 1-naphthyl phosphorothionic acid, *Tetrahedron Lett.*: 4871.
113. Akintonwa, D.A.A. (1978). The synthesis and stereochemical aspects of optically active phosphorothionates, *Tetrahedron*, *34*: 959.
114. Kumli, K.F., McEwen, W.E., and VanderWerf, C.A. (1959). Resolution of a non-heterocyclic quaternary phosphonium iodide, *J. Am. Chem. Soc.*, *81*: 248.
115. Horner, L., and Samaan, S. (1971). Steric course of alkali cleavage of quaternary chiral arsonium salts, *Phosphorus*, *1*: 207.
116. DeBruin, K.E., and Perrin, E.D. (1975). A convenient preparation of simple optically active phosphinate esters and derivatives from the corresponding menthyl esters. Solvolysis of menthoxyphosphonium salts in trifluoroacetic acid, *J. Org. Chem.*, *40*: 1523.
117. DeBruin, K.E., and Thomas, L.L. (1977). Route to chiral imidate esters of phosphorus: synthesis and hydrolysis of (*S*)-(+) *O*-ethyl *N*-*t*-butyl methylphenylphosphinimidate, *J. Chem. Soc., Chem. Commun.*: 33.
118. Bodalski, R., Rutkowska-Olma, E., and Pietrusiewicz, K.M. (1980). Optically active phosphine oxides. Synthesis and absolute configurations of (menthoxycarbonylmethyl)-phenylvinyl phosphine oxide, *Tetrahedron*, *36*: 2353.
119. Pietrusiewicz, K.M., Zablocka, M., and Monkiewicz, J. (1984). Optically active phosphine oxides. 2. Novel approach to enantiomeric dialkylphenylphosphine oxides, *J. Org. Chem.*, *49*: 1522.
120. Imamoto, T., Sato, K., and Johnson, C.R. (1985). A new method for the synthesis of optically pure phosphine oxides, *Tetrahedron Lett.*, *26*: 783.
121. Toda, F., Mori, K., Stein, Z., and Goldberg, I. (1988). Optical resolution of phosphinates and phosphine oxides by complex formation with optically active 2,2'-dihydroxy-1,1'-binaphthyl and crystallographic study of two diastereoiso-

meric complexes with $(CH_3)(C_6H_5)(OCH_3)PO$, *J. Org. Chem.*, *53*: 308.
122. Johnson, C.R., and Imamoto, T. (1987). Synthesis of polydentate ligands with homochiral phosphine centers, *J. Org. Chem.*, *52*: 2170.
123. Pietrusiewicz, K.M., and Zablocka, M. (1988). Optically active phosphine oxides. 5. P-Chiral 2-aminoethyl phosphine oxides, *Tetrahedron Lett.*, *29*: 1991.
124. Pietrusiewicz, K.M., and Zablocka, M. (1988). Optically active phosphine oxides. 3. Conjugate addition to vinyl phosphine oxides in aqueous medium, *Tetrahedron Lett.*, *29*: 937.
125. Maryanoff, C.A., Maryanoff, B.E., Tang, R., and Mislow, K. (1973). A one-step synthesis of optically pure 1,2-ethano bis sulfoxides and phosphine oxides *via* the copper-promoted oxidative dimerization of chiral sulfinyl and phosphinyl carbanions, *J. Am. Chem. Soc.*, *95*: 5839.
126. Knowles, W.S., Sabacky, M.J., Vineyard, B.D., and Weinkauff, D.J. (1975). Asymmetric hydrogenation with a complex of rhodium and a chiral bisphosphine, *J. Am. Chem. Soc.*, *97*: 2567.
127. Vineyard, B.D., Knowles, W.S., Sabacky, M.J., Bachman, G.L., and Weinkauff, D.J. (1977). Asymmetric hydrogenation. Rhodium chiral bisphosphine catalyst, *J. Am. Chem. Soc.*, *99*: 5946.
128. Pietrusiewicz, K.M., and Zablocka, M. (1988). Optically active phosphine oxides. 4. A straightforward synthesis of P-chiral 1,2-diphosphinoylethanes, *Tetrahedron Lett.*, *29*: 1987.
129. Pietrusiewicz, K.M., Wisniewski, W., and Zablocka, M. (1989). Optically active phosphine oxides. 8. Synthesis of nonsymmetrical 1,2-diphosphinylethenes and related systems, *Tetrahedron*, *45*: 337.
130. Hellwinkel, D. (1966). Die Stereochemie organischer Derivat des funf- und sechsbindigen Phosphors. II. Uber ein erstes optisch aktives Pentaarylphosphoran, *Ber.*, *99*: 3642.
131. Acher, F., Juge, S., and Wakselman, M. (1987). Chiral bicyclic spirophosphoranes in an Arbuzov-type reaction, *Tetrahedron*, *43*: 3721.
132. Moriarty, R.M., Hiratake, J., and Liu, K. (1990). New synthetic route to unsymmetrical substituted pentacoordinated phosphorus. Hydrolytically stable chiral monocyclic oxy-

phosphoranes, *J. Am. Chem. Soc.*, *112*: 8575.
133. Casey, J.P., Lewis, R.A., and Mislow, K. (1969). A general method for determining the optical purity of phosphines, *J. Am. Chem. Soc.*, *91*: 2789.
134. Kyba, E.P., and Rines, S.P. (1982). A spectroscopic method for the determination of optical purities of chiral, chelating diphosphines, *J. Org. Chem.*, *47*: 4800.
135. Harger, M.J.P. (1980). The proton magnetic resonance spectra of chiral phosphinate esters. Chemical shift non-equivalence of enantiomers induced by optically active phosphinothioic acids, *J. Chem. Soc., Perkin Trans. II*: 1505.
136. Dunach, E., and Kagan, H.B. (1985). A simple chiral shift reagent for measurement of enantiomeric excess of phosphine oxides, *Tetrahedron Lett.*, *26*: 2649.
137. Pasquier, M.L., and Marty, W. (1985). A new method for determining enantiomeric excess, where the sample serves as its own reference, *Angew. Chem., Int. Ed. Eng.*, *24*: 315.
138. Hall, C.R., and Inch, T.D. (1979). Asymmetric tetracoordinate pentacovalent organophosphorus compounds: their resolution and determination of enantiomeric purity, *Phosphorus Sulfur*, *7*: 171.
139. Pirkle, W.H., Finn, J.M., Schreiner, J.L., and Hamper, B.C. (1981). A widely useful chiral stationary phase for the high-performance liquid chromatography separation of enantiomers, *J. Am. Chem. Soc.*, *103*: 3964.
140. Okamoto, Y., Honda, S., Hatada, K., Okamoto, I., Toga, Y., and Kobayashi, S. (1984). Chromatographic resolution of racemic compounds containing phosphorus or sulfur atom as chiral center, *Bull. Chem. Soc. Jpn.*, *57*: 1681.
141. Brown, T.M., and Grothusen, J.R. (1984). High-performance liquid chromatography of 4-nitrophenyl organophosphinates and chiral-phase separation of enantiomers, *J. Chromatogr.*, *294*: 390.
142. Tambute, A., Gareil, P., Caude, M., and Rosset, R. (1986). Preparative separation of racemic tertiary phosphine oxides by chiral high-performance liquid chromatography, *J. Chromatogr.*, *363*: 81.
143. Pescher, P., Caude, M., Rosset, R., and Tambute, A. (1986). Enantiomeric separation of tertiary phosphine oxides on Pirkle's chiral stationary phase. Mobile phase and temperature optimization, *J. Chromatogr.*, *371*: 159.

144. Baechler, R.D., and Mislow, K. (1970). The effect of structure on the rate of pyramidal inversion of acyclic phosphines, *J. Am. Chem. Soc.*, *92*: 3090.
145. Baechler, R.D., and Mislow, K. (1970). Barrier to pyramidal inversion in silylphosphines, *J. Am. Chem. Soc.*, *92*: 4758.
146. Balzer, W.D. (1966). Ph.D. Dissertation, Univ. Mainz.
147. Denny, D.B., and Adin, N.G. (1966). Solvent effects on the stereochemistry of some reactions of phenylmethylpropylphosphine. (1), *Tetrahedron Lett.*: 2569.
148. Denny, D.B., and Gershman, N.E. (1965). Reactions of chloral with optically active phenylmethylpropylphosphine, *Tetrahedron Lett.*: 3899.
149. Horner, L., and Winkler, H. (1964). Phosphororganische Verbindungen. XL. Reaktionen mit phosphindihalogeniden aus optisch aktivem Methylpropylphenylphosphin, *Tetrahedron Lett.*: 455.
150. Kyba, E.P. (1975). Nucleophilic substitution at phosphorus in tertiary phosphines. Inversion of configuration, *J. Am. Chem. Soc.*, *97*: 2554.
151. Kyba, E.P. (1976). Nucleophilic substitution at phosphorus in tertiary phosphines. Evidence against pseudorotation in a potential intermediate, *J. Am. Chem. Soc.*, *98*: 4805.
152. Smith, D.J.H., and Trippett, S. (1969). Stereochemistry of nucleophilic substitution at tervalent phosphorus. 1-Chloro-2,2,3,4,4-pentamethylphosphetan, *J. Chem. Soc., Chem. Commun.*: 855.
153. Corfield, J.R., Oram, R.K., Smith, D.J.H., and Trippett, S. (1972). The stereochemistry of nucleophilic substitution at phosphorus in P^{III} and P^{V} phosphetans, *J. Chem. Soc., Perkin Trans. I*: 713.
154. Bhattacharya, A.K., and Thyagarajan, G. (1981). The Michaelis-Arbuzov rearrangement, *Chem. Rev.*, *81*: 415.
155. Hudson, H.R., (1983). Quasi-phosphonium intermediates and compounds, *Top. Phosphorus Chem.*, *11*: 339.
156. Mikolajczyk, M., and Krzwanski, J. (1977). Stereochemistry of organophosphorus cyclic compounds. 6. Stereochemistry of the reaction between sulfenyl chlorides and trivalent phosphorus compounds, *J. Org. Chem.*, *42*: 190.
157. Van den Berg, G.R., Platenburg, D.H.J.M., and Benschop, H.P. (1971). Stereochemistry of a Michaelis-Arbusov reaction: alkylation of optically active ethyl trimethylsilyl

phenylphosphonite with retention of configuration, *J. Chem. Soc., Chem. Commun.*: 606.
158. Juge, S., Wakselman, M., Stephan, M., and Genet, J.P. (1990). Evidence of the loss of chirality at the phosphonium step in the Arbuzov rearrangement, *Tetrahedron Lett.*, *31*: 4443.
159. Michalski, J., and Skrzypczynski, Z. (1975). Stereoselective deselenisation of *t*-butylphenylphosphinoselenoic acids. Stereochemical relationship between *t*-butylphenylphosphinoselenoic acids and their sulfur analogues, *J. Organomet. Chem.*, *97*: C31.
160. Xu, Y., and Zhang, J. (1986). Stereochemistry at the phosphorus atom during palladium-catalyzed formation of carbon-phosphorus bonds and mechanistic implications, *J. Chem. Soc., Chem. Commun.*: 1606.
161. Zhang, J., Xu, Y., Huang, G., and Guo, H. (1988). Palladium-catalyzed synthesis of chiral, nonracemic isopropyl arylmethylphosphinates, *Tetrahedron Lett.*, *29*: 1955.
162. Xu, Y., Wei, H., Zhang, J., and Huang, G. (1989). An efficient syntheis of chiral, nonracemic isopropyl alkenylmethylphosphinates *via* palladium route, *Tetrahedron Lett.*, *30*: 949.
163. Horner, L., Fuchs, H., Winkler, H., and Rapp, A. (1963). Phosphororganische Verbindungen. XXXVII. Zur Frage der Konfigurationserhaltung bei der kathodischen Spaltung quartarer Phosphoniumsalze zu tertiaren Phosphinen und bei der Quartarisierung tertairer Phosphine, *Tetrahedron Lett.*: 965.
164. Denney, D.B., and Hanifin, J.W. (1963). The stereochemistry of some oxidations of phenylmethylpropylphosphine, *Tetrahedron Lett.*: 2177.
165. Horner, L., and Winkler, H. (1964). Phosphororganische Verbindungen. XLVI. Zum sterischen Verlauf der Desoxygenierung und Desulfurierung mit tertiaren Phosphinen, *Tetrahedron Lett.*: 3275.
166. Mikolajczyk, M., and Luczak, J. (1978). Dimethyl selenoxide oxidation of trivalent phosphorus compounds, thio-, and selenophosphoryl compounds, and thiocarbonyl compounds. Stereochemical studies and selective modification of the thiocarbonyl-containing nucleic acid components, *J. Org. Chem.*, *43*: 2132.
167. Luckenbach, R. (1972). Zum sterischen Verlauf der Abspal-

tung aromatischer Liganden aus optisch aktiven Phosphoniumsalzen mit Alkalihydroxyd, *Phosphorus*, *1*: 229.
168. Nudelman, A., and Cram, D.J. (1968). The stereochemical course of ester-amide interchange leading to optically active phosphinic and sulfinic amides, *J. Am. Chem. Soc.*, *90*: 3869.
169. Nudelman, A., and Cram, D.J. (1971). A stereochemical reaction cycle with chiral phosphorus, *J. Org. Chem.*, *36*: 335.
170. Benschop, H.P., Van den Berg, G.R., and Boter, H.L. (1968). Organophosphorus compounds. VII. The absolute configuration of Sarin and related anticholinesterases established by chemical correlation, *Rec. Trav. Chim. Pays-Bas*, *87*: 387.
171. Van den Berg, G.R., Platenburg, D.H.J.M., and Benschop, H.P. (1972). Organophosphorus compounds. XI. Stereochemistry of Grignard displacement reactions at phosphorus in isopropyl methylphosphonohalogenates, *Rec. Trav. Chim. Pays-Bas*, *91*: 929
172. Krawiecka, B., Michalski, J., and Skrzypczynski, Z. (1974). Stereochemistry of acid-catalyzed solvolysis at the sterically hindered thiophosphoryl centre, *J. Chem. Soc., Chem. Commun.*: 1022.
173. Horner, L., and Jordan, M. (1980). Phosphororganische Verbindungen. 93. Zum Chemie optisch aktiver Phosphinigsaureamide, *Phosphorus Sulfur*, *8*: 235.
174. Skrzypczynski, Z., and Michalski, J. (1988). Stereoselective synthesis and stereochemistry of optically active *tert*-butylphenylphosphine sulfide, *J. Org. Chem.*, *53*: 4549.
175. Oshiki, T., and Imamoto, T. (1990). The reaction of optically pure menthyloxymethylphenylphosphine-borane with organolithium reagents, *Bull. Chem. Soc. Jpn.*, *63*: 3719.
176. Kumli, K.F., McEwen, W.E., and VanderWerf, C.A. (1959). Stereospecific conversion of methylethylphenylbenzylphosphonium iodide to methylethylphenylphosphine oxide, *J. Am. Chem. Soc.*, *81*: 3805.
177. Luckenbach, R. (1972). Zum sterischen Verlauf der Alkalispaltung optisch aktiver benzylgruppenhaltiger Phosphoniumsalze, *Phosphorus*, *1*: 223.
178. Luckenbach, R. (1972). Zum sterischen Verlauf der Phosphinoxydspaltung optisch aktiver Phosphoniumsalze mit einer *t*-Butylgruppe, *Phosphorus*, *1*: 293.

179. Lewis, R.A., Naumann, K., DeBruin, K.E., and Mislow, K. (1969). *t*-Butylphosphonium salts: nucleophilic displacement at phosphorus with inversion of configuration, *J. Chem. Soc., Chem. Commun.*: 1010.
180. De'ath, N.J., and Trippett, S. (1969). *t*-Butylphosphonium salts: the alkaline hydrolysis of an acyclic phosphonium salt with retention of configuration at phosphorus, *J. Chem. Soc., Chem. Commun.*: 172.
181. DeBruin, K.E., and Jacobs, M.J. (1971). Stereochemistry of the alkaline hydrolysis of dialkoxyphosphetanium salts: nature and energetics of the pentacoordinate intermediates, *J. Chem. Soc., Chem. Commun.*: 59.
182. DeBruin, K.E., Padilla, A.G., and Campbell, M.-T. (1973). Alkaline hydrolysis of 1-X-1-alkoxy-2,2,3,4,4-pentamethylphosphetanium salts. An unusual order of ligand kinetic axiophilicities, *J. Am. Chem. Soc.*, *95*: 4681.
183. DeBruin, K.E., Naumann, K., Zon, G., and Mislow, K. (1969). Topological representation of the stereochemistry of displacement reactions at phosphorus in phosphonium salts and cognate systems, *J. Am. Chem. Soc.*, *91*: 7031.
184. Hawes, W., and Trippett, S. (1968). Alkaline hydrolysis of a phosphonium salt with retention of configuration at phosphorus, *J. Chem. Soc., Chem. Commun.*: 295.
185. Corfield, J.R., Shutt, J.R., and Trippett, S. (1969). The stereochemistry of the alkaline hydrolysis of phosphetanium salts. Change in configuration at phosphorus on ylide formation, *J. Chem. Soc., Chem. Commun.*: 789.
186. Hawes, W., and Trippett, S. (1969). Some substitution reactions at the phosphorus of 2,2,3,4,4-pentamethylphosphetans, *J. Chem. Soc., C*: 1465.
187. Cremer, S.E., Chorvat, R.J., and Trivedi, B.C. (1969). Stereochemistry of the base decomposition of phosphetanium bromides, *J. Chem. Soc., Chem. Commun.*: 769.
188. Cremer, S.E., and Trivedi, B.C. (1969). Stereochemistry of nucleophilic attack on a cyclic phosphinate ester, *J. Am. Chem. Soc.*, *91*: 7200.
189. Ezzell, B.R. (1970). Alkaline cleavage of phosphetane oxides, *J. Org. Chem.*, *35*: 2426.
190. Marsi, K.L. (1968). Stereochemistry of alkaline cleavage of *cis*- and *trans*-1-benzyl-1,3-dimethylphospholanium bromide, *J. Chem. Soc., Chem. Commun.*: 846.
191. Marsi, K.L. (1971). Phosphepanium salts. Nucleophilic

substitution at heterocyclic phosphorus with complete inversion of configuartion, *J. Am. Chem. Soc.*, *93*: 6341.
192. Marsi, K.L. (1969). Stereochemistry of some reactions of phospholane derivatives, *J. Am. Chem. Soc.*, *91*: 4724.
193. Marsi, K.L., and Clark, R.T. (1970). Stereochemistry of alkaline cleavage of *cis*- and *trans*-1-benzyl-4-methyl-1-phenylphosphorinanium bromide, *J. Am. Chem. Soc.*, *92*: 3791.
194. Gorenstein, D.G. (1973). Hydrolysis of a phosphonium salt. Encounter-limited, rate-determining breakdown of a pentacovalent intermediate, *J. Am. Chem. Soc.*, *95*: 8060.
195. Aaron, H.S., Uyeda, R.T., Frack, H.F., and Miller, J.I. (1962). The stereochemistry of asymmetric phosphorus compounds. IV. The synthesis and stereochemistry of displacement reactions of optically active isopropyl methylphosphonochloridate, *J. Am. Chem. Soc.*, *84*: 617.
196. Reiff, L.P., and Aaron, H.S. (1970). Stereospecific synthesis and reactions of optically active isopropyl methylphosphinate, *J. Am. Chem. Soc.*, *92*: 5275.
197. Szafraniec, L.J., Reiff, L.P., and Aaron, H.S. (1970). Stereoselective synthesis and stereochemistry of optically active isopropyl methylphosphinothioate, *J. Am. Chem. Soc.*, *92*: 6391.
198. Donohue, J., Mandel, N., Farnham, W.B., Murray, R.K., Mislow, K., and Benschop, H.P. (1971). Retention stereochemistry in a Grignard displacement reaction at chiral phosphorus. The absolute configuration of menthyl *S*-methyl phenylphosphonothioate, *J. Am. Chem. Soc.*, *93*: 3792.
199. Farnham, W.B., and Mislow, K. (1972). Stereochemistry of methanolysis of menthyl *S*-methyl phenylphosphonothioate, *J. Chem. Soc., Chem. Commun.*: 120.
200. DeBruin, K.E., and Johnson, D.M. (1973). Relative energetics of modes for phosphorane formation and decomposition in nucleophilic displacement reactions at acyclic phosphorus. Alkaline hydrolysis of alkoxy(alkylthio) phosphonium salts, *J. Am. Chem. Soc.*, *95*: 4675.
201. DeBruin, K.E., and Johnson, D.M. (1974). The stereochemistry of the alkaline hydrolysis of *O*-menthyl *S*-methyl phenylphosphodithioates. A comparison to menthoxy(methylthio)phosphonium salt hydrolysis, *Phosphorus*, *4*: 13.
202. DeBruin, K.E., and Johnson, D.M. (1974). The alkaline hydrolysis of a methylphosphonodithioate, *O*-menthyl

S-methyl methylphosphonodithioate, with inversion of configuration at phosphorus, *Phosphorus*, *4*: 17.
203. DeBruin, K.E., and Johnson, D.M. (1975). Alkoxide ion *vs.* methylthiolate ion displacement in the Grignard reaction of *O*-alkyl *S*-methyl phenylphosphonothiolate, *J. Chem. Soc., Chem. Commun.*: 753.
204. Michalski, J., and Skrzypczynski, Z. (1977). Novel reaction of phosphinothioic methanesulphonic anhydride with aluminum halides. Stereoselective synthesis of phosphinothioic halides, *J. Chem. Soc., Chem. Commun.*: 66.
205. Hall, C.R., and Inch, T.D. (1977). Acid and base catalyzed alcoholyses of some chiral *O,S*-dialkyl phosphoramidothioates, *Tetrahedron Lett.*: 3765.
206. Hall, C.R., Inch, T.D., and Pottage, C. (1981). The effect of added lithium cations on the stereochemistry of nucleophilic displacement reactions at phosphorus, *Phosphorus Sulfur*, *10*: 229.
207. Hall, C.R., and Williams, N.E. (1982). Stereospecific halogenation of ethyl methyl phosphorothioic acid, *Tetrahedron Lett.*, *23*: 999.
208. Szafraniec, L.J., Szafraniec, L.L., and Aaron, H.S. (1982). Reaction of (*R*)-(+)-isopropyl methylphosphinate with methyl triflate. Stereospecific synthesis of (*R*)-(+)-isopropyl methyl methylphosphonite, *J. Org. Chem.*, *47*: 1936.
209. DeBruin, K.E., Tang, C.W., Johnson, D.M., and Wilde, R.L. (1989). Kinetic facial selectivity in nucleophilic displacements at tetracoordinate phosphorus: kinetics and stereochemistry in the reaction of sodium ethoxide with *O,S*-dimethyl phenylphosphonothioate, *J. Am. Chem. Soc.*, *111*: 5871.
210. DeBruin, K.E., and Misłow, K. (1969). Stereochemistry of the alkaline hydrolysis of dialkoxyphosphonium salts, *J. Am. Chem. Soc.*, *91*: 7393.
211. Michalski, J., Mikolajczyk, M., Mlotkowska, B., and Omelanczuk, J. (1969). Stereochemistry of nucleophilic substitution reaction at a thiophosphoryl center. IV. Chemical proof of a Walden inversion, *Tetrahedron*, *25*: 1743.
212. Omelanczuk, J., Kielbasinski, P., Michalski, J., Mikolajczak, J., Mikolajczyk, M., and Skowronska, A. (1975). Reaction of oxophosphoranesulphenyl chlorides with phosphorus trichloride. A new synthesis of dialkyl phosphorochloridothionates and their optically active

analogues, *Tetrahedron*, *31*: 2809.
213. Hall, C.R., and Inch, T.D. (1981). The stereochemical course of the alkaline hydrolysis of 1,3,2-oxazaphospholidine-2-thiones, *Am. Chem. Soc. Symp. Ser.*, *171*: 89.
214. Cullis, P.M., and Rous, A.J. (1986). Stereochemical course of the phosphoryl transfer from adenosine 5'-diphosphate to alcohols in acetonitrile and the possible role of monomeric metaphosphate, *J. Am. Chem. Soc.*, *108*: 1298.
215. Omelanczuk, J., and Mikolajczyk, M. (1971). Stereochemistry of the reaction between phosphoryl compounds and phosphorus pentasulphide (P_4S_{10}), *Tetrahedron*, *27*: 5587.
216. Reiff, L.P., Szafraniec, L.J., and Aaron, H.S. (1971). Stereoselective synthesis of phosphonothioates from phosphonate analogues: basic hydrolysis of chiral phosphonothioates to a racemic product, *J. Chem. Soc., Chem. Commun.*: 366.
217. Maryanoff, B.E., Tang, R., and Mislow, K. (1973). Optically active phosphine sulphides from phosphine oxides and boron trisulphide, *J. Chem. Soc., Chem. Commun.*: 273.
218. Herriott, A.W. (1971). Peroxy acid oxidation of phosphinothioates, a reversal of stereochemistry, *J. Am. Chem. Soc.*, *93*: 3304.
219. Mikolajczyk, M., and Luczak, J. (1975). Dimethyl sulphoxide oxidations: an iodine-catalyzed conversion of thio- or selenophosphoryl and thiocarbonyl compounds into their oxygen analogues, *Synthesis*: 114.
220. Luckenbach, R. (1973). Phospin- bzw. Arsinoxide durch Einwirkung von Dimethylsulfoxid auf Phosphin- bzw. Arsin-sulfide in saurer Losung, *Synthesis*: 307.
221. Hall, C.R., Inch, T.D., Pottage, C., and Williams, N.E. (1985). Stereochemistry of some reactions between alkyl *S*-methyl methylphosphonothioates and chiral alkoxides, *Tetrahedron*, *41*: 4909.
222. Helinski, J., Skrzypczynski, Z., Wasiak, J., and Michalski, J. (1990). Efficient oxygenation of thiophosphoryl and selenophosphoryl groups using trifluoroacetic anhydride, *Tetrahedron Lett.*, *31*: 4081.
223. Chan, T.H., and Finkenbine, J.R. (1972). Facile conversion of oxiranes to thiiranes by phosphine sulfides. Scope, stereochemistry, and mechanism, *J. Am. Chem. Soc.*, *94*: 2880.
224. Stec, W.J., Okruszek, A., and Mikolajczyk, M. (1971).

Stereochemistry of the oxidation of thiophosphoryl group in 1,3,2-dioxaphosphorinanes, *Z. Naturforsch. B*, *26*: 855.
225. Stec, W.J., Okruszek, A., and Michalski, J. (1976). Organophosphorus compounds of sulfur and selenium. Stereochemistry of oxidation of thiono- and selenophosphoryl compounds with hydrogen peroxide, *J. Org. Chem.*, *41*: 233.
226. Skowronska, A., and Krawczyk, E. (1983). A general method for the conversion of thiophosphoryl and selenophosphoryl groups into phosphoryl groups by ozone oxidation, *Synthesis*: 509.
227. Bruzik, K.S., and Stec, W.J. (1990). Reversible oxidation of phosphylthionates and phosphylselenoates with trifluoroacetic anhydride, *J. Org. Chem.*, *55*: 6131.

CHAPTER 2

DEVELOPMENTS IN THE PREPARATION AND USE OF SILICON-CONTAINING ORGANOPHOSPHORUS COMPOUNDS

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I. Introduction

Recent years, especially the last two decades, have witnessed a tremendous growth in the area of silicon-containing organophosphorus reagents. Their potential in the synthesis of organophosphorus compounds of industrial, biological, medical, and other synthetic uses have been widely recognized and exploited, and this area is still growing rapidly.

Since there exist already several reviews[1-10] dealing with the chemistry of silicon-containing organophosphorus compounds, the present review deals mainly with the developments that occurred during the past ten years. In this review we will discuss various methods for the preparation of silyl esters of several types of organophosphorus acids along with their utility for further transformations. We will also broadly discuss the synthesis and utility of compounds containing the phosphorus-silicon linkage. Compounds having phosphorus and silicon atoms connected by oxygen, sulfur, or selenium are classified as silyl esters of phosphorus.

II. Synthesis of Phosphorus-Silyl Esters

A. Synthesis of Phosphorus(III) Silyl Esters

An extensive literature exists for the synthesis of silyl esters of phosphorus acids, and this has been thoroughly reviewed.[11] The most common method for the preparation of tervalent phosphorus silicon esters is by silylation of phosphorus acids with active silylating agents. Those reagents most commonly used are halogenosilanes,[12-28] aminosilanes, silazanes, and silyl amides,[14,29-31] alkoxy and acyloxy silanes, siloxanes,[32-34] silanols and silanolates,[35] silanothiolates and silathianes,[33,34,36] and hydrosilanes in catalyzed reactions.[35]

Reaction of phosphorous acid with three equivalents of

trimethylchlorosilane in the presence of three equivalents of triethylamine produces tris(trimethylsilyl) phosphite. The first two silyl groups enter easily to produce bis(trimethylsilyl) phosphite, and its conversion to tris(trimethylsilyl) phosphite requires the use of heating for longer periods of time.[37]

$$H_3PO_3 \xrightarrow[\text{triethylamine}]{Me_3SiCl} H\text{-}\overset{\overset{O}{\|}}{P}(OTMS)_2 \longrightarrow P(OTMS)_3$$

Reaction of monomethyl phosphite with silylating agents such as hexamethyldisilazane under reflux conditions produces bistrimethylsilyl methyl phosphite.[37,38]

$$MeO\text{-}P(OH)_2 \xrightarrow{(TMS)_2NH} MeO\text{-}P(OTMS)_2$$

In a similar fashion reaction of dimethyl phosphite with silylating agents such as hexamethyldisilazane or trimethylchlorosilane produces dimethyl trimethylsilyl phosphite.[37-39]

Dimethyl *t*-butyldimethylsilyl phosphite has been prepared by reaction of dimethyl phosphite with sodium hydride followed by *t*-butyldimethylsilyl chloride.[39] Similarly, triethylsilyl *N,N,N',N'*-tetramethylphosphordiamidite has been prepared by reaction of *N,N,N',N'*-tetramethylphosphordiamido chloride with sodium trimethylsilanoate.[39]

$$Et_3SiOH \xrightarrow{NaH} Et_3SiONa \xrightarrow{[Me_2N]_2PCl} Et_3SiOP[NMe_2]_2$$

α-Naphthylphenylmethylsilyl *t*-butylphenylphosphinite has been prepared by reaction of the corresponding silanolate with *t*-butylphenylchlorophosphine.[40,41] As expected, the stereochemistry at silicon remained intact during this preparation.

Secondary phosphine oxides react with alkali metals producing the corresponding phosphinite anions which yield silyl phosphinites on reaction with silyl halides.[42]

$$Ph_2P\text{-}OH \xrightarrow{K} Ph_2P\text{-}O^-K^+ \xrightarrow{TMSCl} Ph_2P\text{-}OTMS$$

Bis(trimethylsilyl) hypophosphite has been prepared by reaction of hypophosphorous acid with trimethylsilyl chloride or bis(trimethylsilyl)acetamide.[14,43] This compound is extremely pyrophoric so generation *in situ* is preferred.

Recently researchers at Ciba-Geigy reported the preparation of the silyl ester of a hypophosphorous acid synthon.[44,45] Reaction of hypophosphorous acid with triethyl orthoformate produces the intermediate phosphonite which on silylation in refluxing hexamethyldisilazane gives the silylated phosphonite, a versatile phosphorus synthon.

$$H_3PO_2 \xrightarrow{HC(OEt)_3} (EtO)_2CH\text{-}\underset{\displaystyle OEt}{\underset{|}{P}}\text{-}OH \xrightarrow{HMDS} (EtO)_2CH\text{-}\underset{\displaystyle OEt}{\underset{|}{P}}OTMS$$

The reaction of the *trans* isomer of 4-methyl-2-hydro-2-oxo-1,3,2-dioxaphosphorinane with TMSCl in the presence of triethylamine yields the stable *trans*-2-trimethylsilyloxy-4-methyl-1,3,2-dioxaphosphorinane, while the reaction of the corresponding *cis* isomer yields the less stable *cis*-2-trimethylsilyloxy-4-methyl-1,3,2-dioxaphosphorinane. It is essential to conduct this reaction at low temperature (~-10^{o} to prevent the isomerization of the *cis* material to the *trans* isomer. The *cis* compound isomerizes completely to the *trans* isomer at 0^{o} over a period of one week.[46]

A new phosphorylating agent for the hydroxyl group of deoxyribonucleosides, di(2,2,2-trifluoroethyl) trimethylsilyl phosphite, has been prepared by the action of TMSCl and triethylamine on the corresponding di(2,2,2-trifluoroethyl) phosphite.[47]

A highly stereoselective conversion of 2,2,2-trichloroethoxycarbonylphosphonates to silyl phosphites in the presence of TMSCl and zinc has been reported.[30,48]

$$(RO)_2\overset{\displaystyle O}{\overset{\|}{P}}CO_2CH_2CCl_3 \xrightarrow{Zn,\ TMSCl} (RO)_2POTMS$$

B. Experimental Procedures

1. Tris(trimethylsilyl) Phosphite[37]

Commercially available phosphorous acid (40 g, 0.463 mol) of 95% purity is made anhydrous by dissolution in THF (200 mL) and repeatedly coevaporated with dry benzene (3 x 400 mL). The

dry acid is dissolved in a mixture of dry THF (400 mL) and dry ether (1.6 L). To the solution is added trimethylsilyl chloride (166 g, 1.528 mol), and then triethylamine (155 g, 1.528 mol) is added dropwise at room temperature over a period of 1 hr. The mixture is refluxed for 6 hr and cooled to room temperature. The precipitate is filtered and washed with dry ether (200 mL). The combined filtrate and washings are concentrated under reduced pressure and the residue is vacuum distilled to give the title compound (131 g, 86% pure, bp 90-92/20 Torr). This mixture is heated with sodium (3 g, 0.130 mol) at 140-150° for 18 hr and vacuum distilled to give the tris(trimethylsilyl) phosphite (118 g, 82%) of bp 90-92°/20 Torr.

2. Diethyl Trimethylsilyl Phosphite[37]

Sodium (13.8 g, 0.6 g-atom) is added to dry ether (250 mL) and diethyl phosphite (69 g, 0.5 mol) is added dropwise at 10° whereby an exothermic reaction occurs. After evolution of hydrogen gas ceases, the mixture is heated under reflux for 30 min. Trimethylsilyl chloride (65.2 g, 0.6 mol) is added slowly at 10° over a period of 1 hr. After the addition, the mixture is stirred at room temperature for 1.5 hr. The solvent is evaporated under reduced pressure and the residual liquid is vacuum distilled to yield diethyl trimethylsilyl phosphite (97.5 g, 91%) of bp 66°/15 Torr.

3. Dimethyl *t*-Butyldimethylsilyl Phosphite[39]

To a flask equipped with a reflux condenser, mechanical stirrer, and an addition funnel are added anhydrous THF (500 mL) and sodium hydride (7.57. g, 0.315 mol) in mineral oil dispersion. While cooling with an ice bath, dimethyl phosphite (30.8 g, 0.28 mol) is added dropwise. Upon completion of the addition the solution is refluxed for 2.5 hr. Upon cooling to room temperature *t*-butyldimethylsilyl chloride (39.2 g, 0.26 mol) is added in one portion. The reaction mixture is refluxed for 18 hr and filtered. The volatile materials are removed by distillation at atmospheric pressure, and subsequent vacuum distillation yields dimethyl *t*-butyldimethylsilyl phosphite (27.0 g, 46%) of bp 85-90°/16 Torr.

4. Di(2,2,2-trifluoroethyl) Trimethylsilyl Phosphite[47]

Trimethylsilyl chloride (3.7 g, 33 mmol) is added dropwise to a stirred solution of di(2,2,2-trifluoroethyl) phosphite (7.38 g, 30 mmol) in the presence of triethylamine (3.3 g, 0.33 mmol) in dry ether (150 mL) at 0°. The reaction mixture is gradually warmed to room temperature and refluxed with stirring for an additional 2.5

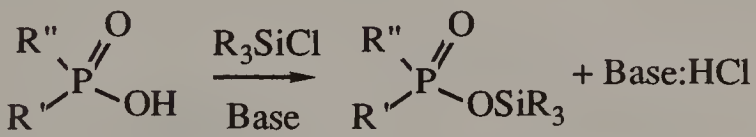
hr. The mixture is filtered and volatile materials are removed by distillation at atmospheric pressure. Vacuum distillation through a Vigreaux column yields the di(2,2,2-trifluoroethyl) trimethylsilyl phosphite (6.26 g, 80%) of bp 37-40°/9 Torr.

C. Synthesis of Phosphorus(V) Silyl Esters

1. Direct Silylation of Phosphorus(V) Acids

As in the case of the preparation of phosphorus(III) silyl esters, several methods exist for the preparation of phosphorus(V) silyl esters. Among these, silylation of phosphorus(V) acids using a variety of silylating agents, transformations of phosphorus(III) silyl esters, and the McKenna reaction[49,50] (exchange of alkyl group by a silyl group) are the most commonly used methods.

Various types of readily available phosphorus(V) acids serve as precursors to the silyl esters by silylation. Trimethylsilyl chloride is the most commonly used silylating agent owing to its ready availability, high reactivity, and low price.



R', R" = alkyl, alkoxy, OH; R = alkyl (for the starting material) and R', R" = alkyl, alkoxy, $OSiR_3$; R = alkyl (for the product)

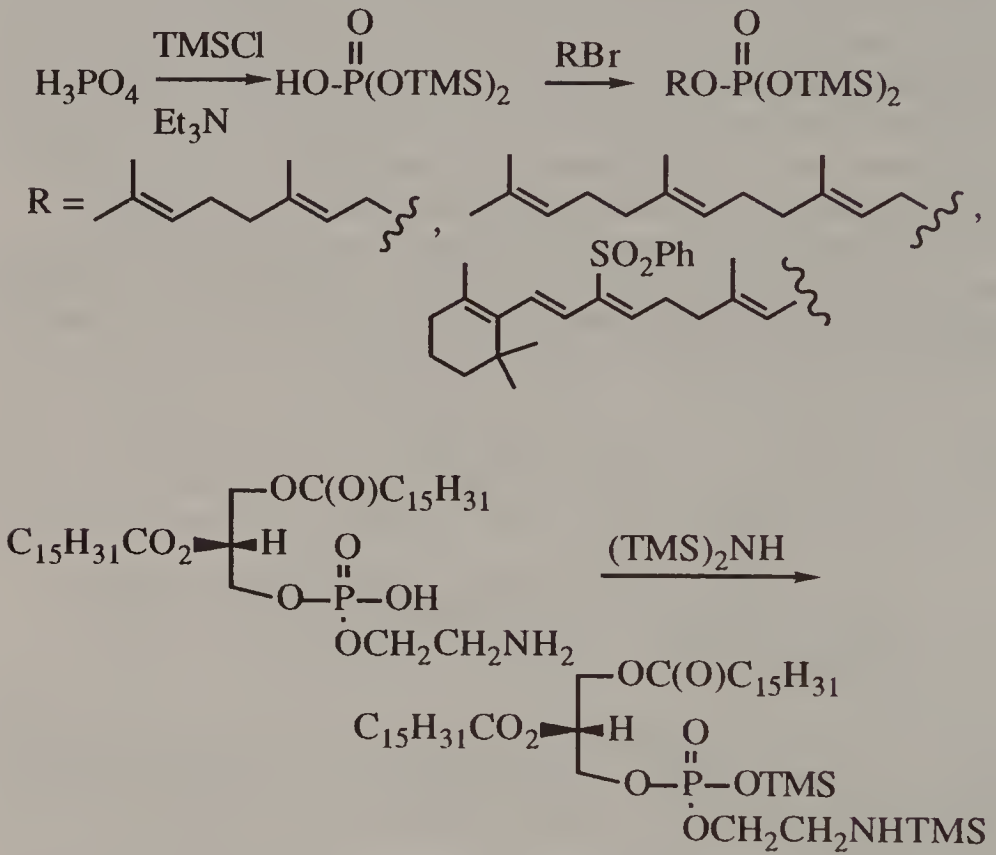
This reaction is usually performed in the presence of a base such as a tertiary amine[11] to remove the HCl from the reaction. Salts of phosphorus(V) acids can also be used for this type of reaction.[15,17]

The recently reported[51] preparation of biologically interesting allylic phosphates utilizes trimethylsilyl chloride silylation of phosphoric acid as the first step.

Silyl esters of *N*-phosphonomethylglycine, a class of post-emergence herbicides, have been prepared by the Monsanto group[52] by silylation of the corresponding phosphonic acid with *t*-butyldiphenylsilyl chloride.

Hexamethyldisilazane and silylamines[33,34] are also frequently used reagents for the preparation of phosphorus(V) silyl esters. Bis(aminomethyl)phosphinic acid on reaction with excess hexamethyldisilazane under reflux gives the corresponding

trisilylated derivative.[53] Similarly, (methyl)phosphinomethylglycine on reaction with excess hexamethyldisilazane gives the corresponding trisilylated derivative.[53] As a part of the synthesis and configurational analysis of 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine (DPPE) chirally labeled with ^{17}O and ^{18}O at the phosphate head group, Tsai and Bruzik[54] recently reported the silylation of DPPE using hexamethyldisilazane.



Silyl amides such as bis(trimethylsilyl)acetamide are also very powerful reagents for the preparation of phosphorus(V) silyl esters from the corresponding acids.[55]

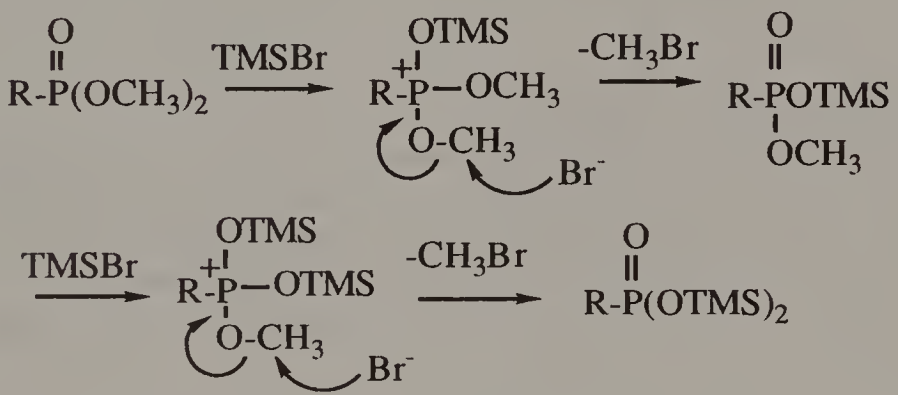
Reaction of trialkylsilanes with phosphorus(V) acids in the presence of transition metal catalysts such as colloidal nickel produces the corresponding silyl esters.[11]

Another source of phosphorus(V) silyl esters is the related phosphorus(III) ester. Various types of reactions of phosphorus(III) silyl esters produce the related phosphorus(V) esters. As a general rule, with a few exceptions, phosphorus(V) silyl esters thus produced usually contain one fewer trialkylsilyl group than is

present in the starting phosphorus(III) silyl ester. More details of this approach will be considered in later sections of this Chapter.

2. The McKenna Reaction

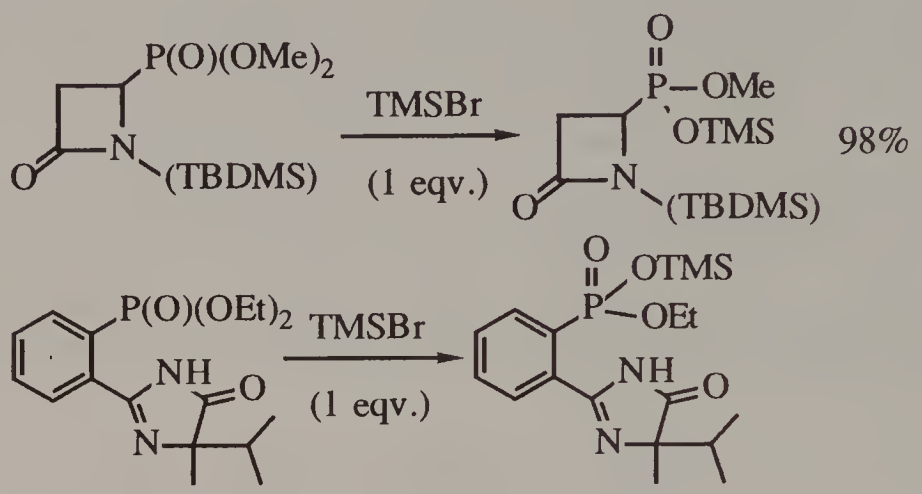
Since McKenna's report[49] on the dealkylation of phosphorus(V) acid dialkyl esters using trimethylsilyl bromide, this method has been widely used for the preparation of phosphorus(V) silyl esters. The popularity of this method for the preparation of phosphorus(V) silyl esters stems from the fact that the procedure is very convenient, mild, facile, and efficient, and can tolerate a wide variety of additional functional groups in the molecule.[50,56] This method is compatible with groups such as benzyl, benzoyl, alkoxyalkyl, alkenyl, trichloromethyl, diazomethyl, and carboxylate esters. The mechanism of this ester exchange can be visualized as shown below.



Competition experiments using TMSBr show that the relative reactivities of dimethyl, diethyl, and diisopropyl acylphosphonates are in the ratio 1:0.25:0.04, suggesting that monosilydealkylation of methyl isopropyl phosphonates should be a useful route to monoisopropyl esters of phosphonic acids *via* the corresponding silyl esters. Various modifications of this reaction have been reported in the literature. By controlling the reaction temperature and stoichiometry of the reagents, one can selectively dealkylate dialkyl phosphonates as shown in the two examples[57,58] shown below. In place of TMSBr, TMSCl can also be used in conjunction with NaI[20,22] or LiI.[59] Trimethylsilyl chloride alone requires days (or even weeks) of reflux for the reaction to proceed to completion.[49] Successful use of TMSI in place of TMSBr also has been reported.[18,60-63] A recent report[64] indicates enhanced rates of alkyl exchange with phosphorus(V) alkyl esters using TMSBr in

the presence of thioanisole.

In Table 1 is presented a compilation of selected examples from recent reports of the dealkylation of phosphorus(V) esters by the exchange reaction.



3. Miscellaneous Methods

The preparation of phosphorus(V) silyl esters by the silylation of halogeno anhydrides has been reported.[33,40,41] However, this method is of limited scope owing to the high nucleophilicity of the reagents used, such as R_3SiOM (M = K, Na, Li) These reagents can react further with the initial product phosphorus(V) silyl esters to produce the corresponding pyro-compounds, as noted below.

$$R_2P(O)Cl + R'_3SiOK \longrightarrow R_2P(O)OSiR'_3 + KCl$$

$$R_2P(O)OSiR'_3 + R'_3SiOK \longrightarrow R_2P(O)OK + (R'_3Si)_2O$$

$$R_2P(O)OK + R_2P(O)Cl \longrightarrow [R_2P(O)]_2O + KCl$$

Reaction of phosphorus(III) acid chlorides with bis(trimethylsilyl) sulfate is known to give the corresponding phosphorus(V) esters in moderate yield.[73] Further, the reaction of phosphorus(V) tin esters with halogenosilanes produces the phosphorus(V) silyl esters *via* an exchange reaction.[41,74]

The reaction of hexaalkyldisiloxanes with phosphorus pentoxide is a convenient method for the preparation of tris(trialkylsilyl) phosphates.[1,9,32] Polymeric products are obtained when hexa-

alkyldisiloxanes react with a large excess of phosphorus pentoxide.[9] For example, trimethylsilyl polyphosphate can be prepared by refluxing hexamethyldisiloxane in an organic solvent such as methylene chloride or chloroform for 20 min with an excess of phosphorus pentoxide.[75]

III. Reactions and Applications of Phosphorus Silyl Esters

A. Introduction

Silyl esters of phosphorus acids have been widely used for various transformations and syntheses of both phosphorus and non-phosphorus containing compounds.[76-78] The reactions and applications of silyl esters of phosphorus acids is very broad, and the synthetic importance of these compounds is rapidly developing. For example, silyl esters of phosphorus acids serve as intermediates for the synthesis of a variety of optically active phosphorus compounds.[78,79] The silyl esters also show a high reactivity toward both nucleophiles and electrophiles. Most reactions of these species have a general feature which involves the nucleophilic phosphorus interacting with an electrophile while silicon is the target for nucleophilic attack.[1] Silyl esters of phosphorus acids very easily undergo hydrolysis or alcoholysis, making possible the generation of the free phosphorus acids under mild conditions.[12]

B. Reactions of Phosphorus(III) Silyl Esters

Trivalent phosphorus silyl esters serve as versatile reagents for the synthesis of a range of organophosphorus compounds. Of particular interest are the three types of silyl phosphite esters, $(TMSO)_3P$, $(TMSO)_2POR$, and $(TMSO)P(OR)_2$, because of their ready availability and reactivity toward organic compounds.

1. The Arbuzov Reaction - Overview

The direct displacement of a suitable leaving group from carbon by a phosphorus(III) silyl ester is one of the most common methods for the formation of carbon-phosphorus bonds in phosphorus(V) compounds. This is due not only to the ready availability of the starting materials, but also to the relative ease of the performance of the reaction. Silyl phosphites react with various types of alkyl halides following the standard mechanism of the Arbuzov reaction. The Arbuzov reaction of a phosphorus(III) silyl

ester concludes with the desilylation of the quasiphosphonium intermediate and the formation of a silyl halide.[80]

The presence of a silyl ester linkage rather than an alkyl ester in the phosphite increases the nucleophilicity of the phosphorus center and thus its reactivity in the Arbuzov reaction. The order of reactivity chages in the following order:[80]

$$(RO)_3P < (RO)_2POTMS < ROP(OTMS)_2 < P(OTMS)_3.$$

Primary alkyl halides react rapidly with tris(trimethylsilyl) phosphite to produce bis(trimethylsilyl) alkylphosphonates.[81]

$$P(OTMS)_3 + RBr \longrightarrow RP(O)(OTMS)_2 + TMSBr$$

$R = PhCH_2$, primary alkyl

Chiral ethyl trimethylsilyl phenylphosphonite reacts cleanly with either methyl or ethyl iodide to yield the ethyl alkyl(phenyl)-phosphinate with virtually complete retention of configuration at phosphorus.[79]

Tris(trimethylsilyl) phosphite is a particularly convenient reagent for the preparation of phosphonolipids.[82-85] After completion of the Arbuzov reaction, the phosphonate silyl esters can be hydrolyzed under sufficiently mild conditions that disruption of the other sensitive functionalities does not occur.

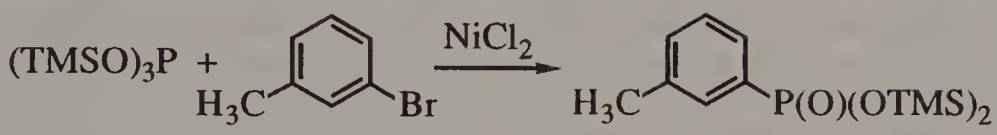
Bis(trimethylsilyl) trimethylsiloxymethylphosphonite reacts with 3-chloropropionitrile yielding 2-cyanoethyl(hydroxyethyl)-phosphinic acid upon aqueous work-up.[86]

An early step in the commercial synthesis of the ACE inhibitor FOSINOPRIL involves the Arbuzov reaction of a silyl ester of 4-phenylbutyl-1-phosphinic acid (formed *in situ*) with an ester of haloacetic acid.[87-88] In a similar manner, Arbuzov reaction of bis(trimethylsilyl) ethoxycarbonylphosphonite with *N*-bromo-methylphthalimide followed by hydrolysis produces aminomethyl-phosphinic acid.[89]

A general procedure for the conversion of nucleoside phosphite mono- and diesters into valuable phosphonate esters involves the Arbuzov reaction of nucleoside silyl phosphites with alkylating agents.[90]

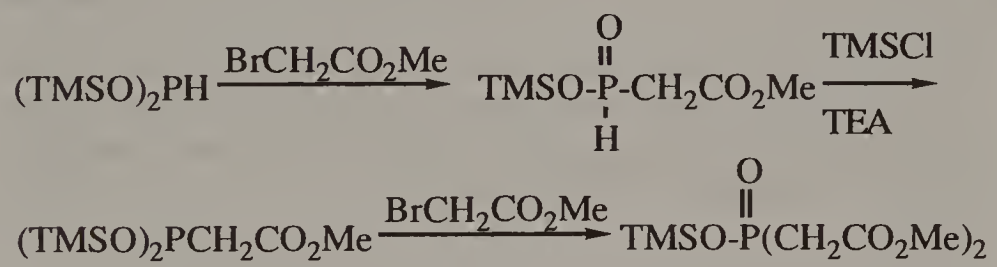
Catalyzed arylations occur with various phosphorus(III) silyl esters by reaction with aryl halides in the presence of a nickel(II)

catalyst.[91-93]



Acyl halides undergo extremely facile Arbuzov reaction with phosphorus(III) silyl esters to produce, after aqueous work-up, acylphosphonic acids.[55,94-96] This reaction proceeds in an analogous fashion to the reaction of trialkyl phosphites with acyl halides.[1,2] The use of acyl halides in the Arbuzov reaction of silyl phosphites has been spurred by activity in several areas of biological and medicinal chemistry. The use of chloroformates as the acyl halide component accomplishes the facile formation of phosphonoformates.[97] A recently published synthesis of various pro-drug esters of the antiviral agent trisodium phosphonoformate utilizes the chloroformate Arbuzov methodology.[98] In contrast with trialkyl phosphites, the reaction of dialkyl trimethylsilyl phosphite with chloroacetyl chloride yields the normal acyl Arbuzov product.[99]

A recently published procedure[100] describes a simple one-pot method for the preparation of dialkylphosphinic acids from bis(trimethylsiloxy)phosphine in the presence of excess silylating agent and reactive alkyl halides.



2. The Arbuzov Reaction - Experimental Procedures

a. 2,3-Dioleoyloxypropylphosphonic Acid[83]

Tris(trimethylsilyl) phosphite (15.05 g, 50 mmol) is added to 2,3-dioleoyloxy-1-iodopropane (3.65 g, 5 mmol) along with a trace amount of butyl hydrogen phthalate. The reaction mixture is stirred under a nitrogen atmosphere at 125° for 16 hr. After this time the volatile materials are evaporated under reduced pressure with heating (100°) and the residue is dissolved in a THF-water mixture

(9:1, 50 mL) and allowed to stand in the dark at ambient temperature for 12 hr. Volatile materials are removed under reduced pressure and the residue is dried by repeated azeotropic distillation with 2-propanol at reduced pressure. The residue is chromatographed on a silicic acid column eluting with chloroform (500 mL) followed by chloroform-methanol (9:1, 500 mL). The eluents are concentrated and the residue is dissolved in a minimum of chloroform and passed through a Gelman Metricel filter (0.45 μ) to remove suspended silicic acid. Evaporation of the solvent under reduced pressure yields the pure 2,3-dioleoyloxypropylphosphonic acid (2.8 g, 81%) as a viscous oil.

b. [(Diphenoxyphosphinyl)methyl]phosphonic Acid[101]

In a 500 mL round-bottomed flask is mixed diphenyl chloromethylphosphonate (282 g, 1 mol) and tris(trimethylsilyl) phosphite (328 g, 1.1 mol). The mixture is heated to 220° with stirring. The flask is equipped with a 50 cm-long column having a distillation condenser at the top. The temperature is maintained at 220-230° for 3 hr while trimethylsilyl chloride distils from the reaction mixture. The heating is continued another 30 min after which the reaction mixture is cooled to room temperature. Then water (700 mL) and 20% aqueous ammonium bicarbonate (1 L) are added and the mixture is extracted with chloroform (2 x 200 mL). The bicarbonate solution is neutralized with 3 *N* HCl, and excess HCl (300 mL) is added. The acidic solution is immediately extracted with chloroform (3 x 500 mL) and the extracts are combined and dried over anhydrous sodium sulfate. Upon addition of 30-60° boiling petroleum ether (500 mL) the crude product precipitates which is recrystallized from chloroform to yield pure [(diphenoxyphosphinyl)methyl]phosphonic acid (160 g, 49%) of mp 150°.

c. Ethoxycarbonyl(phthalimidomethyl)phosphinic Acid[89]

To bis(trimethylsilyl) ethoxycarbonylphosphonite (6.5 g, 0.023 mol) is added bromomethylphthalimide (5 g, 0.021 mol) and the resulting suspension is heated with stirring at 90 ± 5° under an argon atmosphere. After 30 min the reaction mixture becomes homogeneous and heating is continued for another 1 hr. After cooling, ethanol (15 mL) is added and the resulting mixture is stirred for 30 min at room temperature and then evaporated to

dryness under reduced pressure. The oily residue is treated with anhydrous ether (30 mL) and allowed to stand overnight at 4°. The resulting precipitate is recovered by filtration and dried to give the pure ethoxycarbonyl(phthalimidomethyl)phosphinic acid (4.7g, 75%) of mp 131-135°.

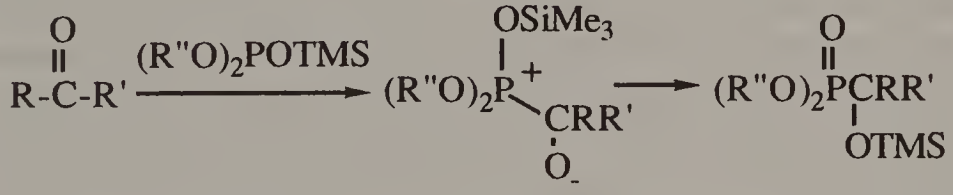
d. Diethyl (2-Chloroacetyl)phosphonate[99]

To freshly distilled chloroacetyl chloride (2.82 g, 0.025 mol) is added dropwise diethyl trimethylsilyl phosphite (5.46 g, 0.026 mol) at such a rate that the temperature does not exceed 30°. Trimethylsilyl chloride is then removed under reduced pressure. Kugelrohr distillation of the residue yields pure diethyl (2-chloroacetyl)phosphonate (2.0 g, 37%) of bp 110-120°/0.1 Torr. (Conventional distillation results in decomposition of the product.)

In Table 2 is presented a compilation of selected examples from recent reports of the Arbuzov reaction of silyl phosphites with alkyl/acyl halides.

3. Addition of Phosphorus(III) Silyl Esters to Carbonyl Compounds - The Abramov Reaction - An Overview

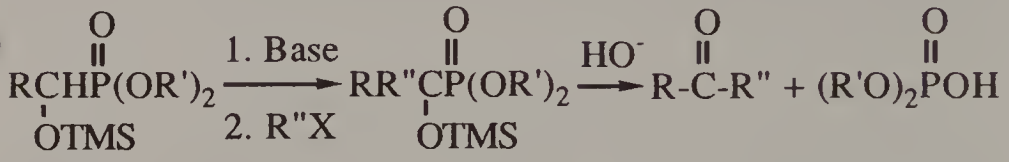
In addition to the nucleophilic substitution reactions discussed in the previous sections, silyl esters of phosphorus(III) acids undergo facile addition reactions to the carbonyl groups of aldehydes and ketones leading to the formation of α-trialkylsiloxyalkylphosphonates.[1,3,5,106,107]



This reaction, commonly known as the Abramov reaction,[108] is described in numerous places. In this section we will discuss recent developments relating to this reaction using silyl phosphorus(III) reagents.

An area of particular interest developing in recent years is that involving *umpolung* chemistry.[109] The products of phosphorus(III) silyl ester addition to carbonyl groups lead directly to phosphorus(V) compounds bearing a hydroxyl group at carbon attached to phosphorus. Such structural elements facilitate both

further functionalization of that carbon and the ultimate cleavage of phosphorus from carbon. Overall, this transformation is equivalent to carbonyl anion chemistry.[110-112]

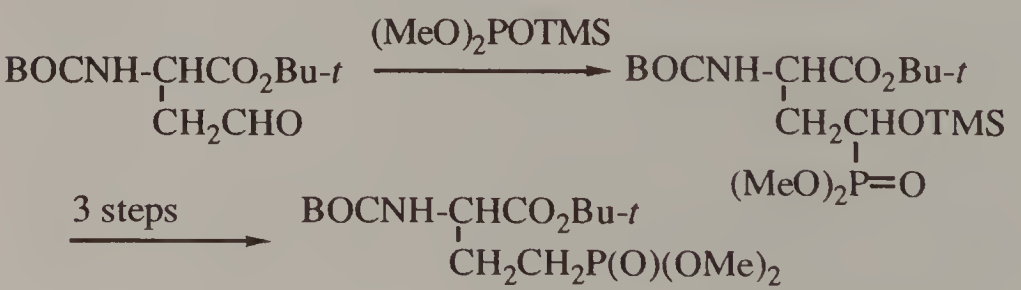


Using mixed silyl and alkyl esters of phosphorus(III) acids, the silyl function exclusively is transferred to the α-oxygen site.[39,113]

An important application of the phosphorus(III) silyl ester addition to carbonyl compounds is in the synthesis of α-hydroxy derivatives of phosphonic and phosphinic acids. Tris(trimethylsilyl) phosphite reacts smoothly with carbonyl compounds giving 1:1 adducts which are easily converted to α-hydroxyphosphonic acids. In the case of α,β-unsaturated aldehydes, silyl phosphites react mainly to give 1,2-addition products, whereas α,β-unsaturated ketones give mixtures of 1,2- and 1,4-addition products.[39,110,114-116]

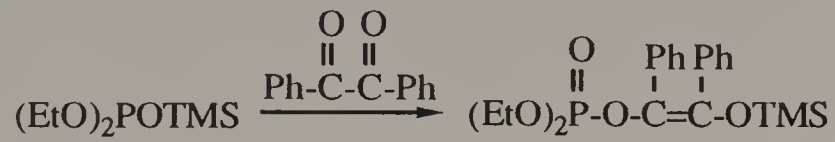
Hata[111] utilized this methodology in combination with the *umpolung* chemistry noted earlier for the synthesis of β-alkyl substituted esters derived from α,β-unsaturated aldehydes.

Synthesis of alkylphosphonic acids *via* the hydrogenolysis of the α-hydroxyphosphonates is a viable alternative to the Arbuzov approach discussed earlier. This approach has been utilized by Johns[117,118] for the synthesis of phosphonic acid derivatives of amino acids.



A recently reported[119] synthesis of furanoside analogues having phosphorus at the anomeric position has been accomplished using the Abramov reaction of silyl phosphites with ketose derivatives.

Addition of silyl phosphites to dicarbonyl compounds is often followed by rearrangements or other intramolecular reactions.[120-125] For example, reactions of silyl phosphites with benzil leads to phosphates rather than phosphonates.

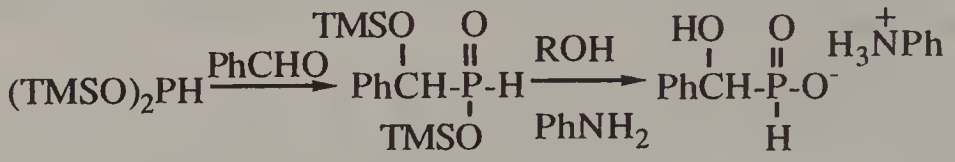


Related rearrangements occur in other systems as well. Aromatic 2,5-diketones add silyl phosphites to produce phospholanes which, on hydrolysis, yield bis(α-hydroxy)phosphonic acids.[124] Hata[122] achieved an interesting synthesis of L-ascorbic acid 2-*O*-phosphate from fully silylated ascorbic acid by the addition of tris(trimethylsilyl) phosphite followed by rearrangement. Similarly, reactions of quinones and quinone imines with silyl phosphites produce phenyl phosphates upon hydrolysis.[126,127]

Phosphorus(III) silyl esters react with α-halocarbonyl compounds by three different routes to produce three different types of adducts, *i.e.* enol phosphates (Perkow reaction), phosphonates (Arbuzov reaction), and the 1:1 adduct (Abramov reaction). The results in a given system depend upon both the nature of the reactants and the reaction conditions.[37,114,128-130]

For example, the reaction of chloroacetone with tris(trimethylsilyl) phosphite gives a 92% yield of the Abramov product.[37] While reaction of phenacyl chloride with the same reagent gives primarily the Abramov product, use of diethyl trimethylsilyl phosphite results in formation of the Perkow product in ~75% yield.[120] Similarly, bromoacetone reacts with tris(trimethylsilyl) phosphite to form 91% of the Abramov product, while its reaction with diethyl trimethylsilyl phosphite produces a mixture of Arbuzov product (24%) and Perkow product (65%).[37] Hata, *et al.* utilized the Perkow reaction of dimethyl trimethylsilyl phosphite for a convenient synthesis of phosphoenolpyruvate from bromopyruvate.[96,129]

Bis(trimethylsilyl) hypophosphite, on reaction with carbonyl compounds, produces the 1:1 (Abramov) adduct in good yield.[14]



However, when the same reaction is performed in the presence of excess silylating agent and excess carbonyl compound, the bis(1-hydroxyalkyl)phosphinic acid is produced in good yield.[131]

4. The Abramov Reaction - Experimental Procedures

a. Diethyl 1-(Trimethylsiloxy)benzylphosphonate[112]

To a solution of diethyl trimethylsilyl phosphite (6.18 g, 29.4 mmol) in dry benzene (5 mL) is added dropwise benzaldehyde (3.21 g, 30.2 mmol) with continuous stirring. The mixture is stirred at room temperature for 6 hr. The solvent is evaporated under reduced pressure and vacuum distillation of the residue gives pure diethyl 1-(trimethylsiloxy)benzylphosphonate (8.49 g, 91%) of bp 118-123°/0.08 Torr.

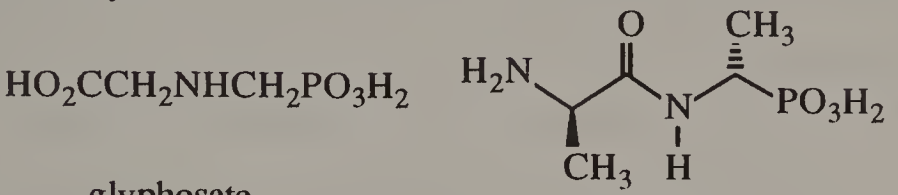
b. 1-Hydroxybenzylphosphonous Acid Anilinium Salt[14]

The pyridinium salt of hypophosphorous acid (1.45 g, 10 mmol) is rendered anhydrous by repeated evaporation with excess dry pyridine and is then dissolved in dry THF (20 mL). To this solution is added benzaldehyde (1.06 g, 10 mmol) at room temperature, and the mixture is stirred for 3 hr. The resultant precipitate is removed by filtration and the filtrate is concentrated under reduced pressure. The residue is dissolved in ethanol (20 mL) and aniline (2.79 g, 30 mmol) is added. Ether (150 mL) is added and the resultant precipitate is collected by filtration. The crystals are dried over phosphorus pentoxide to give the pure 1-hydroxybenzylphosphonous acid anilinium salt of mp 157-160°.

Selected examples of the Abramov reaction of P(III) silyl esters are shown in Table 3.

5. Addition of Phosphorus(III) Silyl Esters to Imines, Schiff Bases, Aminals, Acetals, Ortho Esters, and Other Carbonyl Carbon Equivalents - An Overview

As in the case of the fundamental Abramov reaction, phosphorus(III) silyl esters undergo facile addition reactions with carbonyl carbon equivalents such as imines, aminals, acetals, and ortho esters.[133-141] In recent years 1-aminophosphonic acids have become an important class of organic compounds largely due to their structural relationship to α-aminocarboxylic acids.[142] Several 1-aminophosphonic acid derivatives, such as the herbicide glyphosate and the antibacterial alafosfalin are widely used commercially.



glyphosate

alafosfalin

The addition of phosphorus(III) silyl esters to imines (preformed or generated *in situ*) provides a mild and facile route to 1-amnioalkylphosphonates and 1-aminoalkylphosphinates. For example, 2,2-diethoxyacetaldehyde *N*-benzylimine, on reaction with diethyl trimethylsilyl phosphite, produces the 1:1 Abramov-type adduct in 79% yield.[133] Moreover, 1,3,5-tribenzylhexahydro-1,3,5-triazine, a precursor of *N*-benzylmethanalimine, reacts with diethyl trimethylsilyl phosphite in boiling 1,2-dichloroethane to produce diethyl 1-(benzylamino)methylphosphonate,[133] and tris(trimethylsilyl) phosphite readily adds to pyrimidinones to produce the 3,4-adducts in moderate yield.[134]

Aldimines which are prepared from aldehydes and optically active 1-phenylethylamine react with silyl phosphites to form adducts exhibiting asymmetric induction.[133,142,143] The extent of asymmetric induction found in these reactions depends on the structures of the the original aldehyde and the specific reaction conditions employed, at times as high as 80%.

Bis(trimethylsilyl) hypophosphite adds to *N*-(diphenylmethyl)imines to form bis(trimethylsilyl) 1-(diphenylmethylamino)alkylphosphonates which, on hydrolytic work-up, produce the corresponding phosphonous acids.[139] Tris(trimethylsilyl) phosphite, in the presence of Lewis acids, reacts with *N*-glycosylnitrones to produce 1:1 adducts in excellent yield. On hydrolysis these adducts form 1-aminophosphonic acids in yields >90% with enantiomeric excesses up to 97%.[140]

The reaction of tris(trimethylsilyl) phosphite and triazines derived from glycine produce phosphonomethylglycines in good yield.[144]

Aminals also react with phosphorus(III) silyl esters in the presence of Lewis acids to produce the corresponding 1-aminomethylphosphonates.[136,145,146] For example, the reaction of diethyl trimethylsilyl phosphite with bis(trimethylsilyl) methoxymethylamine in the presence of Sn(IV) chloride produced the 1-aminomethylphosphonate in excellent yield.[136] Various 1-phosphonylated-1-aminocarboxylic acid derivatives have been synthesized by the reaction of methyl α-methoxyglycinates with silyl phosphites in the presence of Lewis acids such as boron trifluoride etherate.[145]

Acetals also react with phosphorus(III) silyl esters in the presence of Lewis acids to produce 1-alkoxymethylphosphonates.[137,138] For example, the reaction of benzaldehyde dimethyl acetal with diethyl trimethylsilyl phosphite in the presence of Sn(IV) chloride gave diethyl α-methoxybenzylphosphonate in 90% yield.[137]

Completely protected sugars react with phosphorus(III) silyl esters to produce 1-α-phosphonyl sugars. When 2,3,4,6-tetrakis-*O*-(phenylmethyl)-1-acetyl-α-D-galactopyranoside was condensed with tris(trimethylsilyl) phosphite, 2,3,4,6-tetrakis-*O*-(phenylmethyl)-α-D-galactopyranosylphosphonic acetic anhydride was obtained. Hydrolysis followed by hydrogenolysis produced α-D-galactopyranosylphosphonic acid in 70% overall yield.[138]

Thioacetals similarly undergo condensation reactions with phosphorus(III) silyl esters in the presence of Lewis acids.[141] Related reactions involving ortho esters and thio ortho esters are reported in the recent literature.[147,148] In the case of DMF-dimethyl acetal, phosphorus(III) silyl ester condensation reaction gives the bis-phosphonylated product in 36-66% yield.[149]

6. Additions of Phosphorus(III) Silyl Esters to Carbonyl Carbon Equivalents - Experimental Procedures

a. α-(Diphenylmethylamino)benzylphosphonous Acid[139]

To a solution of *N*-diphenylmethylbenzylimine (8.14 g, 0.03 mol) in benzene (25 mL) is added bis(trimethylsilyl) phosphonite (7.01 g, 0.031 mol) at room temperature under an argon atmosphere. After standing overnight at ambient temperature, the mixture is poured into 85% ethanol (50 mL) under an argon atmospherer. The resultant mixture is allowed to stand at room temperature for 24 hr. The precipitate which forms is collected by filtration, washed with ethanol (20 mL) and ether (20 mL) and dried under vacuum to give pure α-(diphenylmethylamino)-benzylphosphonous acid (7.3 g, 72%) of mp 208-209°.

b. 5-Chloro-1-(4-chlorobenzyloxy)methyl-2-oxo-3,4-dihydropyrimidine-4-phosphonic acid[134]

A mixture of tris(trimethylsilyl) phosphite (1.40 g, 6.0 mmol) and 5-chloro-1-(4-chlorobenzyloxy)methyl-2(1*H*)-pyrimidone (0.87 g, 3.0 mmol) in dry benzene (15 mL) is stirred under nitrogen atmosphere at ambient temperature for 4 hr. The volatile materials are evaporated under reduced pressure and the residue is treated with methanol (7 mL) and stirred at ambient temperature for 3 hr. The resultant precipitate is collected by filtration to give pure 5-chloro-1-(4-chlorobenzyloxy)methyl-2-oxo-3,4-dihydropyrimidine-4-phosphonic acid (0.60 g, 54%) of mp > 260°.

c. α-D-Glucopyranosylphosphonate[138]

In a 50 mL flask is mixed 2,3,4,6-tetrakis-*O*(phenylmethyl)-1-*O*-acetyl-α-D-glucopyranose (10 g, 19.3 mmol), a catalytic amount of trimethylsilyl triflate, and tris(trimethylsilyl) phosphite (15 g, 50 mmol), and the mixture is heated to 80° with stirring for 30 min. After removal of the volatile materials under reduced pressure the residual solution is cooled to room temperature and water (30 mL) is added and the mixture shaken vigorously. The water is separated and the residue is dissolved in a mixture of 95% ethanol (40 mL) and cyclohexene (60 mL) and refluxed overnight in the presence of palladium hydroxide on carbon (1.5 g). The boiling reaction mixture is filtered and, upon cooling, the crude product precipitates. The precipitate is redissolved in water (5 mL) and recrystallized by the addition of hot ethanol (80 mL) to give pure α-D-glucopyranosylphosphonate (3.95 g, 78%).

Selected examples of these reactions are shown in Table 4.

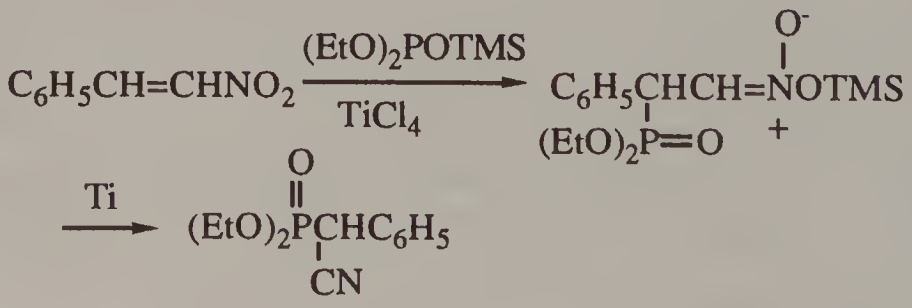
7. Addition of Silyl Phosphites to Activated Conjugated Systems - General Overview

The previous two sections have been concerned with the nucleophilic addition of phosphorus(III) silyl esters to carbonyl-type centers. An obvious extension of this type of reaction is the addition of phosphorus(III) silyl esters to activated α,β-unsaturated systems in a Michael-type fashion. Nucleophilic phosphorus(III) silyl esters undergo a facile conjugate addition with a wide range of Michael-type substrates.[39,43,44,116,150-154]

In the case of α,β-unsaturated aldehydes, addition of silyl phosphites afford 1,2-addition products while α,β-unsaturated ketones give a mixture of 1,2- and 1,4-addition products. The α,β-unsaturated esters give 1,4-addition products.[39,110,115,116,150,151] Often the immediate product of these reactions is the enol ether and the isolation of the free carbonyl compound is accomplished by hydrolysis of the reaction mixture.[39,116] In conjugate addition reactions involving mixed silyl ester reagents it is the silyl group that is transferred from the phosphorus atom to the oxygen of the carbonyl group.[39,150,151]

In addition to aldehydes, ketones, and esters, acrylonitrile and α-substituted acrylonitriles react with phosphorus(III) silyl esters to give conjugate adducts in good yields.[116,152,155,156] Similarly, α,β-unsaturated nitro compounds,[45,153,157,158] acrylamides, and related compounds provide good yields of 1,4-addition products.[4]

Recently a Korean research team has reported[153] the preparation of substituted 1-cyanomethylphosphonates *via* the reduction of the *in situ* generated nitronates using low valent titanium.



The Pfizer group[43] has reported a convenient and simple procedure for the preparation of phosphinic acids. Bis(trimethylsilyl) hypophosphite, in the presence of excess silylating agent, undergoes double Michael addition to α,β-unsaturated esters to produce phosphinic acids in good yields.

Tris(trimethylsilyl) phosphite has also been used in conjugate addition reactions for the synthesis of phosphonic acids.[115] Michael addition of phosphorus(III) silyl esters to acetamido acrylic acid, followed by acidic hydrolysis, gives the phosphorus analogue of aspartic acid in good yield.[45] In this instance, a second equivalent of phosphorus(III) silyl ester is involved in the silylation of the carboxylic acid site.

8. Addition of Silyl Phosphites to Activated Conjugated Systems - Experimental Procedures

a. Ethyl Methyl(2-carbomethoxy-3-phenylpropyl)phosphinate[116]

To a solution of ethyl methylphosphonite (0.66 g, 0.006 mol) in methylene chloride (7.5 mL) is added methyl 2-benzylacrylate (0.9 g, 0.0047 mol) and bis(trimethylsilyl)acetamide (1.03 g, 0.00474 mol). The reaction mixture is stirred at room temperature overnight, after which the reaction mixture is washed with water followed by extraction with ether. The volatile materials of the extract are removed under reduced pressure and the residue is subjected to chromatographic purification using neutral alumina (activity 3) from which is isolated the pure ethyl methyl(2-carbomethoxy-3-phenylpropyl)phosphinate (1.14 g, 81%).

b. Ethyl 2-Nitroethyl(diethoxymethyl)phosphinate[45]

Ethyl trimethylsilyl diethoxymethylphosphonite (2.7 g, 10.0 mmol) is cooled to 0^{o} under a nitrogen atmosphere. Nitroethylene (1.6 g, 21.9 mmol) is added cautiously with stirring. After stirring for 30 min, chloroform (50 mL) is added followed by water (20 mL) and the mixture is stirred a further 10 min. The organic layer is separated, dried, and evaporated under reduced pressure to give the pure ethyl 2-nitroethyl(diethoxymethyl)phosphinate (2.0 g, 74%).

Selected examples of these reactions are shown in Table 5.

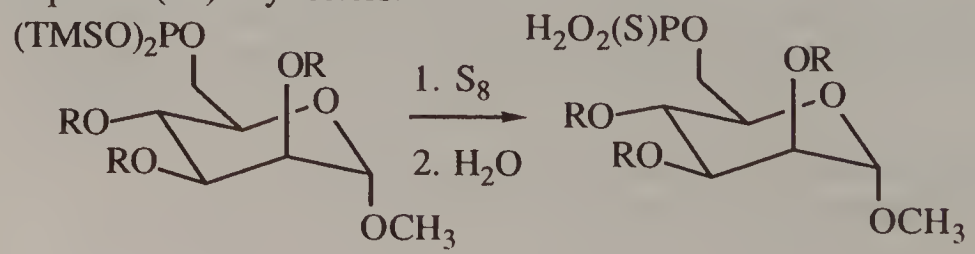
9. Oxidation of Phosphorus(III) Silyl Esters to Phosphorus(V) Compounds

Dialkyl and monoalkyl phosphites exist in solution principally in the hydrogen-phosphonate form; thus, they are quite resistant to oxidation or the addition of sulfur or selenium. Silyl phosphites exist in the trivalent form and thus can be oxidized much more easily. Phosphorus(III) silyl esters undergo a wide variety of reactions in which the net result is oxidation to a phosphorus(V).

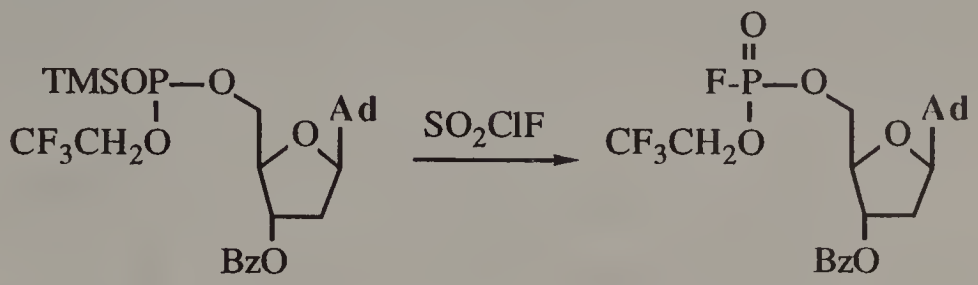
Phosphorus(III) silyl esters react with disulfides to give phosphorus(V) acid derivatives under mild conditions and in good yield.[160-163] Dialykl trimethylsilyl phosphites react with *S*-trifluoro- methyl disulfide at -85° in methylene chloride to give the dialkyl *S*-trifluoromethyl thiophosphate in very good yield.[163] Similarly, the cyclohexylammonium salts of *S,S*-diarylphosphorodithioates have been prepared[162] in good yield by the reaction of diaryl disulfides with bis(trimethylsilyl) hypophosphite. *S*-*p*-nitrobenzyl[$^{17}O_3$]phosphorothioate was prepared[161] in quantitative yield by the reaction of *p*-nitrobenzyl disulfide with ^{17}O labeled tris(trimethylsilyl) phosphite.

Shadid, *et al.* recently reported[160] a method for the mono phosphorylation of allylic alcohols in which the mixed allylic silyl phosphites were oxidized using disulfides to produce thioates which, upon mild hydrolysis, produced monophosphorylated products in very good yield.

Oxidation of phosphorus(III) silyl ester functions has been used extensively in the area of nucleoside chemistry in recent years.[29,47,90,164-166] Nucleoside bis(trimethylsilyl) phosphites have been used to produce the trivalent phosphorus form of the phosphites thus promoting their oxidation under very mild conditions.[164-166] The preparation of phosphorothioates has been reported[29] by the reaction of elemental sulfur with nucleoside phosphorus(III) silyl esters in yields of 75%. Reaction of the same nucleoside phosphites with iodine followed by hydrolysis produces the corresponding phosphate derivatives. In recent years various other laboratories have also reported[46,166,167] the preparation of phosphorothioates by the reaction of elemental sulfur with phosphorus(III) silyl esters.



Sulfuryl chloride reacts with mixed silyl phosphites to give high yields of the corresponding phosphorochloridates.[168] When the analogous reaction is performed using sulfuryl chloride fluoride, the exclusive product is the corresponding phosphorofluoridate.[168,169]



Reaction of tris(trimethylsilyl) phosphite with halogens at -110° gives cleanly and quantitatively the corresponding phosphonyl halides.[170]

Sulfoxides oxidize silyl phosphites giving the corresponding phosphates and the sulfides. Similarly, nitro compounds are deoxygenated yielding amines while the silyl phosphite is oxidized to phosphate.[171]

Dialkyl phosphoryl selenenyl and sulfenyl chlorides react with phosphorus(III) silyl esters to produce mixed anhydrides of selenophosphoric and thiophosphoric acids with phosphoric acid.[172-174] The reactions of diphosphoryl diselenides with dialkyl trimethylsilyl phosphites also produce the mixed anhydrides in good yields.[175]

Good results have been obtained by the use of bis(trimethylsilyl) peroxides for the oxidation of phosphorus(III) silyl esters with chemo- and stereoselectivity. This reagent permits the preparation of phosphorus(V) silyl esters in high yields under mild conditions. The reaction proceeds with retention of configuration at the phosphorus center.[176,177]

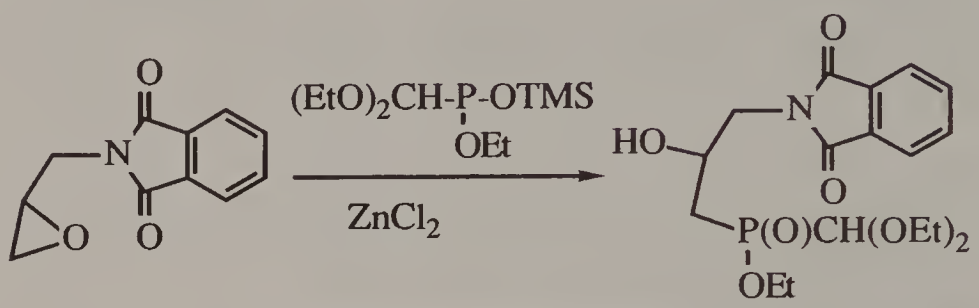
Selected examples of these oxidations are shown in Table 6.

10. Miscellaneous Reactions

Silyl esters of phosphorus(III) acids undergo a wide variety of less general and less frequently used reactions.

For example, silyl phosphites react with epoxides in the presence of Lewis acids or butyl lithium to yield products of ring opening and addition.[180] Diethyl trimethylsilyl phosphite reacts regioselectively with propylene oxide to form diethyl 2-(trimethyl-

silyloxy)propylphosphonate. No regioselectivity has been observed in the use of phenyloxirane. When zinc(II) iodide was used as catalyst, an almost equimolar mixture of the regioisomers was produced. A recently disclosed patent application[181] for the preparation of GABA antagonists makes use of the opening of *N*-(2,3-epoxypropyl)phthalimide with silyl phosphites as the key step in the synthesis.



In a similar manner *N*-activated aziridines react with silyl phosphites to yield amidoethylphosphonates in good yield.[182] Silyl phosphites also undergo facile addition-elimination reactions with perfluorinated olefins giving fluorinated vinylphosphonates.[183,184]

Hata, *et al.* reported[132] that silyl phosphites react with isocyanates giving rise to carbamoylphosphonic acid derivatives. In the case of tris(trimethylsilyl) phosphite, the products are isolated as the monoanilinium salts by treating the initially formed adducts with aniline in methanol. In a similar fashion, isothiocyanates react with tris(trimethylsilyl) phosphite followed by work-up with aniline in methanol to give the anilinium salts of thiocarbamoylphosphonic acids.[132]

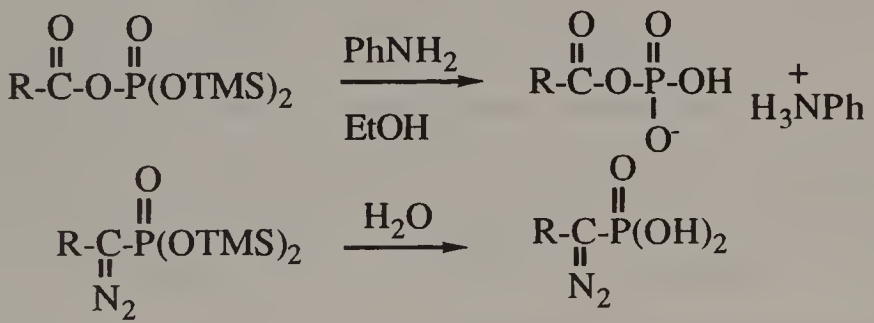
Tris(trimethylsilyl) phosphite reacts with alkyl azides to form the corresponding *N*-alkyl *O,O*-bis(trimethylsilyl) phosphoramidates.[114,185] These materials are hydrolyzed to the free acids, usually without isolation. This type of reaction has been utilized in nucleoside chemistry. 3',5'-Dinucleoside phosphoramidates were prepared starting from 5'-azido-5'-deoxyribonucleosides and nucleoside bis(trimethylsilyl) phosphites.[185,186] Application of the reaction of silyl phosphites with azides to the synthesis of oligonucleotides was also demonstrated by Gibbs.[187] This reaction has been further used for the preparation of β-lactam phosphoramidates starting from β-lactam azides and silyl phosphites.[188]

C. Reactions of Phosphorus(V) Silyl Esters

1. General Overview

Compared to phosphorus(III) silyl esters, the reactions and synthetic applications of phosphorus(V) silyl esters are limited. One of the general applications of phosphorus(V) silyl esters is in the generation of the corresponding phosphorus acid by facile hydrolysis of the silyl ester linkage. In contrast with the cleavage of alkyl ester groups, the silyl ester function is cleaved quite readily by water or alcohol[61,165,189] involving nucleophilic attack on silicon.

The by-products of hydrolysis or alcoholysis are the neutral, volatile siloxanes, silyl ethers, and silanols, which are easily removed from the phosphorus acid by distillation or crystallization. The phosphorus acids are often isolated as salts[24,29,38] using amines such as cyclohexylamine, dicyclohexylamine, aniline, *p*-anisidine, or triethylamine. At times they are isolated as the metal salts.[129] Two examples of these conversions of phosphorus(V) silyl esters are shown below.[29,165]



Silyl esters of phosphorus(V) acids are often convenient intermediates for the synthesis of anhydrides of of those acids as well as mixed anhydrides with carboxylic or inorganic acids. For example, mixed phosphoric-sulfonic anhydrides are easily prepared from phosphorus(V) silyl esters and sulfonic anhydrides.[190,191] The reactions involving methanesulfonic anhydride proceed in methylene chloride solution at ambient temperature in excellent yield. It has been shown using low temperature experiments that phosphonium intermediates are involved.

Reaction with triflic anhydride is complicated by the high silylating capability of the silyl ester of triflic acid. The reaction can be applied only to the synthesis of anhydrides of phosphinic acids.

With phosphonates or phosphates the successive silylation with trimethylsilyl triflate leads to a mixture of products. Since silyl esters of phosphinic acids also react at room temperature with trimethylsilyl triflate producing mixed anhydrides, the silyl phosphinates can be used in reaction with triflic anhydride in a 2:1 molar ratio. Similarly, reaction of triflic anhydride with diethyl trimethylsilyl phosphate gives a good yield of the corresponding mixed anhydride.[191]

Another important application of phosphorus(V) silyl esters is for the preparation of phosphorochloridates. Conversion of the silyl ester into a chloro substituent may be accomplished using phosphorus pentachloride,[21,192,193] oxalyl chloride,[193-195] or thionyl chloride.[97]

Morita, *et al.* prepared a variety of phosphonyl dichlorides by the reaction of bis(trimethylsilyl) alkylphosphonates with phosphorus pentachloride.[21] Bhongle, *et al.* also prepared numerous phosphonyl dichlorides by the reaction of the bis(trimethylsilyl) alkylphosphonates with oxalyl chloride in the presence of DMF.[193] Vaghefi, *et al.* prepared ethoxycarbonylphosphonyl dichloride in 80% distilled yield by the reaction of the corresponding bis(trimethylsilyl) phosphonate with thionyl chloride.[97]

The reaction of sulfuryl chloride with tris(trimethylsilyl) thionophosphate proceeds quantitatively to form bis(trimethylsilyl) phosphoryl sulfenyl chloride.[196] Stec and Uzanski showed that chlorination of a trimethylsilyl selenophosphate proceeds to the unstable corresponding phosphoryl selenenyl chloride, which decomposed above -50°.[174,197]

2. Experimental Procedures

a. Ethoxycarbonylphosphonyl Dichloride[97]

Bis(trimethylsilyl) ethoxycarbonylphosphonate (60.0 g, 0.2 mol) is placed in a 250 mL flask and thionyl chloride (163 g, 1.37 mol) is added. The mixture is heated at reflux for 4 hr. Volatile materials are removed by distillation and the pure ethoxycarbonylphosphonyl dichloride (31 g, 81%) is isolated by vacuum distillation at 53°/0.05 Torr.

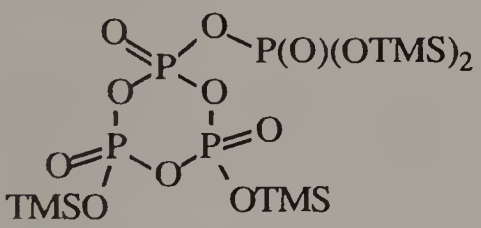
b. 3-Bromopropylphosphonyl Dichloride[193]

To a solution of freshly prepared bis(trimethylsilyl) 3-bromopropylphosphonate (1.34 g, 3.86 mmol) in dry methylene chloride

(5 mL) containing 2 drops of DMF is added dropwise oxalyl chloride (1.47 g, 11.58 mmol) at room temperature. Vigorous evolution of gas occurs. The reaction mixture is stirred at room temperature for 30 min after which the volatile materials are evaporated and the residue is vacuum distilled to give pure 3-bromopropylphosphonyl dichloride (0.818 g, 88%) of bp 76-78°/0.03 Torr.

IV. Trimethylsilyl Polyphosphates (PPSE)

Polyphosphate silyl ester, PPSE, prepared by Imamoto[198] is a very useful and versatile reagent in promoting many types of organic transformations.[1,32] The PPSE polymers are synthesized by condensation of P_4O_{10} with bis(trimethylsilyl) ether at reflux in an inert solvent and in the absence of any catalyst.[32] The PPSE is a viscous liquid soluble in many organic solvents. As noted by Watanabe and Yamamoto,[199] the major components of PPSE are isocyclotetraphosphate (1), cyclotetraphosphate (2), and linear tetraphosphate (3).



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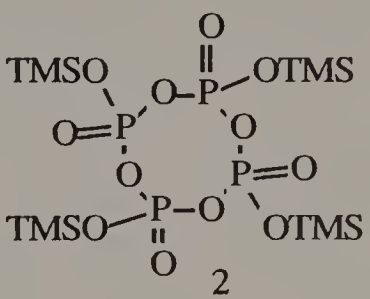

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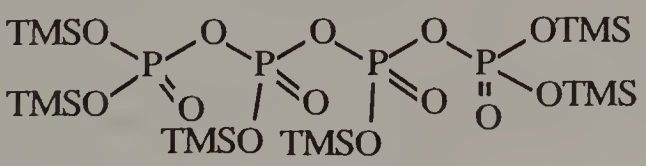

3

The PPSE is a good catalyst for the Beckmann rearrangement of ketoximes,[198,199] for the conversion of alcohols to alkyl iodides with NaI,[200] for the dehydration of carboxamides and aldoximes to nitriles,[75,201] and for the promotion of aldol condensations of ketones with aldehydes.[32,202] Synthesis of 2*H*-1,2,4-benzothiadiazine 1,1-dioxide, a potential antihypertensive and antimicrobial agent, also utilizes PPSE as a catalyst.[203] Additional examples of the use of PPSE are in the synthesis of

amidines from carboxylic acids and primary amines,[204] and the synthesis of benzimidazole and its analogues.[199]

V. The Chemistry of the Phosphorus-Silicon Linkage: The Silyl Phosphines

A. The Synthesis of Silyl Phosphines

In this section we will briefly discuss the chemistry of the phosphorus-silicon linkage. An explosive growth has taken place in studies of this linkage over the past ten years, although most of it falls in the realm of inorganic or organometallic chemistry.

A word of caution is in order to begin this section. Silylated phosphines are particularly sensitive to reaction with oxygen and moisture, and are pyrophoric. All operations involving these materials should be performed in an inert atmosphere as well as a functioning hood.[205]

Reaction of white phosphorus with sodium/potassium alloy in refluxing dimethoxyethane gives the phosphorus trianion which, on reaction with trimethylsilyl chloride, forms tris(trimethylsilyl)-phosphine in good yield.[206]

Niecke and Westermann recently reported[207] an alternative and simpler procedure for the preparation of tris(trimethylsilyl)-phosphine. Reaction of piperidino(dichloro)phosphine with lithium and trimethylsilyl chloride in boiling THF followed by fractionation gives the desired phosphine in good yield.

The reaction of allylphosphine with excess trimethylsilyl iodide in the presence of excess pyridine gives bis(trimethylsilyl)-allylphosphine in good yield.[208] However, with large excesses of allyl phosphine, the unsymmetrical allyl(trimethylsilyl)phosphine is produced as the major product which disproportionates at higher temperatures to allylphosphine and bis(trimethylsilyl)allylphos-phine.

Reaction of tris(trimethylsilyl)phosphine with alkyllithiums produces bis(trimethylsilyl)phosphide which, on reaction with alkyl halides, produces the corresponding bis(trimethylsilyl)alkylphos-phine.[206]

Metallation of 2,4,6-tri-*t*-butylphenylphosphine with butyl-lithium followed by silylation with *t*-butyldimethylsilyl chloride gives the stable mono-silyl phosphine in quantitative yield.[209] The use of dimesitylsilyl dichloride in place of *t*-butyldimethylsilyl chloride as the silylating agent gives chlorodimesitylsilyl-2,4,6-tri-*t*-butylphenylphosphine.[210] Similar metallation followed by

silylation reactions have been used recently for the preparation of 2-pyridylbis(trimethylsilyl)phosphines[211] and other oligophosphinylmethyltrimethylsilylphosphines.[212]

The phosphorus-carbon bond of triphenylphosphine is easily cleaved by lithium metal in THF at room temperature producing lithium diphenylphosphide in quantitative yield. The by-product, phenyllithium, produced in this reaction is destroyed *in situ* by reaction with *t*-butyl chloride. Isobutylene gas evolves and the diphenylphosphide anion is allowed to react with trimethylsilyl chloride to produce diphenyl(trimethylsilyl)phosphine in 80% yield.[205]

B. Experimental Procedures

1. Tris(trimethylsilyl)phosphine[206]

Caution: tris(trimethylsilyl)phosphine is pyrophoric and must be handled in an inert atmosphere. White phosphorus (22.8 g, 0.736 mol) is cut under water and quickly trransferred to a 2 L two-neck flask equipped with a reflux condenser and previously purged with argon and vacuum dried for 4 hr. Dimethoxyethane (1.7 L) is added under an inert atmosphere and a high-torque mechanical stirrer is inserted. Sodium-potassium alloy prepared from a mixture of potassium (60.5 g, 1.55 g-atom) and sodium (26.8 g, 1.16 g-atom) is added to the vigorously stirred mixture using a syringe over a period of 15 min. The reaction mixture is heated at reflux for 24 hr. To the black refluxing solution is added slowly, degassed trimethylsilyl chloride (291 g, 2.68 mol). At the end of the addition the reaction mixture is grey and rather thick with precipitate. Good stirring must be maintained, or else the yield of the desired material will be lowered. The mixture is refluxed for 72 hr. After cooling, the reaction mixture is filtered in a glovebox and the precipitate is washed with several portions of hexane. (As the waste precipitate usually catches fire on exposure to air, caution must be used in its disposal.) The hexane washings are combined with the filtrate and the solvent evaporated under vacuum at room temperature. The residue is distilled to give tris(trimethylsilyl)phosphine (134 g, 73%) of bp 54-57°.

2. Diphenyl(trimethylsilyl)phosphine[205]

A clean, dry 100 mL two-neck round-bottomed flask equipped with air cooled reflux condenser, Teflon coated magnetic stirrer, and septum is assembled in a nitrogen-filled glove bag.

Freshly dried THF (25 mL) and triphenylphosphine (10.5 g, 0.04 mol) is added to the flask. There is added lithium (0.55 g, 0.08 g-atom) which has been cleaned, scraped, and pressed into flat rods. The mixture is stirred for 3 hr. There is then added slowly *via* syringe 2-chloro-2-methylpropane (3.7 g, 0.04 mol). The solution is then filtered in the glove bag and the filtrate is placed in a pressure-equalizing dropping funnel and attached to a 200 mL two-neck flask containing trimethylsilyl chloride (4.32 g, 0.04 mol) in THF (25 mL), and fitted with an air cooled condenser. The solution is added over a 30 min period. The mixture is then filtered and washed with THF. The combined filtrate and washings are evaporated under argon and the residue is vacuum distilled to give pure diphenyl(trimethylsilyl)phosphine (8.3 g, 80%) of bp 126-127°/1 Torr.

C. Reactions of Silyl Phosphines

Since silyl phosphines contain the highly reactive silicon-phosphorus bond, they undergo a variety of reactions and offer considerable potential for novel organophosphorus compound synthesis.[213]

Silyl phosphines undergo facile hydrolysis with deoxygenated water to give primary and secondary phosphines in quantitative yield.[214]

Lindner studied extensively the reaction between silyl phosphines and acyl chlorides.[215-218] Diphenyl(trimethylsilyl)-phosphine reacts with acyl halides to give the corresponding acyldiphenylphosphines in good yield. In addition to diphenyl(trimethylsilyl)phosphine, Lindner utilized various other silyl phosphines in the acyl halide reaction.[218] Bis(trimethylsilyl)alkyl- and arylphosphines react with phthaloyl chloride to produce the heterocyclic phosphorus-substituted phthaloylphosphine in virtually quantitative yield.[219] Diphenic chloride and naphthalic anhydride react in a similar manner to generate phosphorus heterocycles. Bis(trimethylsilyl)phenylphosphine reacts with succinyl chloride to form the diphospha-1,5-hexadiene, which in turn undergoes spontaneously a [3,3']-diphospha-Cope rearrangement.[220]

A similar reaction of bis(trimethylsilylphenylphosphine with *trans*-1,2-cyclohexanedicarboxylic acid dichloride produces the ten-membered ring compound, 1,2-diphenyl-3,10-bis(trimethylsiloxy)-1,2-diphospha-3,9-cyclodecadiene in 75% yield.[221,222] Similar reactions of tris(trimethylsilyl)phosphine with cyclic 1,2-dicarboxy dichlorides produces isophosphindoles in good

yield.[223] The immediate product in this reaction using phthaloyl chloride rapidly undergoes a [2+2] cycloaddition *via* the isophosphindole intermediate.

The reaction of highly hindered acid chlorides with tris(trimethylsilyl)phosphine produces stable phospha-ethyne derivatives.[224-226]

$$RC(O)Cl \xrightarrow{P(TMS)_3} RC(O)P(TMS)_2 \longrightarrow \underset{\displaystyle OTMS}{\underset{|}{RC}}{=}PTMS \longrightarrow R\text{-}C{\equiv}P$$

On the other hand, the reaction of highly hindered *P*-substituted bis(trimethylsilyl)phosphines with phosgene gives the stable phospha-ketenes.[227,228] Reaction with oxalyl chloride produces 1,2-diphosphacyclobutenes *via* [2+2] cycloadditions of the initially formed species.[229]

When a large excess of acetyl chlroide is used with tris(trimethylsilyl)phosphine, triacetylphosphine results.[230] Phosphinotriacetic acid and its derivatives have been prepared in 45-70% yield by the reaction of chloroacetic acid derivatives with tris(trimethylsilyl)phosphine.[231,232]

Phenyl bis(trimethylsilyl)phosphine on reaction with formaldehyde gives an 83% yield of phenylbis(trimethylsiloxymethyl)phosphine.[233] It also reacts with DMF *via* addition-elimination to give *P*-phenylphosphinylidenemethyl dimethylamine in 74% yield.[233]

Finally, Markl has used tris(trimethylsilyl)phosphine extensively for the synthesis of various types of phosphorus heterocycles.[234-237]

VI. Conclusions

The chemistry of silyl esters of phosphorus and the silyl phosphines is very broad and the field is still growing rapidly. Thus, the area covered in this review was necessarily limited. Many aspects of the chemistry of these compounds were treated only marginally and others remained beyond its scope. Attempts have been made to include the latest developments in this rapidly expanding area.

Table 1. Preparation of Phosphorus(V) Silyl Esters by the McKenna Reaction

Starting Material	Product	Method	Yield	Reference
CH_2=CH-P(O)$(OEt)_2$	CH_2=CHP(O)$(OTMS)_2$	TMSBr	99	49
$(EtO)_2P(O)CH_2P(O)(OMe)_2$	$(EtO)_2P(O)CH_2P(O)(OTMS)_2$	TMSBr	97	49
$(MeO)_2CHP(O)(OMe)_2$	$(MeO)_2CHP(O)(OTMS)_2$	TMSBr	99	56
$MeC(O)P(O)(OEt)_2$	$MeC(O)P(O)(OTMS)_2$	TMSBr	91	56
$PhOC(O)CH_2P(O)(OEt)_2$	$PhOC(O)CH_2P(O)(OTMS)_2$	TMSBr	90	56
$EtOCH=CHP(O)(OMe)_2$	$EtOCH=CHP(O)(OTMS)_2$	TMSBr	92	56
$Cl_3CP(O)(OMe)_2$	$Cl_3CP(O)(OTMS)_2$	TMSCl/NaI	100	20
$MeOC(O)CH_2P(O)(OEt)_2$	$MeOC(O)CH_2P(O)OTMS)_2$	TMSCl/NaI	98	20
$Et_2NC(O)P(O)(OEt)_2$	$Et_2NC(O)P(O)(OTMS)_2$	TMSCl/NaI	98	20
$PhCH_2P(O)(OEt)_2$	$PhCH_2P(O)(OTMS)_2$	TMSI	100	18
$MeC(O)P(O)(OMe)_2$	$MeC(O)P(O)(OTMS)_2$	TMSI	100	18
$(EtO_2C)_2CHCH_2P(O)(OEt)_2$	$(EtO_2C)_2CHCH_2P(O)(OTMS)_2$	TMSI	100	18
$H(CF_2)_2O(CF_2)_2P(O)(OEt)_2$	$H(CF_2)_2O(CF_2)_2P(O)(OTMS)_2$	TMSBr	58	65
H-Pro-Tyr(PO_3Me_2)-Val-OH	H-Pro-Tyr(PO_3H_2)-Val-OH	TMSBr/PhSMe	75	64
$NCCH(OTMS)CH_2CF_2P(O)(OEt)_2$	$NCCH(OTMS)CH_2CF_2P(O)(OTMS)_2$	TMSBr	100	66
$CH_2=C[P(O)(OEt)_2]_2$	$CH_2=C[P(O)(OTMS)_2]_2$	TMSBr	90	26

$CF_2[P(O)(OEt)_2]_2$	$CF_2[P(O)(OTMS)_2]_2$	TMSBr	91	67,68
$CHF[P(O)(OEt)_2]_2$	$CHF[P(O)(OTMS)_2]_2$	TMSBr	72	68
$PhC(N_2)P(O)(OMe)Ph$	$PhC(N_2)P(O)(OTMS)Ph$	TMSBr	69	24
o-HO-$C_6H_4P(O)(OEt)_2$	*o*-HO-$C_6H_4P(O)(OTMS)_2$	TMSCl/NaI	65	27
$EtO_2CCF_2P(O)(OEt)_2$	$EtO_2CCF_2P(O)(OTMS)_2$	TMSBr	97	63
$(EtO)_2P(O)C{\equiv}CP(O)(OEt)_2$	$(TMSO)_2P(O)C{\equiv}CP(O)(OTMS)_2$	TMSBr	98	69
$(MeO)_2P(O)CH_2C(O)(CH_2)_3CO_2$-Bu-*t*		TMSBr		
	$(TMSO)_2P(O)CH_2C(O)(CH_2)_3CO_2$-Bu-*t*		88	70
Z-AlaNHCH[P(O)$(OMe)_2$]CH_2CO_2Me		TMSBr		
	Z-AlaNHCH[P(O)$(OTMS)_2$]CH_2CO_2Me		94	56
$HO(CH_2)_2P(O)(OMe)_2$	$HO(CH_2)_2P(O)(OTMS)_2$	TMSBr	88	71
$ClP(O)(OEt)_2$	$ClP(O)(OTMS)_2$	TMSBr	52	60
$CH_2{=}CO(Ph)P(O)(OMe)_2$	$CH_2{=}C(Ph)OP(O)(OTMS)_2$	TMSBr	78	72
$HC{\equiv}C\text{-}P(O)(OEt)_2$	$HC{\equiv}C\text{-}P(O)(OTMS)_2$	TMSI	100	62
$HOCH_2CH(OH)CH_2CF_2P(O)(OEt)_2$		TMSBr		
	$HOCH_2CH(OH)CH_2CF_2P(O)(OTMS)_2$		73	66
$PhC(O)C(N_2)P(O)(OMe)_2$	$PhC(O)C(N_2)P(O)(OTMS)_2$	TMSBr	78	24
$(EtO)_2P(S)\text{-}O\text{-}P(O)(OEt)_2$	$(TMSO)_2P(S)\text{-}O\text{-}P(O)(OTMS)_2$	TMSI	20	60

Table 2. Arbuzov Reaction of Silyl Phosphites with Alkyl/Acyl Halides

Phosphorus Reagent	Product	Method	Yield	Reference
$TMSOCH_2P(OTMS)_2$	$NCCH_2CH_2P(O)(OH)CH_2OH$	RX, heat	91	86
$(TMSO)_3P$	$(TMSO)_2P(O)C(O)CF_3$	AcX	46	102
$(TMSO)_3P$	$(TMSO)_2P(O)$-Bu-*n*	RX, heat	90	103
Ph_2POTMS	$Ph_2P(O)CH_3$	RX	93	104
$(TMSO)_3P$	$(TMSO)_2P(O)CH_2Ph$	RX	80	81
$(TMSO)_3P$	$(TMSO)_2P(O)C(O)Ph$	AcX	72	94
$(TESO)_3P$	$(TESO)_2P(O)C(O)CH(CF_3)_2$	AcX	52	102
$(TESO)_3P$	$(TESO)_2P(O)C_7H_{15}$-*n*	RX, heat	80	103
$(TMSO)_3P$	$(HO)_2P(O)CH_2P(O)(OPh)_2$	RX, heat; water	49	101
$TMSOP(OEt)_2$	$(EtO)_2P(O)C(O)CH_2Cl$	AcX	37	99
$(TMSO)_3P$	$(TMSO)_2P(O)CH_2CH_2Br$	RX, heat	84	105
$(TMSO)_3P$	$(TMSO)_2P(O)C(O)C_6H_4$-*o*	AcX	72	94
$(TMSO)_2PH$	$(PhCH_2)_2P(O)OTMS$	RX, Et_3N, TMSCl	79	100
$(TMSO)_3P$	$(TMSO)_2P(O)C(O)OCH_2CCl_3$	AcX	91	94
$(TMSO)_3P$	$(TMSO)_2P(O)C(O)Et$	AcX	63	94
$(TMSO)_2PH$	$(CH_2=CHCH_2)_2P(O)OTMS$	RX, Et_3N, TMSCl	59	100
$(TESO)_3P$	$(TESO)_2P(O)Me$	RX	100	103
$(TMSO)_3P$	$(TMSO)_2P(O)C(O)Me$	AcX	50	94

Table 3. Reaction of Carbonyl Compounds with Phosphorus(III) Silyl Esters

Phosphorus Reagent	Product	Yield	Reference
$(EtO)_2POTMS$	$(EtO)_2P(O)CH(OTMS)CH_3$	88	112
$(EtO)_2POTMS$	$(EtO)_2P(O)CH(OTMS)CH(CH_3)_2$	83	112
$(MeO)_2POTMS$	$(MeO)_2P(O)CH(OTMS)Ph$	62	39
$(TMSO)_3P$	$(TMSO)_2P(O)CH(OTMS)CH{=}CH_2$	94	115
$(Me_2N)_2POTES$	$(Me_2N)_2P(O)CH(OTES)CH{=}CH_2$	90	113
$(TMSO)_3P$	$(TMSO)_2P(O)CH(OTMS)CH{=}CHCH_3$	89	115
$(EtO)_2POTMS$	$(EtO)_2P(O)CH(OTMS)Ph$	91	112
$(t\text{-}BuMe_2SiO)P(OMe)_2$	$(MeO)_2P(O)CH(C_5H_{11}\text{-}n)OSIMe_2Bu\text{-}t$	81	39
$(TMSO)_3P$	$(TMSO)_2P(O)CH(OTMS)Ph$	88	115
$(EtO)_2POTMS$	$(EtO)_2P(O)C(OTMS)(CH_3)Ph$	78	110
$(EtO)_2POTMS$	$(EtO)_2P(O)CH(OTMS)CH{=}CH_2$	89	110
$(TMSO)_3P$	$(TMSO)_2P(O)CH(OTMS)Et$	85	115
$(EtO)_2POTMS$	$(EtO)_2P(O)C(OTMS)(Me)CH_2Cl$	86	128,132
$(EtO)_2POTMS$	$(EtO)_2P(O)CH(OTMS)CH{=}CHCH_3$	73	110
$MeOP(OTMS)_2$	$CH_2{=}C(CO_2Et)\text{-}O\text{-}P(O)(OTMS)OMe$	61	96,129
$(TMSO)_3P$	$(TMSO)_2P(O)\text{-}O\text{-}C(CO_2Et){=}CH_2$	36	96,129
$(TMSO)_2PH$	$TMSOP(O)[CH(Ph)OTMS]_2$	92	131
$(TMSO)_2PH$	$PhC(CH_3)(OTMS)P(O)H(OTMS)$	48	14

Table 4. Addition of Phosphorus(III) Silyl Esters to Imines, Aminals, Acetals, and Other Carbonyl Carbon Equivalents

Substrate	Phosphorus Reagent	Product	Yield	Reference
$(EtO)_2CHCH=NCH_2Ph$	$(EtO)_2POTMS$	$(EtO)_2CHCH[P(O)(OEt)_2]NHCH_2Ph$	76	133
$(EtO)_2CHCH=NCH_2Ph$	*n*-BuO(Ph)POTMS	$(EtO)_2CHCH[P(O)OBu\text{-}n)Ph]NHCH_2Ph$	81	133
$PhCH=NCHPh_2$	$(TMSO)_2PH$	$PHCH(PO_2H_2)NCHPh_2$	72	139
$MeOCH_2N(TMS)_2$	$(MeO)_2POTMS$	$(MeO)_2P(O)CH_2N(TMS)_2$	75	136
$PhC(O)NHCH(OMe)CO_2Me$	$(MeO)_2POTMS$	$PhC(O)NHCH[P(O)(OMe)_2]CO_2Me$	78	145
$PhCH(OMe)_2$	$(EtO)_2POTMS$	$PhCH(OMe)P(O)(OEt)_2$	90	137
$PhCH(SEt)_2$	$(EtO)_2POTMS$	$PhCH(SEt)P(O)(OEt)_2$	75	141
$Me_2CHCH=NCH_2Ph$	Ph(EtO)POTMS	$Me_2CHCH[Ph(OEt)P(O)]NCH_2Ph$	87	133
$PhCH=NCH_2CH=CH_2$	$(EtO)_2POTMS$	$PhCH[P(O)(OEt)_2]NHCH_2CH=CH_2$	74	133
PhCH(Me)N=CHPh	$P(OTMS)_3$	$(TMSO)_2P(O)CH(Ph)N(TMS)CH(Me)Ph$	88	143
$MeOCH_2N(TMS)_2$	$P(OTMS)_3$	$(TMSO)_2P(O)CH_2N(TMS)_2$	56	136
$PhCH(OEt)_2$	$(EtO)_2POTMS$	$PhCH(OEt)P(O)(OEt)_2$	92	137
PhCH(SBu-*n*)	$(EtO)_2POTMS$	$PhCH(SBu\text{-}n)P(O)(OEt)_2$	80	141

Table 5. Michael Addition of Phosphorus(III) Silyl Esters to Activated α,β-Unsaturated Systems

Phosphorus Reagent	Product	Substrate Type	Yield	Reference
$(MeO)_2POTMS$	$(MeO)_2P(O)CH(CCl_3)CH_2NO_2$	nitro	86	158
$(EtO)_2POTMS$	$(EtO)_2P(O)CH_2CH=C(CH_3)OTMS$	ketone	91	110
$(EtO)_2POTMS$	$(EtO)_2P(O)CH_2CH_2CO_2C_4H_9$-*n*	ester	82	159
$(MeO)_2POTMS$	$(MeO)_2P(O)CH(CH_3)CH=C(CH_3)OTMS$	ketone	64	39
$(EtO)_2POTMS$	$(EtO)_2P(O)CH_2CH(CN)TMS$	nitrile	62	152
$(Me_2N)_2POTMS$	$(Me_2N)_2P(O)CH_2CH=C(CH_3)OTMS$	ketone	82	39
$(TMSO)_3P$	$H_2O_3PCH(Ph)CH_2C(O)Ph$	ketone	75	115
$(TMSO)_3P$	$(TMSO)_2P(O)CH_2CH=C(CH_3)OTMS$	ketone	84	115
$(EtO)_2CHP(OEt)OTMS$	$(EtO)_2CHP(O)(OEt)CH_2CH_2NO_2$	nitro	75	45
$(TMSO)_3P$	$(TMSO)_2P(O)CH_2CH(TMS)CN$	nitrile	52	152
Ph_2POTMS	$Ph_2P(O)CH_2CH=CHP(O)Ph_2$	allyl acetate	72	154
$(TMSO)_2PH$	$HOP(O)[CH_2CH_2CO_2Me]_2$	ester	90	43
$(TMSO)_2PH$	$(TMSO)_2PCH_2CH_2CN$	nitrile	36	156
$(MeO)_2POTMS$	$(MeO)_2P(O)CH(CHMe_2)CH_2NO_2$	nitro	87	157
$MeP(OEt)OTMS$	$MeP(O)(OEt)CH_2CH_2CN$	nitrile	63	116
$(TMSO)_2PH$	$HOP(O)(H)CH_2CH_2CO_2Et$	ester	85	43
$(EtO)_2POTMS$	$(EtO)_2P(O)CH(CN)Ph$	nitro	86	153

Table 6. Oxidation of Phosphorus(III) Silyl Esters to Phosphorus(V) Compounds

Phosphorus Reagent	Product	Oxidizing Agent	Yield	Reference
$(TMSO)_3P$	$p\text{-}NO_2C_6H_4CH_2SPO_3H_2$	$(p\text{-}NO_2C_6H_4CH_2S)_2$	100	161
$(TMSO)_2PH$	$(PhS)_2PO_2^- {}^+NH_3C_6H_{11}$	$(PhS)_2$	83	162
$(TMSO)_3P$	$(TMSO)_3P(O)$	sulfoxide	72	171
$(TMSO)_3P$	$(HO)_3P(O)$	nitro	84	171
$(MeO)_2POTMS$	$(MeO)_2P(O)SP(O)(OEt)_2$	sulfenyl chloride	95	173
$(MeO)_2POTMS$	$[(MeO)_2P(O)]_2Se$	selenenyl chloride	80	172,174
$(EtO)_2POTMS$	$[(EtO)_2P(O)]_2Se$	$[(EtO)_2P(O)Se]_2$	100	175
$(MeO)_2POTMS$	$(MeO)_2P(O)F$	perfluoropropylene oxide	37	178
$(TMSO)_3P$	$(TMSO)_2P(O)Br$	Br_3CCHO	83	179
$(TMSO)_3P$	$(TMSO)_2P(O)I$	I_2	100	170

VII. Bibliography

1. Wozniak, L., and Chojnowski, J. (1989). Silyl esters of phosphorus - Common intermediates in synthesis, *Tetrahedron*, *45*: 2465.
2. Engel, R. (1987). Nucleophilic displacement at carbon by phosphorus, in *Synthesis of Carbon-Phosphorus Bonds*, CRC Press, Inc., Boca Raton, FL, p. 7.
3. Engel, R. (1987). Trivalent phosphorus addition to carbonyl carbon - the Abramov and Pudovik reactions, in *Synthesis of Carbon-Phosphorus Bonds*, CRC Press, Inc., Boca Raton, FL, p. 77.
4. Engel, R. (1987). Conjugate addition reactions of trivalent phosphorus reagents, in *Synthesis of Carbon-Phosphorus Bonds*, CRC Press, Inc., Boca Raton, FL, p. 137.
5. Kutyrev, G.A., and Cherkasov, R.A. (1984). The reactivity of organo silicon derivatives of phosphorus in addition reactions, *Russ. Chem. Rev.*, *53*: 971.
6. Bhattacharya, A.K., and Thyagarajan, G. (1981). The Michaelis-Arbuzov rearrangement, *Chem. Rev.*, *81*: 415.
7. Yudelevich, V.I., Sokolov, L.B., and Ionin, B.I. (1980). Phosphinates ("hypophosphites") and their reactivity, *Russ. Chem. Rev.*, *49*: 92.
8. Nifant'ev, E.E. (1978). Chemistry of phosphinylidene compounds - advances and prospects of development, *Russ. Chem. Rev.*, *47*: 1565.
9. Chernyshev, E.A., and Bugerenko, E.F. (1968). Organosilicon compounds containing phosphorus, *Organomet. Chem. Rev. A*, *3*: 469.
10. Weber, W.P. (1983). Silicon reagents for organic synthesis, in *Silicon-Phosphorus*, Springer-Verlag, Berlin, p. 358.
11. Borisov, S.A., Voronkov, M.S., and Lukevits, E.J., (1971). *Organo Silicon Derivatives of Phosphorus and Sulfur*, Plenum Press, New York.
12. Rabinowits, R. (1963). The reaction of phosphonic acid esters with acid chlorides. A very mild hydrolytic route, *J. Org. Chem.*, *28*: 2975.
13. Newlands, M.J. (1960). Silicon-phosphorus compounds, *Proc. Chem. Soc.*: 123.
14. Hata, T., Mori, H., and Sekine, M. (1977). The reactions of bis(trimethylsilyl) phosphites with carbonyl compounds, *Chem. Lett.*: 1431.
15. Ugi, I., Ramirez, F., Hinrichs, E.V., Lemmen, P., and Firl,

J. (1974). Silyl esters of a five-membered cyclic acyl phosphate, *J. Chem. Soc., Chem. Commun.*: 979.
16. Sarin. V., Tropp, B.E., and Engel, R. (1977). Isosteres of natural phosphates. 7. The preparation of 5-carboxy-4-hydroxy-4-methylpentyl-1-phosphonic acid, *Tetrahedron Lett.*: 351.
17. Brazier, J.F., Houall, D., and Wolf, R. (1970). Synthese et quelques proprietes d'esters organo-phosphores comportant les substituents R_3SiO- et R_3GeO-, *Bull. Soc. Chim. Fr.*: 1089.
18. Blackburn, G.M., and Ingleson, D. (1978). Specific dealkylation of phosphonate esters using iodotrimethylsilane, *J. Chem. Soc., Chem. Commun.*: 871.
19. Zygmunt, J., Kafarski, P., and Mastalerz, P. (1978). Preparation of oxoalkane phosphonic acids, *Synthesis*: 609.
20. Morita, T., Okamoto, Y., and Sakurai, H. (1978). A convenient dealkylation of dialkyl phosphonates by chlorotrimethylsilane in the presence of sodium iodide, *Tetrahedron Lett.*: 2523.
21. Morita, T., Okamoto, Y., and Sakurai, H. (1980). A mild and facile synthesis of alkyl- and arylphosphonyl dichlorides under neutral conditions. Reaction of bis(trimethylsilyl) phosphonates with PCl_5, *Chem. Lett.*: 435.
22. Morita, T., Okamoto, Y., and Sakurai, H. (1981). Dealkylation reaction of acetals, phosphonates, and phosphate esters with chlorotrimethylsilane/metal halide reagent in acetonitrile and its application to the synthesis of phosphonic acids and vinyl phosphates, *Bull. Chem. Soc. Jpn.*, *54*: 267.
23. Machida, Y., Nomoto, S., and Saito, I. (1979). A useful method for the dealkylation of dialkyl phosphonates, *Synth. Commun.*, *9*: 97.
24. Regitz, M., and Martin, R. (1985). Untersuchungen an Diazoverbindungen und Aziden - IL. *tert*-Butylammonium Salze von α-Diazophosphin- und α-Diazophosphonsauren, *Tetrahedron*, *41*: 819.
25. Blackburn, G.M., and Maciej, T.W. (1985). The synthesis of *O,O*-bistrimethylsilyl *S*-trihalogenomethyl phosphorothioates, *J. Chem. Soc., Perkin Trans. I*: 1419.
26. Degenhardt, C.R., and Burdsall, D.C. (1986). Synthesis of ethynylidenebis(phosphonic acid) and its tetraalkyl esters, *J.*

Org. Chem., *51*: 3488.
27. Dhawan, B., and Redmore, D. (1984). *o*-Hydroxyaryldiphosphonic acids, *J. Org. Chem.*, *49*: 4019.
28. Yamashita, M., Sugiura, M., Oshikawa, T., and Inokawa, S. (1987). Synthesis of dimethyl (1-nitromethylalkyl)phosphonates and their conversion to dimethyl (1-formylalkyl)-phosphonates by oxidation with ozone, *Synthesis*: 62.
29. Kume, A., Fujii, M., Sekine, M., and Hata, T. (1984). Acylphosphonates. 4. Synthesis of dithymidine phosphonate: A new method for generation of phosphonate function *via* aroylphosphonate intermediates, *J. Org. Chem.*, *49*: 2139.
30. Sekine, M., Yamagata, H., and Hata, T. (1981). Silyl phosphite equivalents: 2,2,2-trichloromethoxycarbonylphosphonates, *J. Chem. Soc., Chem. Commun.*: 970.
31. Bruynes, C.A., and Jurriens, T.K. (1982). Catalysts for silylations with 1,1,1,3,3,3-hexamethyldisilazane, *J. Org. Chem.*, *47*: 3966.
32. Imamoto, T., Matsumoto, T., Yokoyama, H., Yokoyama, M., and Yamaguchi, K. (1984). Preparation and synthetic use of trimethylsilyl polyphosphate. A new stereoselective aldol-type reaction in the presence of trimethylsilyl polyphosphate, *J. Org. Chem.*, *49*: 1105.
33. Cavell, R.G., Leary, R.D., and Tomlinson, A.J. (1972). Trimethylsilyl esters of phoshporus acids. 1. Preparation and properties of esters of difluoro- and bis(trifluoromethyl)phosphinic, thiophosphinic and dithiophosphinic acids, *Inorg. Chem.*, *11*: 2573.
34. Cavell, R.G., Leary, R.D., Sanger, A.R., and Tomlinson, A.J. (1973). Trimethylsilyl esters of phosphorus acids. III. Esters of difluoro- and bis(trifluoromethyl)phosphinous and thiophosphinous acids, *Inorg. Chem.*, *12*: 1374.
35. Chojnowski, J., Cypryk, M., Michalski, J., and Wozniak, L. (1986). Optically active triorganosilyl esters of phosphorus. Synthesis and structure, *Tetrahedron*, *42*: 385.
36. Michalski, J., Chojnowski, J., Jezierska, B., and Borecka, B. (1980). Reactions of compounds of phosphorus having positively polarized divalent sulfur with disilathianes. Synthetic and mechanistic aspects, *Phosphorus Sulfur*, *8*: 263.
37. Sekine, M., Okimoto, K., Yamada, K., and Hata, T. (1981). Silyl phosphites. 15. Reactions of silyl phosphites

with α-halocarbonyl compounds. Elucidation of the mechanism of the Perkow reaction and related reactions with confirmed experiments, *J. Org. Chem.*, *46*: 2097.

38. Sekine, M., Futatsugi, T., Yamada, K., and Hata, T. (1982). Silyl phosphites. Part 20. A facile synthesis of phosphoenolpyruvate and its analogue utilizing *in situ* generated trimethylsilyl bromide, *J. Chem. Soc., Perkin Trans. I*: 2509.
39. Evans, D.A., Hurst, K.M., and Takacs, J.M. (1978). New silicon-phosphorus reagents in organic synthesis. Carbonyl and conjugate addition reactions of silicon phosphite esters and related systems, *J. Am. Chem. Soc.*, *100*: 3467.
40. Wozniak, L., Cypryk, M., Chojnowski, J., and Lanneau, G. (1989). Optically active silyl esters of phosphorus. 11. Stereochemistry of reactions with nucleophiles, *Tetrahedron*, *45*: 4403.
41. Chojnowski, J., Cypryk, M., Michalski, J., Wozniak, L., Corriu, R., and Lanneau, G. (1986). Optically active triorganosilyl esters of phosphorus. Synthesis and structure, *Tetrahedron*, *42*: 385.
42. Issleib, K., and Walther, B. (1967). Synthesis of silyl phosphinites, *Angew. Chem., Int. Ed. Engl.*, *6*: 88.
43. Boyd, E.A., Corless, M., James, K., and Regan, A.C. (1990). A versatile route to substituted phosphinic acids, *Tetrahedron Lett.*, *31*: 2933.
44. Dingwall, J.G., Ehrenfreund, J., Hall, R.G., and Jack, J. (1987). Synthesis of γ-aminopropylphosphoonous acids using hypophosphorus acid synthons, *Phosphorus Sulfur*, *30*: 571.
45. Dingwall, J.G., Ehrenfreund, J., and Hall, R.G. (1989). Diethoxymethylphosphonites and phosphinates. Intermediates for the synthesis of α-, β- and γ-aminoalkylphosphonous acids, *Tetrahedron*, *45*: 3787.
46. Lopusinski, A., Michalski, J., and Potrzebowski, M. (1986). Preparation of diastereoisomeric 2-trimethylsiloxy-4-methyl-1,3,2-dioxaphosphorinanes, *Phosphorus Sulfur*, *28*: 299.
47. Imai, K., Ito, T., Kondo, S., and Takaku, H. (1985). A new phosphorylating agent, di(2,2,2-trifluoroethyl) trimethylsilyl phosphite, *Nucleosid. Nucleotid.*, *4*: 669.
48. Fujii, M., Ozaki, K., Kume, A., Sekine, M., and Hata, T.

(1986). Acylphosphonates. 6. Reaction mechanism of Zn/Me_3SiCl mediated conversion of 2,2,2-trichloroethoxycarbonylphosphonates to silyl phosphites, *Tetrahedron Lett.*, *27*: 3365.

49. McKenna, C.E., Higa, M.T., Cheung, N.H., and McKenna, M.C. (1977). The facile dealkylation of phosphonic acid dialkyl esters by bromotrimethylsilane, *Tetrahedron Lett.*: 155.
50. McKenna, C.E., and Schmidhauser, J. (1979). Functional selectivity in phosphonate ester dealkylation with bromotrimethylsilane, *J. Chem. Soc., Chem. Commun.*: 739.
51. Montero, J.L., Toiron, C., Claval, J.L., and Imbach, J.L. (1988). Phosphorylation of hydroxy groups *via* silylated intermediates, *Rec. Trav. Chim. Pays-Bas*, *107*: 570.
52. Franz, J.E. (1984). Silyl esters of *N*-phosphonomethylglycine, *U.S. Patent 4,471,131*.
53. Maier, L. (1983). Advances in the chemistry of aminophosphinic acids, *Phosphorus Sulfur*, *14*: 295.
54. Bruzik, K., and Tsai, M.D. (1984). phospholipids chiral at phosphorus. 5. Synthesis and configurational analysis of chiral [^{17}O,^{18}O]-phosphatidylethanolamine, *J. Am. Chem. Soc.*, *106*: 747.
55. Sekine, M., Mori, H., and Hata, T. (1982). Protection of phosphonate function by means of ethoxycarbonyl group. A new method for generation of reactive silyl phosphite intermediates, *Bull. Chem. Soc. Jpn.*, *55*: 239.
56. Morita, T., Okamoto, Y., and Sakurai, H. (1978). The preparation of phosphonic acid having labile functional groups, *Bull. Chem. Soc. Jpn.*, *51*: 2169.
57. Campbell, M.M., Carruthers, N.I., and Mickel, S.J. (1982). Aminophosphonic and aminophosphinic acid analogues of aspartic acid, *Tetrahedron*, *38*: 2513.
58. Takenaka, H., and Hayase, Y. (1989). Facile synthesis of 2-(5-isopropyl-5-methyl-4-oxo-2-imidazolin-2-yl)phenylphosphonates, *Heterocycles*, *29*: 1185.
59. Machida, Y., Nomoto, S., and Saito, I. (1979). A useful method for the dealkylation of dialkyl phosphonates, *Synth. Commun.*, *9*: 97.
60. Chojnowski, J., Cypryk, M., and Michalski, J. (1978). The selective displacement of *O*-alkyl by trialkylsilyl in some derivatives of acids of phosphorus, *Synthesis*: 777.

61. Zygmunt, J., Kafarski, P., and Mastalerz, P. (1978). Preparation of oxoalkanephosphonic acids, *Synthesis*: 609.
62. Blackburn, G.M., and Ingleson, D. (1980). The dealkylation of phosphate and phosphonate esters by iodotrimethylsilane: A mild and selective procedure, *J. Chem. Soc., Perkin Trans. I*: 1150.
63. Burton, D.J., Sprague, L.G., Pietrzyk, D.J., and Edelmuth, S.H. (1984). A safe facile synthesis of difluorophosphono-acetic acid, *J. Org. Chem.*, *49*: 3437.
64. Su, D., Guo, C.Y., Willett, R.D., Scott, B., Kirchmeier, R.L., and Shreeve, J.M. (1990). Synthesis of *trans*-1,2-difluoroethenediylbis(phosphonic acid) and other unsaturated phosphonic acids, *J. Am. Chem. Soc.*, *112*: 3152.
65. Su, D., Cen, W., Kirchmeier, R.L.m and Shreeve, J.M. (1989). Synthesis of fluorinated phosphonic, sulfonic and mixed phosphonic/sulfonic acids, *Can. J. Chem.*, *67*: 1795.
66. Chambers, R.D., Jaouhari, R., and Hagan, D.O. (1989). Fluorine in enzyme chemistry. Part 2. The preparation of difluoromethylenephosphonate analogues of glycolytic phosphates, *Tetrahedron*, *45*: 5101.
67. Davisson, V.J., Woodside, A.B., Neal, T.R., Stremler, K.E., Muehlbacher, M., and Poulter, C.D. (1986). Phosphorylation of isopernoid alcohols, *J. Org. Chem.*, *51*: 4768.
68. McKenna, C.E., and Shen, P.D. (1981). Fluorination of methanediphosphonate esters by perchloryl fluoride. Synthesis of fluoromethane diphosphonic acid and difluoromethanediphosphonic acid, *J. Org. Chem.*, *46*: 4573.
69. Blackburn, G.M., Kent, D.E., and Kolkmann, F. (1984). The synthesis and metal binding characteristics of novel isopolar phosphonate analogues of nucleotides, *J. Chem. Soc., Perkin Trans. I*: 1119.
70. Tang, K.-C., and Coward, J.K. (1983). Synthesis of acylphosphonate analogues of biologically important acyl phosphates, *J. Org. Chem.*, *48*: 5001.
71. Gloede, J., Weight, E., and Gross, H. (1980). Notiz zur Synthese von β-Hydroxyethanphosphonsaure, *J. prakt. Chem.*, *322*: 327.
72. Hata, T., Yamada, K., Futatsugi, T., and Sekine, M. (1979). Facile synthesis of unesterified enolphosphates, *Synthesis*: 189.

73. Pudovik, A.N., Romanov, G.V., and Stepanova, T.Y. (1979). Reaction of bis(trimethylsilyl) sulphate with phosphorus acid chlorides, *Izv. Akad. Nauk S.S.S.R., Ser. Khim., 11*: 2644.
74. Yamaguchi, K., Kamimura, T., and Hata, T. (1980). A method for the preparation of unesterified acyl phosphates *via* stannyl phosphate intermediates, *J. Am. Chem. Soc., 102*: 4534.
75. Yokoyama, M., Yoshida, S., and Imamoto, T. (1982). Organic reactions using trimethylsilyl polyphosphate (PPSE): a convenient synthesis of nitriles from carboxamides, *Sythesis*: 591.
76. Lopusinski, A., Michalski, J., and Potrzebowski, M. (1986). Reaction of dialkoxythioxaphosphoranesulfenyl chlorides with dialkyl trimethylsilyl phosphites. New stereoselective route to the unsymmetrical tetraalkyl dithiopyrophosphates. Preparation of diastereoisomeric 2-trimethylsiloxy-4-methyl-1,3,2-dioxaphosphorinanes, *Phosphorus Sulfur, 28*: 299.
77. Dembinski, R., Koninski, R., Michalski, J., and Skowronska, A. (1986). Synthesis of symmetrical tetraalkyl monoselenopyrophosphates: compounds containing a selenium bridge between two phosphoryl centers, *J. Chem. Soc., Chem. Commun.*: 1770.
78. Michalski, J., Lopusinski, A., Jezierska, B., Luczak, L., and Potrzebowski, M. (1987). A new approach towards organophosphorus sulfenyl and selenyl halides, *Phosphorus Sulfur, 30*: 221.
79. van den Berg, G.R., Platenburg, D.H.J.M., and Benschop, H.P. (1971). Stereochemistry of a Michaelis-Arbuzov reaction: alkylation of optically active ethyl trimethylsilyl phenylphosphonite with retention of configuration, *J. Chem. Soc., Chem. Commun.*: 606.
80. Chojnowski, J., Cypryk, M., and Michalski, J. (1981). The mechanism of the reaction of organic phosphites with trialkylsilyliodides. Iodoanhydrides of phosphorus(III) acids and intermediates, *J. Organomet. Chem., 215*: 355.
81. Hata, T., Sekine, M., and Kagawa, N. (1975). Silyl phosphites. II. Reactions of tris(trimethylsilyl) phosphite with alkyl halides, *Chem. Lett.*: 635.
82. Rosenthal, A.F., Vargas, L.A., Isaacson, Y.A., and Bittman, R. (1975). A simple synthesis of phosphonate

contianing lipids. Introduction of the phosphonic acid moiety with hydrolytically labile compounds, *Tetrahedron Lett.*: 977.

83. Deroo, P.W., Rosenthal, A.F., Isaacson, Y.A., Vargas, L.A., and Bittman, R. (1976). Synthesis of DL-2,3-diacyl-oxypropylphosphonyl cholines from DL-2,3-diacyloxyiodo-propanes, *Chem. Phys. Lipids*, *16*: 60.
84. Tang, J.-C., Tropp, B.E., Engel, R., and Rosenthal, A.F. (1976). Isosteres of natural phosphates. 4. The synthesis of phosphonic acid analogues of phosphatidic acid and acyldihydroxyacetone phosphate, *Chem. Phys. Lipids*, *17*: 169.
85. Doerr, I.L., Tang, J.-C., Rosenthal, A.F., Engel, R., and Tropp, B.E. (1977). Synthesis of phosphonate and ether analogs of *rac*-phosphoatidyl-L-serine, *Chem. Phys. Lipids*, *19*: 185.
86. Rosenthal, A.F., Gringauz, A., and Vargas, L.A. (1976). Bis(trimethylsilyl) trimethylsiloxymethylphosphonite: a useful reagent for the introduction of the hydroxymethyl-phosphinate group, *J. Chem. Soc., Chem. Commun.*: 384.
87. Thottathil, J.K., and Moniot, J.L. (1985). Phosphinic acid intermediates, *Eur. Patent 138,403*.
88. Thottathil, J.K., Przybyla, C.A., and Moniot, J.L. (1984). Mild Arbuzov reactions of phosphonous acids, *Tetrahedron Lett.*, *25*: 4737.
89. Grobelny, D. (1989). A convenient synthesis of amino-methylphosphonous acids, *Synth. Commun.*, *19*: 1177.
90. deVroom, E., Spierenburg, M.L., Dreef, C.E., van der Marel, G.A., and van Boom, J.H. (1987). A general procedure to convert H-phosphonate mono- or diesters of nucleic acids into valuable phosphate di- or triesters, *Rec. Trav. Chim. Pays-Bas*, *106*: 65.
91. Issleib, K., Balszuweit, A., Koetz, J., Richter, S., and Leutloff, R. (1985). Synthesis of aryl bis(trimethylsilyl) phosphonic acid esters *via* tris(trimethylsilyl) phosphite - a contribution to the nickel catalyzed Michaelis-Arbuzov reaction, *Z. anorg. allgem. Chem.*, *529*: 151.
92. Sentimov, V.V., Krasilnikova, E.A., and Berdnik, I.V. (1990). Mechanism of catalysis of the Arbuzov reaction by transition metal complexes. IV. Effect of phosphorus(III) derivatives on metal-complex catalysis of the Arbuzov reaction, *Zh. Obshch. Khim. S.S.S.R.*, *60*: 58.

93. Sentemov, V.V., Shagvaleev, F.S., Zykova, T.V., and Krasilnikova, E.A. (1988). Reactions of aryl bromides with dialkyl trimethylsilyl phosphites in the presence of nickel chloride, *Zh. Obshch. Khim. S.S.S.R.*, *58*: 302.
94. Sekine, M., and Hata, T. (1987). Convenient synthesis of unesterified acylphosphonic acids, *J. Chem. Soc., Chem. Commun.*: 285.
95. Terauchi, K., and Sakurai, H. (1970). Photochemical studies of the esters of aroylphosphonic acids, *Bull. Chem. Soc. Jpn.*, *43*: 883.
96. Sekine, M., Tetsuaki, T., Yamada, K., and Hata, T. (1982). A facile synthesis of phosphoenolpyruvate and its analogue utilizing *in situ* generated trimethylsilylbromide, *J. Chem. Soc., Perkin Trans. I*: 2509.
97. Vaghefi, M.M., McKernan, P.A., and Robins, R.K. (1986). Synthesis and antiviral activity of certain nucleoside 5'-phosphonoformates, *J. Med. Chem.*, *29*: 1389.
98. Iyer, R.P., Phillips, L.R., Biddle, J.A., Thakker, D.R., Egan, W., Aoki, S., and Mitsuya, H. (1989). Synthesis of acyloxyalkyl acylphosphonates as potential prodrugs of the antiviral trisodium phosphonoformate (Foscarnet sodium), *Tetrahedron Lett.*, *30*: 7141.
99. Brittelli, D.R. (1985). A study of the reaction of 2-haloacyl halides with trialkyl phosphites. Synthesis of (2-substituted-acyl)phosphonates, *J. Org. Chem.*, *50*: 1845.
100. Majewski, P. (1989). New synthetic route to dialkylphosphinic acids, *Phosphorus Sulfur*, *45*: 151.
101. Vaghefi, M.M., Bernacki, R.J., Hennen, W.J., and Robins, R.K. (1987). Synthesis of certain nucleoside methylenediphosphonate sugars as potential inhibitors of glycosyltransferases, *J. Med. Chem.*, *30*: 1391.
102. Dyakov, V.M., and Voronkov, M.G. (1973). Trialkylsilyl esters of polyfluoroacylphosphonic acids, *Bull Acad. Sci. U.S.S.R., Engl. Transl.*: 379.
103. Belokrinitsky, M.A., and Orlov, N.F. (1971). Reactions of alkyl halides with triorganosilyl derivatives of phosphorous acid, *Kremniiorg. Mater.*: 145.
104. Issleib, K., and Walther, B. (1970). Silyl, germanyl, and stannyl esters of phosphinous acids of the R_2POER type (E = silicon, germanium, tin), *J. Organomet. Chem.*, *22*: 375.
105. Dreef, N.E., Valentijn, A.R.P.M., deVroom, E., van der

Marel, G.A., and van Boom, J.H. (1988). An approach towards the formation of an ester bond between the primary hydroxyl of a β-D-galactopyranoside and 2-aminoethylphosphonic acid and its *N*-methyl substituted derivatives, *Tetrahedron Lett.*, *29*: 1199.

106. Nesterov, L.V., Krepyschev, N.E., Sabirova, R.A., and Romanova, G.N. (1971). Phosphorus derivatives. VIII. Reactions of dialkyl trialkylsilyl phosphites with aldehydes and ketones, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *41*: 2474.
107. Engel, R. (1988). Phosphorus addition at sp^2 carbon, *Organic Reactions*, *36*: 175.
108. Abramov, V.S. (1954). Reactions of aldehydes with phosphites, *Dokl. Akad. Nauk S.S.S.R.*, *95*: 991.
109. Seebach, D. (1979). Methods of reactivity *umpolung*, *Angew. Chem., Int. Ed. Engl.*, *18*: 239.
110. Hata, T., Hashizume, A., Nakajima, M., and Sekine, M. (1978). A convenient method of ketone synthesis utilizing the reaction of diethyl trimethylsilyl phosphite with carbonyl compounds, *Tetrahedron Lett.*: 363.
111. Hata, T., Nakajima, M., and Sekine, M. (1979). Facile synthesis of β-alkyl-substituted esters from α,β-unsaturated aldehydes, *Tetrahedron Lett.*: 2047.
112. Sekine, M., Nakajima, M., Kume, A., Hashizume, A., and Hata, T. (1982). Silyl phosphites. XVIII. Versatile utility of α-(trimethylsiloxy)alkylphosphonates as key intermediates for transformations of aldehydes into several carbonyl derivatives, *Bull. Chem. Soc. Jpn.*, *55*: 224.
113. Evans, D.A., Takacs, J.M., and Hurst, K.M. (1979). Phosphonamide stabilized allylic carbanions. New homoenolate anion equivalents, *J. Am. Chem. Soc.*, *101*: 371.
114. Hata, T., and Sekine, M. (1980). Silyl and stannyl esters of phosphorus oxyacids - intermediates for the synthesis of phosphate derivatives of biological interest, in *Phosphorus Chemistry Directed towards Biology*, (Stec, W.J., ed.), Pergamon Press, Oxford, p. 197.
115. Sekine, M., Yamamoto, I., Hashizume, A., and Hata, T. (1977). The reaction of tris(trimethylsilyl) phosphite with carbonyl compounds, *Chem. Lett.*: 485.
116. Thottathil, J.K., Ryono, D.E., Przybyla, C.A., Moniot,

J.L., and Neubeck, R. (1984). Preparation of phosphinic acids: Michael additions of phosphonous acids/esters to conjugated systems, *Tetrahedron Lett.*, *25*: 4741.

117. Tong, G., Perich, J.W., and Johns, R.B. (1990). Synthesis of Leu-Abu(P) and Glu-Abu(P)-Leu. Isosteres of Ser(P)-peptides, *Tetrahedron Lett.*, *31*: 3759.
118. Valerio, R.M., Alewood, P.F., and Johns, R.B. (1988). Synthesis of optically active 2-(*tert*-butyloxycarbonylamino)-4-dialkoxy-phosphoryl-butanoate protected isosteres of *O*-phosphoserine for peptide synthesis, *Synthesis*: 786.
119. Wroblewski, A.E. (1986). Analogues of branched chain tetrahydrofuranosides having phosphorus in the anomeric position, *Tetrahedron*, *42*: 3595.
120. Sekine, M., Nakajima, M., and Hata, T. (1981). Silyl phosphites. 16. Mechanism of the Perkow reaction and the Kukhtin-Ramirez reaction. Elucidation by means of a new type of phosphoryl rearrangement utilizing silyl phosphites, *J. Org. Chem.*, *46*: 4030.
121. Schomburg, D., Weferling, N., and Schmutzler, R. (1981). A rigid double spirocyclic λ^5P-O-λ^5P oxydiphosphorane with a boat shaped six-membered ring; X-ray crystal structure, *J. Chem. Soc., Chem. Commun.*: 810.
122. Sekine, M., Futatsugi, T., and Hata, T. (1982). Silyl phosphites. 21. A new method for the synthesis of L-ascorbic acid 2-*O*-phosphate by utilizing phosphoryl rearrangement, *J. Org. Chem.*, *47*: 3453.
123. Vysotskii, V.I., Levankov, S.V., and Prikhod'ko, Y.V. (1989). Reactions of 1,5-diketones. LI. Reaction of aryl aliphatic 1,5-diketones with bis(trimethylsiloxy)phosphine, *Zh. Obshch. Khim. S.S.S.R.*, *59*: 2223.
124. Nifant'ev, E.E., Kukhareva, T.S., Popkova, T.N., and Bekker, A.R. (1987). Addition of silyl phosphites to 2,5-diacetyl-4-methylphenol, *Zh. Obshch. Khim. S.S.S.R.*, *57*: 2003.
125. Zhao, Y.F., Wei, S.Z., and Song, A.T. (1987). The reaction of acetylacetone with dialkyl phosphites: Synthesis of dialkyl 1-methyl-3-oxo-1-butenylphosphonates, *Phosphorus Sulfur*, *33*: 53.
126. Avdeenko, A.P., Ryazantsev, V.P., and Evgrafov, N.I. (1987). Reaction of *N*-(arylsulfonyl)-*p*-quinone imines with dialkyl trimethylsilyl phosphites, *Zh. Obshch. Khim. S.S.S.R.*, *57*: 1254.

127. Avdeenko, A.P., Ryazantsev, V.P., and Mischenko, A.I. (1986). Reaction of *N,N'*-bis[aryl(alkyl)sulfonyl]-*p*-quinone imines with dialkyl trimethylsilyl phosphites, *Zh. Obshch. Khim. S.S.S.R.*, *56*: 2491.
128. Sekine, M., Okimoto, K., and Hata, T. (1978). Silyl phosphites. 6. Reactions of tris(trimethylsilyl) phosphite with α-halocarbonyl compounds, *J. Am. Chem. Soc.*, *100*: 1001.
129. Sekine, M., Futatsugi,oi T., Yamada, K., and Hata, T. (1980). A convenient synthesis of phosphoenolpyruvate *via* silyl-ester intermediates, *Tetrahedron Lett.*, *21*: 371.
130. Majewski, P. (1989). Reaction of bis(trimethylsiloxy)-phosphine with α-halocarbonyl compounds. A new route to substituted *O,O*-divinyl-*O*-trimethylsilyl phosphates, *Phosphorus Sulfur*, *45*: 177.
131. Majewski, P. (1987). A new method for the preparation of bis(1-hydroxyalkyl)phosphinic acids, *Synthesis*: 555.
132. Sekine, M., Yamagata, H., and Hata, T. (1979). A general and convenient method for the synthesis of unesterified carbamoyl and thiocarbamoylphosphonic acids, *Tetrahedron Lett.*: 3013.
133. Afarinkia, K., Rees, C.W., and Cadogan, J.I.G. (1990). Synthesis of organophosphorus compounds *via* silyl esters of phosphorus acids, *Tetrahedron*, *46*: 7175.
134. Benneche, T., Strande, P., and Undheim, K. (1987). Sulfonic and phosphonic acids formed by bisulfite and phosphite adduct formation with pyrimidones, *Acta Chem. Scand.*, *B41*: 448.
135. Maier, L., and Rist, G. (1983). Organic phosphorus compounds. 77. Synthesis and properties of phosphinothricin homologs and analogs, *Phosphorus Sulfur*, *17*: 21.
136. Morimoto, T., Aono, M., and Sekiya, M., (1984). *N,N*-bis-(trimethylsilyl)methoxymethylamine as a convenient synthetic equivalent for $+CH_2NH_2$: *N,N*-bis(trimethyl-silyl)aminomęthylation of silyl sulfides and phosphites, *J. Chem. Soc., Chem. Commun.*: 1055.
137. Kim, D.Y., and Oh, D.Y. (1986). A facile synthesis of diethyl 1-alkoxy-1-arylmethanephosphonates, *Synth. Commun.*, *16*: 859.
138. Vaghefi, M.M., Bernacki, R.J., Dalley, N.K., Wilson,

B.E., and Robins, R.K. (1987). Synthesis of glycopyranosyl phosphonate analogues of certain natural nucleoside diphosphate sugars as potential inhibitiors of glycosyltransferases, *J. Med. Chem.*, *30*: 1383.

139. Grobelny, D. (1987). A new synthetic route to 1-aminoalkylphosphonous acids, *Synthesis*: 942.
140. Huber, R., and Vasella, A. (1987). Nucleophilic additions to *N*-glycosylnitrones. Part IV. Asymmetric synthesis of *N*-hydroxy-α-aminophosphonic acid and α-aminophosphonic acids, *Helv. Chim. Acta*, *70*: 1461.
141. Kim, D.Y., Kim, T.H., and Oh, D.Y. (1987). Facile synthesis of 1-(substitutedaryl)alkylthiomethanephosphonates, *Phosphorus Sulfur*, *34*: 179.
142. Dhawan, B., and Redmore, D. (1987). Optically active 1-aminoalkylphosphonic acids, *Phosphorus Sulfur*, *32*: 119.
143. Zon, J. (1981). Asymmetric addition of tri(trimethylsilyl) phosphite to chiral aldimines, *Pol. J. Chem.*, *55*: 643.
144. Franz, J.E. (1985). *N*-Phosphonomethylglycine derivatives, *Belg. Patent 900,682*.
145. Ku, B., and Oh, D.Y. (1988). Facile synthesis of α-phosphorylated α-amino acids, *Tetrahedron Lett.*, *29*: 4465.
146. Nifant'ev, E.E., Popkova, T.N., Kukhareva, T.S., and Bekker, A.R. (1988). Reaction of silyl phosphites with 2-(*o*-hydroxybenzyl)oxazolidines, *Zh. Obshch. Khim. S.S.S.R.*, *58*: 1550.
147. Nesterov, L.V., and Aleksandrova, N.A. (1985). Arbuzov reaction of dialkyl trialkylsilyl phosphites with esters of orthocarbonic acids - New chain heterolytic process in the chemistry of organophosphorus compounds, *Zh. Obshch. Khim. S.S.S.R.*, *55*: 222.
148. Kim, D.Y., and Oh, D.Y. (1986). A facile synthesis of bis-(alkylthio)methanephosphonates, *Bull. Korean Chem. Soc.*, *7*: 486.
149. Nesterov, L.V., Krepysheva, N.E., and Aleksandrova, N.A. (1989). Reaction of DMF dimethyl acetal with silyl phosphites, *Zh. Obshch. Khim. S.S.S.R.*, *59*: 725.
150. Liotta, D., Sunay, U., and Ginsberg, S. (1982). Phosphonosilylations of cyclic enones, *J. Org. Chem.*, *47*: 2227.
151. Evans, D.A., Hurst, K.M., Truesdale, L.K., and Takacs, J.M. (1977). The carbonyl insertion reactions of mixed

tervalent phosphorus-organosilicon reagents, *Tetrahedron Lett.*: 2495.
152. Nakano, M., Okamoto, Y., and Sakurai, H. (1982). Preparation of dialkyl 2-cyano-2-(trimethylsilyl)methanephosphonates, *Synthesis*: 915.
153. Kim, D.Y., and Oh, D.Y. (1987). A new facile synthesis of diethyl 1-aryl-1-cyanomethanephosphonates, *Synth. Commun.*, *17*: 953.
154. Lu, X., Tao, X., Zhu, J., Sun, X., and Xu, J. (1989). Regio- and stereoselective synthesis of symmetrical and unsymmetrical 1,3-diphosphoryl(phosphonyl, phosphinyl)-substituted (*E*)-propenes, *Synthesis*: 848.
155. Novikova, Z.S., Mososhina, S.N., Sapozhnikova, T.A., and Lutsenko, I.F. (1971). Reactions of diethyl trimethylsilyl phosphite with carbonyl compounds, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *41*: 2655.
156. Issleib, K., Mogelin, W., and Balszuweit, A. (1985). Bis-(trimethylsilyl) Hypophosphite und Alkoxycarbonylphosphonigsaure-bis(trimethylsilyl) Ester als Schlusselsubstanzen fur die Synthese von Organophosphorverbindungen, *Z. anorg. allgem. Chem.*, *530*: 16.
157. Gareev, R.D., Loginova, G.M., and Pudovik, A.N. (1977). Some reactions of completely esterified phosphites with nitro-olefins, *Zh. Obshch. Khim. S.S.S.R.*, *47*: 2676.
158. Borisova, E.E., Gareev, R.D., and Shermergorn, I.M. (1980). Reactions of neutral phosphorus(III) esters with 3,3,3-trichloro-1-nitropropene, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *50*: 1786.
159. Okomoto, Y., and Sakurai, H. (1982). Preparation of (dialkylphosphinyl)methyl-substituted ketone alkyl trimethylsilyl acetal derivatives, *Synthesis*: 497.
160. Shadid, B.R., van der Plas, H.C., deVroom, E., van der Marel, G.A., and van Boom, J.H. (1987). Phosphorylation of allylic hydroxy groups *via* phosphite intermediates, *Recl. Trav. Chim. Pays-Bas*, *106*: 509.
161. Bethel, R.C., and Lowe, G. (1986). Synthesis of adenosine 5'-[γ(*R*)-^{17}O,^{18}O-thio]triphosphate, *J. Chem. Soc., Chem. Commun.*: 1341.
162. Sekine, M., Hamaoki, K., and Hata, T. (1979). Synthesis and properties of *S,S*-diarylnucleoside phosphorodithioates in oligonucleotide synthesis, *J. Org. Chem.*, *44*: 2326.
163. Lopusinski, A. (1989). Chemistry of *S*-trifluoromethyl

organophosphorothioates and their structural analogs. A convenient synthesis of organo-phosphorus fluorides, *Phosphorus Sulfur*, *45*: 137.
164. Dabkowski, W., Cramer, F., and Michalski, J. (1987). A new strategy for dinucleotide synthesis *via* phosphite route involving phosphorochloridates as intermediates, *Tetrahedron Lett.*, *28*: 3559.
165. Hata, T., and Sekine, M. (1974). Silyl phosphites. 1. The reaction of silyl phosphites with diphenyl disulfide. Synthesis of *S*-phenyl nucleoside phosphorothioates, *J. Am. Chem. Soc.*, *96*: 7363.
166. deVroom, E., Dreef, C.E., van den Elst, H., van der Marel, G.A., and van Boom, J.H. (1988). Preparation of internucleotide phosphate analogues *via* the corresponding H-phosphonate diester, *Recl. Trav. Chim. Pays-Bas*, *107*: 592.
167. Dreef, C.E., van der Marel, G.A., and van Boom, J.H. (1987). Phosphorylation of benzyl-protected sugar derivatives *via* 1-H-phosphonate intermediates: Synthesis of DL-*myo*-inositol 1,4,5-tris-1-H-phosphonate, *Recl. Trav. Chim. Pays-Bas*, *106*: 512.
168. Dabkowski, W., and Michalski, J. (1987). Fluorination of trimethylsilyl phosphites and their structural analogues by sulfuryl chloride fluoride. A facile preparation of phosphoro-fluoridates and related compounds, *J. Chem. Soc., Chem. Commun.*: 755.
169. Dabkowski, W., Cramer, F., and Michalski, J. (1988). A novel approach to the synthesis of deoxynucleoside phosphorofluoridates - II, *Tetrahedron Lett.*, *29*: 3301.
170. Michalski, J., Pakulski, M., and Skowronska, A. (1980). Arbuzov reactions of alkyl and silyl phosphites with halogens involving four and five co-ordinate intermediates, *J. Chem. Soc., Perkin Trans. I*: 833.
171. Sekine, M., Yamagata, H., and Hata, T. (1979). Silyl phosphites. 8. Deoxygenation reactions by means of tris(trimethylsilyl) phosphite, *Tetrahedron Lett.*: 375.
172. Dembinski, R., Kaminski, R., Michalski, J., and Skowronska, A. (1986). Synthesis of symmetrical tetra-alkyl monoselenopyrophosphates. Compounds containing a selenium bridge between two phosphoryl centres, *J. Chem. Soc., Chem. Commun.*: 1770.
173. Skowronska, A., Dembinski, R., Kaminski, R., and

Michalski, J. (1987). Novel synthesis of symmetrical tetra-alkyl monothio pyrophosphates, *Tetrahedron Lett.*, *28*: 4209.
174. Skowronska, A., Dembinski, R., Kaminski, R., and Michalski, J. (1988). Reaction of oxophosphorane - sulphenyl and selenenyl chlorides with dialkyl trimethylsilyl phosphites. Novel synthesis of compounds containing a sulphur or selenium bridge between two phosphoryl centers, *J. Chem. Soc., Perkin Trans. I*: 2197.
175. Dembinski, R., Krawczyk, E., and Skowronska, A. (1988). Reaction of diphosphoryl diselenides with dialkyl trimethylsilyl phosphites. A new route to symmetrical monoselenopyrophosphates, *Phosphorus Sulfur*, *35*: 345.
176. Wozniak, L., Kowalski, J., and Chojnowski, J. (1985). Bis(trimethylsilyl) peroxide as a versatile reagent for selective generation of oxyphosphoryl group, *Tetrahedron Lett.*, *26*: 4965.
177. Kowalski, J., Wozniak, L., and Chojnowski, J. (1987). Silyl peroxides as selective oxygenation reagents in phosphorus chemistry, *Phosphorus Sulfur*, *30*: 125.
178. Lermontov, S.A., Rakov, I.M., and Martynov, I.V. (1989). Fluorination of silyl phosphites by perfluoropropylene oxide, *Izv. Akad. Nauk S.S.S.R., Ser. Khim.*: 2149.
179. Mironov, V.F., Sinyashina, T.N., Ofitserov, E.N., Konovalova, I.V., and Pudovik, A.N. (1989). Reaction of tris(trimethylsilyl) phosphite with tribromoacetaldehyde, *Zh. Obshch. Khim. S.S.S.R.*, *59*: 1681.
180. Azuhata, T., and Okamoto, Y. (1983). Synthesis of diethyl 2-(trimethylsiloxy)alkane phosphonates from epoxides and diethyl trimethylsilyl phosphite, *Synthesis*: 916.
181. Baylis, E.K., Bittiger, H., Froestl, W., Hall, R.G., Maier, L., Mickel, S.J., and Olpe, H.R. (1989). Preparation of aminopropylphosphinic acids as GABA antagonists, *Eur. Patent Appl. 319,479.*
182. Lazukina, L.A., and Kukhar, V.P. (1988). Amidoethylation of tris(trimethylsilyl) phosphite with *N*-acyl aziridines, *Zh. Obshch. Khim. S.S.S.R.*, *58*: 939.
183. von Allwoerden, U., and Roeschenthaler, G.V. (1985). New phosphorus derivatives of perfluoropropene, *Chem.-Ztg.*, *109*: 81.
184. Heine, J., and Roeschenthaler, G.V. (1988). (*Z*/*E*)-[1,3,3,3-Tetrafluoro-2-(phosphinyl)oxypropenyl]phosphonates,

Chem.-Ztg., *112*: 246.
185. Hata, T., Yamamoto, I., and Sekine, M. (1976). Silyl phosphites. IV. A new method for the synthesis of 5'-aminonucleosides and their phosphoramidate derivatives, *Chem. Lett.*: 601.
186. Hata, T., Yamamoto, I., and Sekine, M. (1975). Simple method for the synthesis of 5'-azido-5'-deoxyribonucleosides, *Chem. Lett.*: 977.
187. Gibbs, D.E. (1977). The synthesis of phosphoramidates from silyl phosphites and azides, *Tetrahedron Lett.*: 679.
188. Dimukhametov, M.N., and Nuretdinov, I.A. (1983). Optically active silyl phosphites in a Staudinger reaction, *Izv. Akad. Nauk S.S.S.R., Ser. Khim.*: 1214.
189. McKenna, C.E., and Levy, J.N. (1989). α-Ketophosphonoacetates, *J. Chem. Soc., Chem. Commun.*: 246.
190. Dabkowski, W., Michalski, J., and Skrzypczynski, Z. (1985). Mixed anhydrides of phosphoric, phosphonic and phosphinic acids with sulfonic acids and sulfuric monoimidazolide. New methods of synthesis, novel structures, phosphorylating properties, *Ber.*, *118*: 1809.
191. Dabkowski, W., Michalski, J., and Skrzypczynski, Z. (1986). Process for manufacturing phosphoric carboxylic and phosphoric sulfonic anhydrides, *Pol. Patent 134,263.*
192. Burton, D.J., and Sprague, L.G. 91988). Preparation of difluorophosphonoacetic acid and its derivatives, *J. Org. Chem.*, *53*: 1523.
193. Bhongle, N.N., Notter, R.H., and Turcotte, J.G. (1987). Expedient and high-yield synthesis of alkylphosphonyl dichlorides under mild neutral conditions: reaction of bis(trimethylsilyl) alkylphosphonates with oxalyl chloride/dimethylformamide, *Synth. Commun.*, *17*: 1071.
194. van der Klein, P.A.M., Dreef, C.E., van der Marel, G.A., and van Boom, J.H. (1989). A new and versatile phosphonylation approach, *Tetrahedron Lett.*, *30*: 5473.
195. Biller, S.A., and Forster, C. (1990). The synthesis of isoprenoid (phosphinylmethyl)phosphonates, *Tetrahedron*, *46*: 6645.
196. Chojnowski, J., Cypryk, M., Fortuniak, W., and Michalski, J. (1977). Methods of synthesis of *O,O*-bis(trimethylsilyl) phosphorothiolates, *Synthesis*: 683.
197. Stec, W.J., and Uznanski, B. (1978). Synthesis of dialkyl phosphoroselenocyanatidates and their rearrangement to

dialkyl phosphoroisoselenocyanatidates, *Synth. Commun.*, *8*: 473.
198. Imamoto, T., Yokoyama, H., and Yokoyama, M. (1981). Trimethylsilyl polyphosphate (PPSE). A useful reagent for the Beckmann rearrangement, *Tetrahedron Lett.*, *22*: 1803.
199. Yamamoto, K., and Watanabe, H. (1982). Composition of polyphosphoric acid trimethylsilyl ester (PPSE) and its use as a condensation reagent, *Chem. Lett.*: 1225.
200. Imamoto, T., Matsumoto, T., Kusumoto, T., and Yokoyama, M. (1983). A convenient method for the preparation of alkyl iodides from alcohols, *Synthesis*: 460.
201. Walba, D.M., Eidman, K.F., and Haltiwanger, R.C. (1989). Ferroelectric liquid crystals. 6. Synthesis of nonracemic aryl cyanohydrin ethers, *J. Org. Chem.*, *54*: 4939.
202. Imamoto, T., Yokoyama, H., and Yokoyama, M. (1982). The reaction of aryl methyl ketones with aromatic aldehydes in trimethylsilyl polyphosphate (PPSE). Formation of *meso*-2,4,6-trisubstituted-5-acyl-1,3-dioxanes, *Tetrahedron Lett.*, *23*: 1467.
203. Imai, Y., Mochizuki, A., and Kakimoto, M. (1983). A convenient synthesis of 2*H*-1,2,4-benzothiadiazine 1,1-dioxides from 2-aminobenzenesulfonamide and carboxylic acids by using polyphosphoric acid trimethylsilyl ester as condensing agent, *Synthesis*: 851.
204. Kakimoto, M., Ogata, S., Mochizuki, A., and Imai, Y. (1984). A novel direct synthesis of amidines from carboxylic acids and amines using polyphosphoric acid trimethylsilyl ester (PPSE) as condensing agent, *Chem. Lett.*: 821.
205. Luther, G.W, and Beyerle, G. (1977). Lithium diphenylphosphide and diphenyl(trimethylsilyl)phosphine, *Inorg. Synth.*, *17*: 186.
206. Askham, F.R., Stanley, G.G., and Marques, E.C. (1985). A new type of transition-metal dimer based on a hexaphosphine ligand system: $Co_2(CO)_4(eHTP)^{2+}$ [eHTP = $(Et_2PCH_2CH_2)_2PCH_2P(CH_2CH_2PEt_2)_2$], *J. Am. Chem. Soc.*, *107*: 7423.
207. Niecke, E., and Westermann, H. (1988). Ein einfaches Verfahren zur Herstellung von Tris(trimethylsilyl)phosphan, *Synthesis*: 330.
208. Schubert, D.M., and Norman, A.D. (1985). Synthesis of (trimethylsilyl)- and (trimethylgermyl)allylphosphine, *Inorg.*

Chem., *24*: 1107.
209. Yoshifuji, M., Toyota, K., Shibayama, K., and Inamoto, N. (1983). Isolation and characterization of stable alkylidenephosphines, *Chem. Lett.*: 1653.
210. Smit, C.N., Lock, F.M., and Bickelhaupt, F. (1984). 2,4,6-Tri-*tert*-butylphenylphosphane - dimesitylsilene, *Tetrahedron Lett.*, *25*: 3011.
211. Spiegel, G.U., and Stelzer, O. (1990). Synthesis and reactions of 2-pyridylphosphane, 2-$(C_5NH_4)PH_2$, *Ber.*, *123*: 989.
212. Langhans, K.P., Stelzer, O., and Weferling, N. (1990). Linear oligophosphaalkanes. 25. Synthesis of $PH_2PCH_2PH_2$ and $(PH_2PCH_2)_2PH$ by phosphinomethylation of PH_3 with phase-transfer catalysis, *Ber.*, *123*: 995.
213. Weber, W.P. (1983), *Silicon-Phosphorus Reagents for Organic Synthesis*, Springer Verlag, Berlin, p. 360.
214. Schubert, D.M., and Norman, A.D. (1984). Synthesis of novel oragno(silyl)phosphine synthons and their conversion to new organophosphines, *Inorg. Chem.*, *23*: 4130.
215. Lindner, E., Steinwand, M., and Hoehne, S. (1982). (Chloroacyl)diphenylphosphanes as sources of hlaogenated ketenes, *Angew. Chem. Int. Ed. Engl.*, *21*: 355.
216. Lindner, E., and Tamoutsidis, E. (1983). Das reaktive Verhalten von methylsubstituierten Propenoyldiphenylphosphanen und deren Oxide, *Ber.*, *116*: 3141.
217. Lindner, E., and Hubner, D. (1983). Untersuchungen uber elektronische Einflusse auf die Reaktivitat von Aroyl- und Acyldiphenylphosphanen und deren Folgeprodukte, *Ber.*, *116*: 2574.
218. Lindner, E., and Hubner, D. (1980). Untersuchungen uber sterische und elektronische Einflusse auf die Reaktivitat von Acetyl(diorganyl)phosphanen und deren Oxide, *Ber.*, *113*: 3268.
219. Barron, A.R., Hall, S.W., and Cowley, A.H. (1987). Cyclic carboxylic monophosphides: a new class of phosphorus heterocycle, *J. Chem. Soc., Chem. Commun.*: 1753.
220. Appel, R., Barth, V., and Halstenberg, M. (1982). Pericyclische Reaktionen an Phospha-1,5-hexadienderivaten, *Ber.*, *115*: 1617.
221. Appel, R., Hunerbein, J., and Knoch, F. (1983). Ring

opening by [3,3]-diphospha Cope-rearrangement, *Angew. Chem., Int. Ed. Engl.*, *22*: 61.

222. Appel, R., Hunerbein, J., Knoch, F., Korte, S., Kundgen, U., Paulen, W., and Zimmermann, R. (1983). Pericyclic reactions with participation of the PC-double bond, *Phosphorus Sulfur*, *18*: 19.
223. Appel, R., Casser, C., Knoch, F., and Niemann, B. (1986). Reaktionen von 1,2-Dicarbonyldichloriden mit Tris(trimethylsilyl)phosphan zu Isophosphindolen, *Ber.*, *119*: 2915.
224. Markl, G., and Sejpka, H. (1985). Direkte Bildung von 2-[9-Triptycyl]1-phosphaethinen aus Triptycylcarbonsaure Chloriden, *Tetrahedron Lett.*, *26*: 5507.
225. Markl, G., and Sejpka, H. (1986). 2-(2,4,6-Tri-*tert*-butylphenyl)1-phosphaethin, 1,4-Bis-(trimethylsiloxy)-1,4-bis-(2,4,6-tri-*tert*-butylphenyl)-2,3-diphosphabutadien, *Tetrahedron Lett.*, *27*: 171.
226. Allspach, T., Regitz, M., Becker, G., and Becker, W. (1986). Unusually coordinated phosphorus compounds; 7. Adamanta-1-yl-methylidynephosphine, a new, stable phosphaalkyne, *Synthesis*: 31.
227. Appel, R., and Paulen, W. (1983). Das erste Phospha-keten, spektroskopischer Nachweis und Folgeraktionen, *Tetrahedron Lett.*, *24*: 2639.
228. Appel, R., and Paulen, W. (1983). The first stable phosphaketene, *Angew. Chem., Int. Ed. Engl.*, *22*: 785.
229. Appel, R., and Barth, V. (1980). Eine neue Synthese von 1,2-Diphosphacyclobutenen, *Tetrahedron Lett.*, *21*: 1923.
230. Becker, G. (1981). Acyl- and alkylidenephosphines from tris(trimethylsilyl)phosphine, *Z. anorg. allgem. Chem.*, *480*: 21.
231. Tzschach, A., Friebe, S., and Klepel, M. (1980). Phosphinotriacetic acid and its derivatives, *DDR Patent 144,265*.
232. Tzschach, A., and Friebe, S., (1979). Preparation of phosphinotriacetic acid, $P(CH_2CO_2H)_3$, *Z. Chem.*, *19*: 375.
233. Becker, G., and Mundt, O. (1980). Synthesis and properties of acylphosphines. IX. Reaction of phenylbis(trimethylsilyl)-phosphine with formaldehyde and dimethyl formamide, *Z. anorg. allgem. Chem.*, *462*: 130.
234. Markl, G., and Dorfmeister, G. (1987). $1,3\lambda^3$-Azaphosphinine durch unsetzung von 3-Azapyryliumsalzen mit Tris-(trimethylsilyl)phosphan, *Tetrahedron Lett.*, *28*: 1093.

235. Markl, G., and Dorfmeister, G., (1987). 4-Hydroxy-1,3λ^3-azaphosphole, *Tetrahedron Lett.*, *28*: 1089.

236. Markl, G., and Dorfmeister, G. (1986). 1-*R*-1,3λ^3-Azaphosphole, *Tetrahedron Lett.*, *27*: 4419.

237. Markl, G., and Pflaum, S. (1987). 1,3λ^3-Azaphospholo-[1,2-α]pyridine, 1,2,4λ^3-Diazaphospholo[1,5-α]pyridine, 1,3λ^3-Azaarzolo[1,5-α]pyridine, 1,2,4λ^3-Diazaarzolo-[1,5-α]pyridine, *Tetrahedron Lett.*, *28*: 1541.

CHAPTER 3

THE PERKOW AND RELATED REACTIONS

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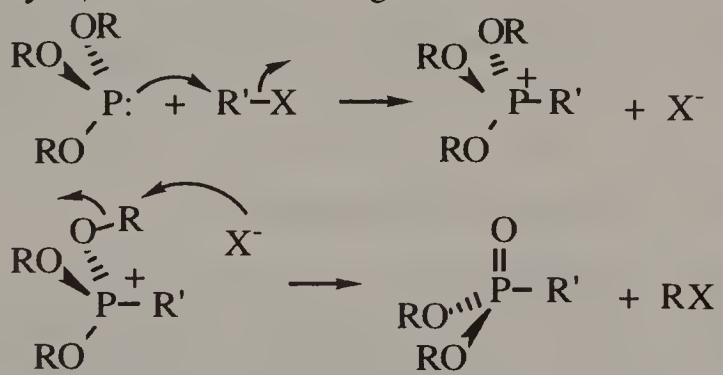
I. The Perkow Reaction

A. Introduction and Historical Development

1. The Michaelis-Arbuzov Reaction

The cleavage step of the Michaelis-Arbuzov reaction, or rearrangement, is an integral part of the Perkow reaction. Therefore, we shall briefly explore its nature and history first. The reaction was discovered by Michaelis[1] in 1898 and subsequently extended by Arbuzov[2,3] and others. It is used to synthesize phosphonates, in its most popular application, as well as phosphine oxides and phosphinic acid esters. The general reaction using a trialkyl phosphite and a simple alkyl halide, not an α-haloketone or α-haloaldehyde, is illustrated in Fig. 1.



R = alkyl, aryl; R' = alkyl, acyl; X = Cl, Br, I

Fig. 1. - The Michaelis-Arbuzov reaction

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2. The Perkow Reaction for Enol Phosphate Synthesis

In 1952 Perkow[4] discovered that a new type of rearrangement, not the Michaelis-Arbuzov reaction, took place when trialkyl phosphites reacted with α-haloaldehydes. This "anomalous Arbuzov reaction" which resulted in the formation of dialkyl vinyl phosphates subsequently became known as the "Perkow reaction." It is to be noted that the Shell Development Company had also done pioneering work on this reaction as evidenced by a 1960 patent.[5] The Perkow reaction, as known today, includes the reactions of phosphites [$(RO)_3P$], phosphonites [$(RO)_2PR'$], and phosphinites [$ROP(R')_2$] with a spectrum of mono-, di-, and tri- α-halo, α-OMes, and α-OTos carbonyl compounds. The chemistry and properties of enol phosphates, the name succeeding vinyl phosphates in *Chemical Abstracts*, was reviewed in detail by Lichtenthaler in 1961.[6] The general reaction is illustrated in Fig. 2.

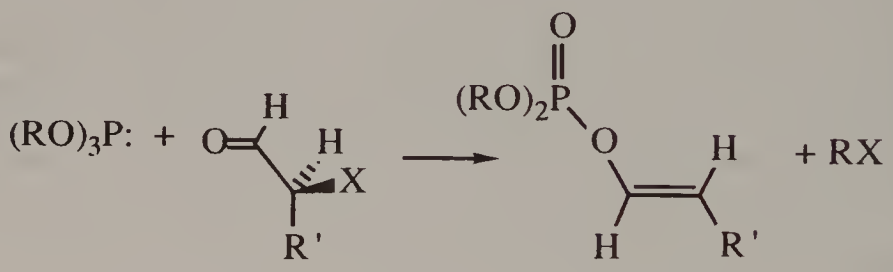


Fig. 2 - The Perkow reaction of α-haloaldehydes

B. Scope of the Perkow Reaction

1. General Conditions

Perkow reactions occur with any trivalent organophosphorus reagent that contains at least one alkoxy group. Usually tertiary phosphites [$(RO)_3P$] are employed. Part IIA of this Chapter will review the related reactions of phosphinites and phosphonites. These species are intermediate in their halophilicities when

compared to phosphites, which are least halophilic, and tertiary phosphines, which are most halophilic.

While some combination of reactants react at room temperature exothermically, *e.g.* chloral with triethyl phosphite, most cases require the reaction to be heated, usually to 85-110°. The reactions are best carried out in a solvent ,which can be an ether, alcohol, or other non-reactive species. Halogen reactivity is stated to be I > Br > Cl[6] but, at least for those cases where carbonyl addition is rate determining, the ratios $k_2Cl/k_2Br \geq 1$ are observed, as detailed in Part IC of this Chapter. Other reaction details have been previously noted.[6]

2. Requirements of the Phosphites Used

The most commonly used trialkyl phosphites are triethyl phosphite (TEP) and trimethyl phosphite (TMP), which is somewhat less reactive. In phosphites containing one or two phenoxy groups, the alkyl group is replaced. Trialkyl phosphites having different alkyl groups usually eliminate the smallest group as the alkyl halide. Further structural details, including the range of cyclic phosphites and equivalent derivatives of arsenic and antimony, have been reviewed.[6]

3. α-Halocarbonyl Compounds Used

a. mono α-Halocarbonyl Compounds

The substrate is usually an aldehyde or ketone with at least one α-halogen or other good leaving group, such as mesylate or tosylate. Usually α-haloaldehydes are more reactive than are α-haloketones. The reactivity of α-haloaldehydes increases as the number of halogen atoms on the α-carbon increases. These reactions give enol phosphates as the major product. The reactions of α-bromoacetophenones and other primary α-bromoketones with triethyl phosphite and other trialkyl phosphites give enol phosphates (1) and β-ketophosphonates (2), with the latter often as the major product.

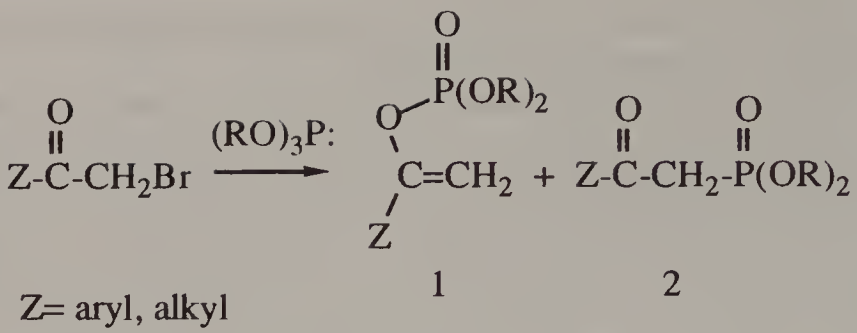


Fig. 3 - The Perkow reaction with α-bromoketones

The ratio of (2):(1) decreases for α-bromoacetophenones with electron-withdrawing groups. Thus, α-bromo-*p*-nitroacetophenone reacts with triethyl phosphite to give only 19% of (2) and 68% of (1).[7] The presence of ethanol in the reactions of triethyl phosphite with α-bromoacetophenones decreases the amount of (2)[7] and even eliminates the formation of (2) at 0°.[8] Also, in the presence of ethanol the additional product (3), the dehalogenated ketone, has been found[7,8] as well as (4), the α-hydroxyphosphonate.[8] In the presence of acetic acid the major product becomes (1) and no (2) is formed. However, starting haloketone and (3) are also obtained. The structures of (3) and (4) are shown in Fig. 4.

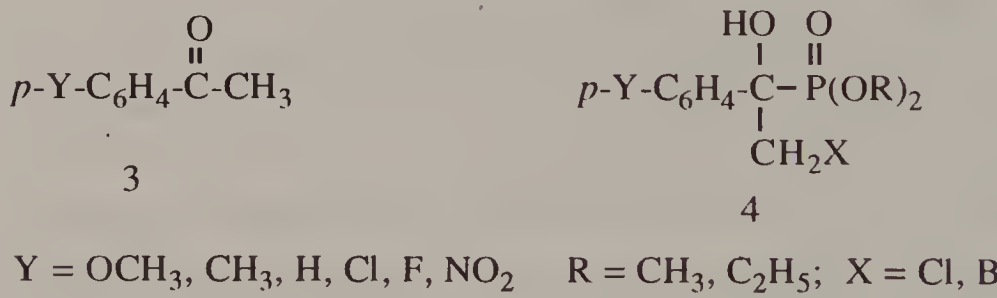


Fig. 4 - Perkow reaction by-products

The corresponding α-chloroacetophenones give mostly (1) and no (2) in the presence or absence of protic solvents[7,8] and (4)[8] is formed in the presence of protic solvents. If the aryl α-haloalkyl ketone has a hindered carbonyl, only β-ketophosphonate products

result.[9] Discussion of this point follows in Part IC.

Secondary α-bromoketones such as α-bromopropiophenone (5) react with triethyl phosphite to give enol phosphate:β-ketophosphonate products in 4:1 ratio. Desyl bromide (6),[7] 2-bromocyclohexanone (7),[6] and the α-chloroketones corresponding to (5), (6), and (7) give only enol phosphates. Tertiary α-haloketones such as α-bromo- or α-chloroisobutyrophenones (8) and (9) give only enol phosphates. These structures are shown in Fig. 5.

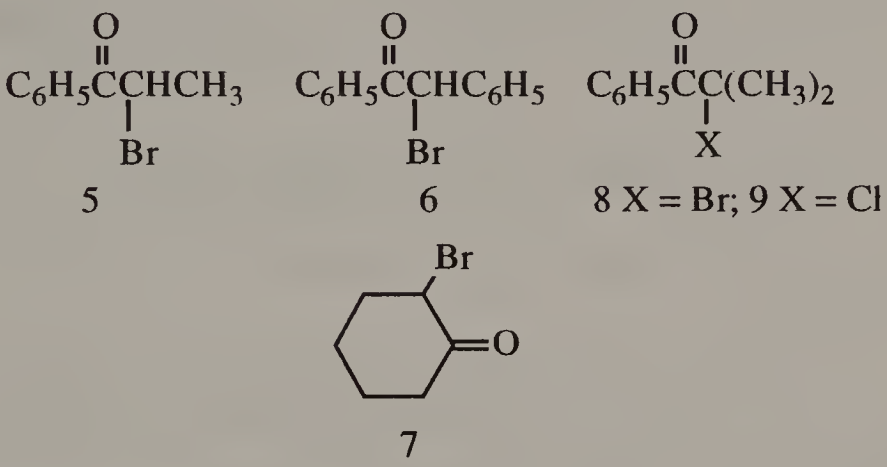


Fig. 5 - Secondary and tertiary α-haloketones

The reactions of 2-halo-1,3-dicarbonyl compounds with trialkyl phosphites give enol phosphates as shown in Fig. 6 and as previously reviewed.[6]

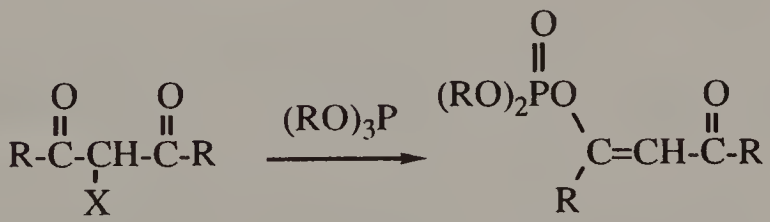


Fig. 6 - The Perkow reaction of 2-halo-1,3-dicarbonyl compounds

α-Halo acyl halides react with two moles of trialkyl

phosphites to give first a phosphonate, which is also an α-haloketone, and then to form an enol phosphate, as shown in Fig. 7.[6] Other α-halocarbonyl compounds, such as mono α-haloamides, mono α-haloesters, and α-halonitroalkanes react with trialkyl phosphites to give Michaelis-Arbuzov reaction products, possibly *via* halide displacement.[6]

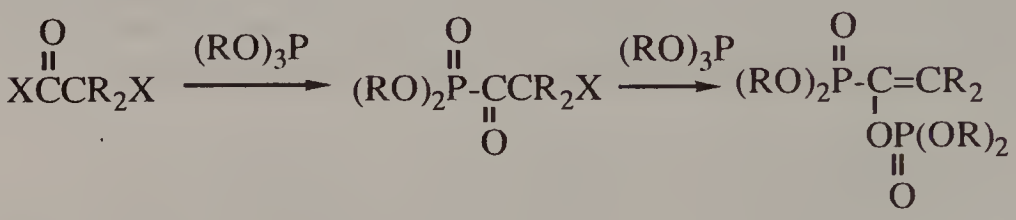


Fig. 7 - The Perkow reaction: α-haloacyl halides

b. α,α-Dihalo and α,α,α-Trihalocarbonyl Compounds

α,α-Dihaloaldehydes and α,α-dihaloketones react with trialkyl phosphites to give the corresponding enol phosphates in which one halogen has been removed.[6] Several such enol phosphates have important biological applications and will be discussed in Part IF. In the presence of protic species such as acetic acid[9] or alcohols[9,10] monodebromination of the α,α-dibromoketones to α-bromoketones occurs with trialkyl phosphites. α,α-Dichloroketones give enol phosphates under these conditions, not dechlorination, as shown in Fig. 8.

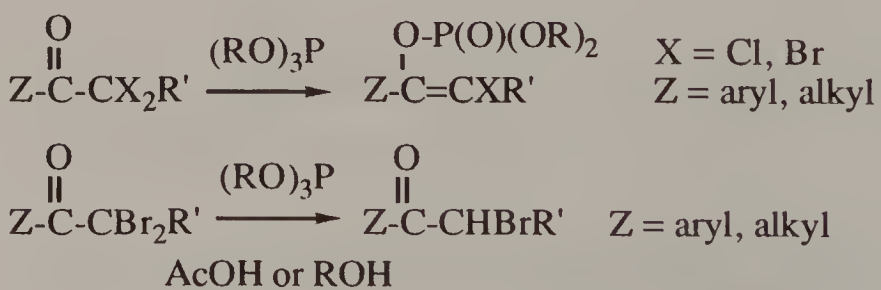


Fig. 8 - Conversions of α,α-dihaloketones to enol phosphates or to α-bromoketones

α,α-Dihaloamides and α,α-dihaloesters react with trialkyl phosphites to give the Michaelis-Arbuzov reaction products, probably *via* halide displacement.[6] α,α,α-Trihaloaldehydes, notably chloral and bromal, react vigorously with triethyl phosphite to give 2,2-dihalovinyl enol phosphates.[6] In Fig. 9 is shown the reaction of chloral with excess triethyl phosphite to give a phosphorane (10),[11] which is of mechanistic interest as discussed in Part IC. α,α,α-Trichloroacetate esters react with trialkyl phosphites to give enol phosphates.[6]

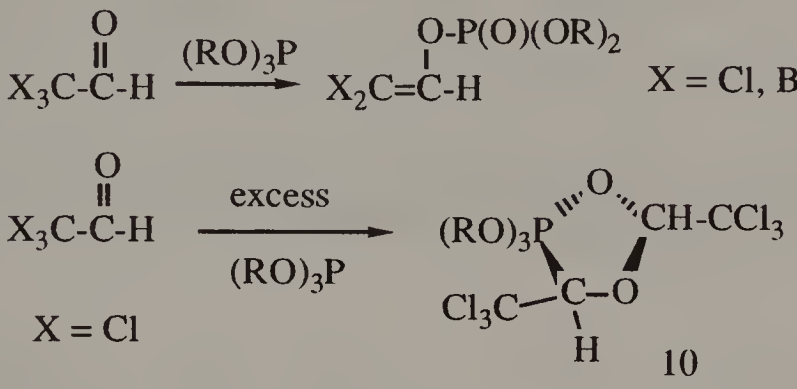


Fig. 9 - The reaction of chloral with $(RO)_3P$

C. Mechanism of the Perkow Reaction

1. With Mono α-Halocarbonyls

Many different mechanisms have been proposed for the Perkow reaction. Of these, one of the more plausible ones for mono α-halocarbonyl compounds was originally proposed by Allen and Johnson[12] and also by Kharasch and Bengelsdorf.[13] It has been modified by Borowitz,[7,14,15] Gaydou,[16] and others.[17-20] It involves an initial addition of the trialkyl phosphite to carbonyl carbon to give an intermediate. This addition is followed by a rearrangement of the phosphorus moiety to oxygen to give enol phosphonium halides which are then converted to enol phosphates (11) and (12). The conversion proceeds *via* a Michaelis-Arbuzov cleavage of an alkoxy group by halide ion as shown in Figs. 10 and 11.

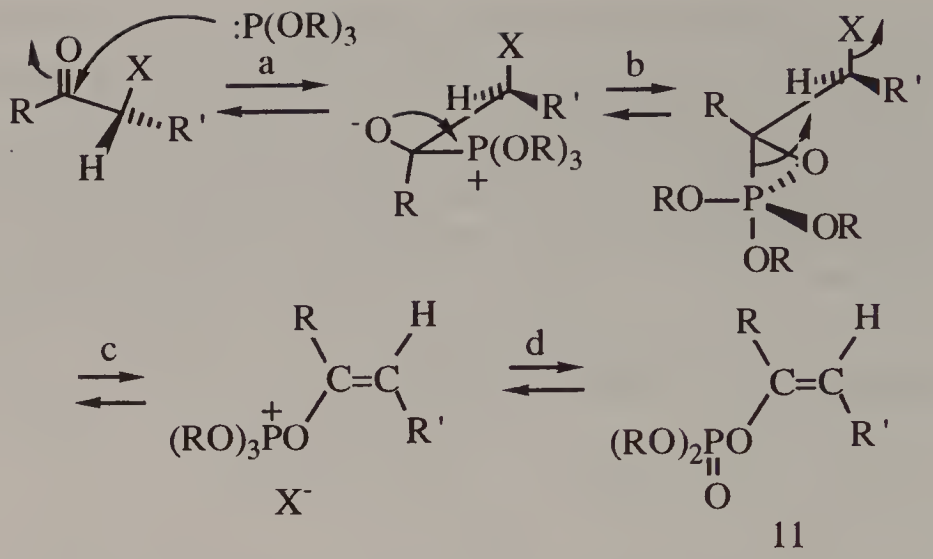


Fig. 10 - Mechanism of the Perkow reaction - formation of the major product, the (*Z*)-enol phosphate - Steps b and c may be concerted.

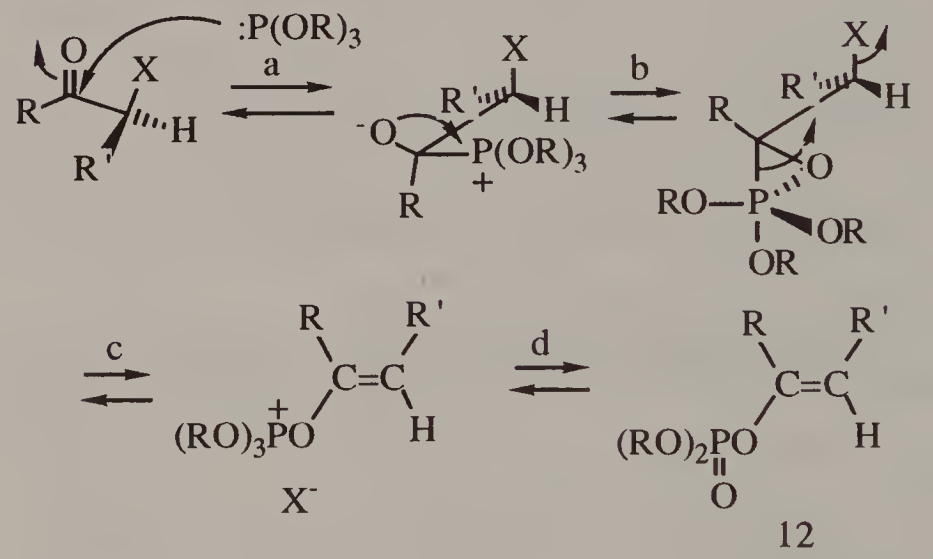


Fig. 11 - Mechanism of the Perkow reaction - formation of the minor product, the (*E*)-enol phosphate - Steps b and c may be concerted.

This last step has been shown to be rapid and not rate determining in the reaction of triethyl phosphite with ethyl iodide.[21] It can be reasonably assumed not to be the rate determining step in the Perkow reaction as shown by the following

analysis of the kinetic data.

Rate determining *reversible* addition of the phosphite to carbonyl and an *anti*-elimination step was proposed by Borowitz[14,15] in order to explain several facts about the Perkow reaction. These include the predominant formation of the thermodynamically more stable isomeric enol phosphate, *i.e.* the (*E*)-isomer, from α-haloaldehydes, as shown in Fig. 2, and the (*Z*)-isomer (11) from α-haloketones, as shown in Fig. 10.

Other facts include k_2Cl/k_2Br ratios which are ≥ 1 for α-isobutyrophenones and α-halocyclohexanones.[15] These ratios indicate that halide ion loss is not the rate determining step, at least for these Perkow reactions. The data in Table 1[14] support a carbonyl addition mechanism when it is compared to other reactions involving carbonyl addition. Thus, the Wittig reaction of carbomethoxymethylenetriphenylphosphorane with substituted benzaldehydes has E_a = 10.7 kcal/mol, $\Delta S^{\neq}$ = -41.6 eu, ρ = 2.7 (in benzene).[22] Similarly, the reaction of semicarbazide with substituted benzaldehydes has ρ = 1.81[23a] and the saponification of benzoate esters has ρ = 1.9-2.4.[23b]

Table 1. Activation parameters/ρ values for α-haloisobutyrophenone/triethyl phosphite reactions

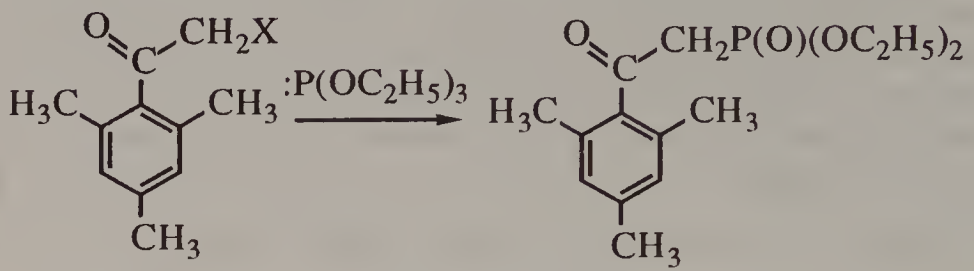
Halogen	E_a*	$\Delta S^{\neq}$ ¶	$\Delta H^{\neq}$*	$\Delta G^{\neq}$*	ρ
Br	13.3	-41	12.7	25.8	1.89
Cl	12.8	-42	12.2	25.6	2.37

All measured in benzene solution

* kcal/mol ¶ eu

Finally, we cite the pair of α-bromo- and α-chloro-2,4,6-trimethylacetophenones, (13) and (14), which both slowly react with triethyl phosphite to give only ketophosphonate (15),[14,24] as shown in Fig. 12. The k_2 bromo/chloro ratio is very large as befits an S_N2-type displacement of halide ion, as in the Arbuzov reaction. The steric hindrance of the carbonyl groups in (13) and (14)

presumably precludes enol phosphate formation.

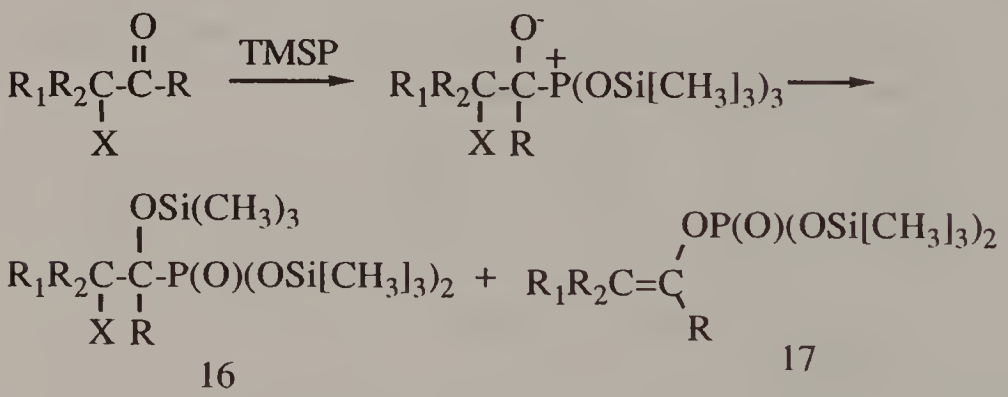


13 X = Br
14 X = Cl

15

Fig. 12 - Mechanism of the Perkow reaction - steric hindrance preventing carbonyl addition

There have been several mechanistic studies of the Perkow reaction in the last 15 years. Much of the evidence supports the carbonyl addition mechanism. In addition to enol phosphate, Hata[19] has isolated several carbonyl adducts from the reactions of tris(trimethylsilyl) phosphite (TMSP) with several α-haloaldehydes and α-haloketones, as shown in Fig. 13. No ketophosphonate products were observed.



16 17

Fig. 13 - TMSP addition in the Perkow reaction

Toke, *et al.* have published a series of papers including kinetic analyses[25,26] and the effect of reaction conditions on product distribution[8,7,29] for the reactions of α-haloacetophenones with trialkyl phosphites. Their data confirm the carbonyl addition mechanism for the Perkow reaction. In addition, they

propose that the carbonyl adduct (18) is a common intermediate for both the dehalogenated ketone and the α-hydroxyphosphonate by-products that occur under alcoholic solvent conditions. Most recently they have proposed[29] that even β-ketophosphonates, resulting from the Michaelis-Arbuzov reactions, arise from this common adduct, as shown in Fig. 14. In view of the reactions of (13) and (14) above, this is a somewhat controversial proposal. We believe that if the Michaelis-Arbuzov formation of β-ketophosphonates occurred *via* carbonyl addition, then these hindered haloketones should not have reacted at all. Also, it would be difficult to explain why the bromoketone (13) reacts faster than the chloroketone (14) does. Gaydou's finding of $\rho = -0.22$ for β-ketophosphonate formation from aryl substituted α-bromoacetophenones is also evidence for S_N2 displacement of bromide ion, not carbonyl addition.[30]

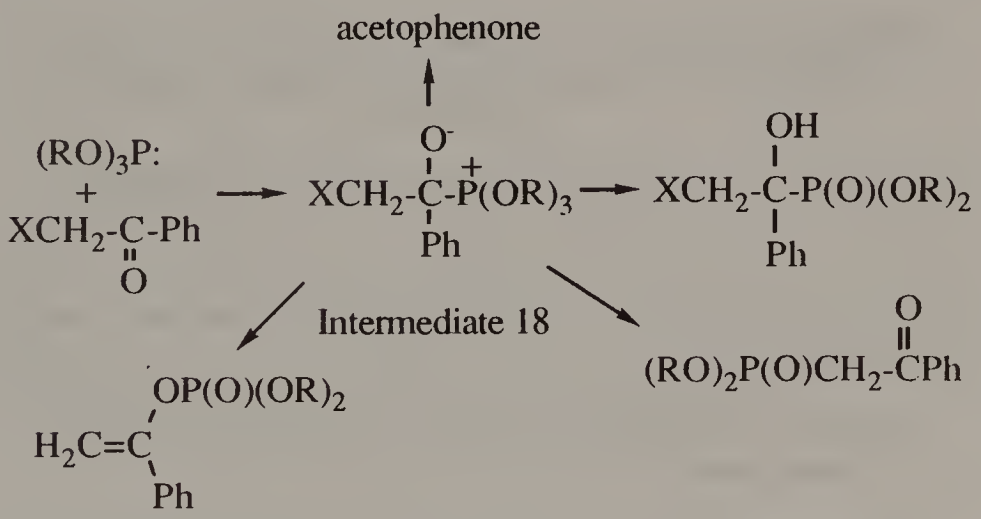


Fig. 14 - Toke's mechanism

2. With α,α-Di- and α,α,α-Trihalocarbonyls

The mechanisms of the reactions of α,α-dihaloketones and α,α,α-trihaloketones with triethyl phosphite to give halogen-substituted enol phosphates have also continued to be investigated in recent years. Our earlier work[9] which demonstrated that triethyl

phosphite monodebrominated α,α-dibromoketones in the presence of either one equivalent of acetic acid or of excess ethanol suggested, at least under these specified conditions, that these reactions proceed *via* nucleophilic attack on bromine. Attack on bromine would also explain why α,α-dibromoacetophenone (19) reacts at least 200 times faster with triethyl phosphite than does α,α-dichloroacetophenone (20), as shown in Figs. 15 and 16. This ratio is in contrast to other sets of α-bromo- and α-chloroketones which react with triethyl phosphite at comparable rates.

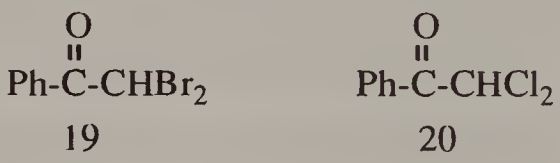


Fig. 15 - α,α-Dihaloketones

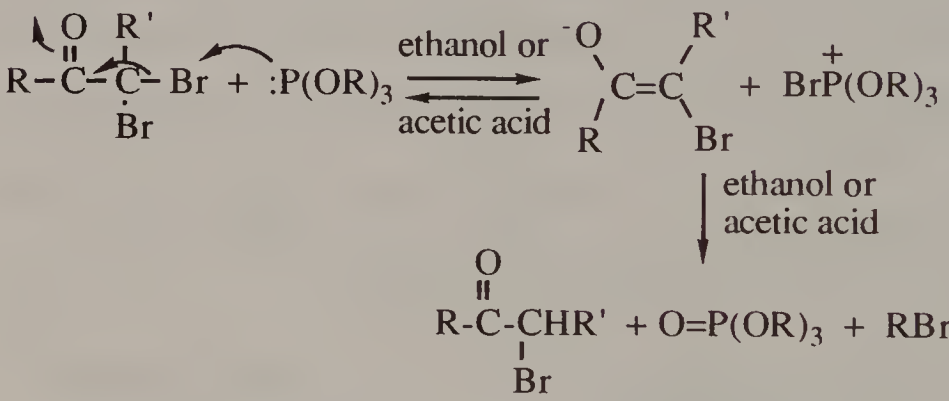


Fig. 16 - α-Haloketone reactions with trialkyl phosphites in the presence of acetic acid or ethanol

In contrast, α,α-dichloroketones react with trialkyl phosphite under these conditions to give the chloro-substituted enol phosphates, as shown in Fig.17.[9]

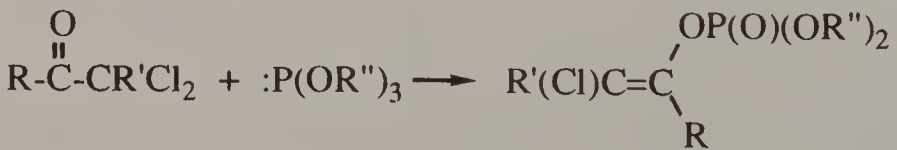


Fig. 17 - α,α-Dihaloketone reaction with $(R"O)_3P$

Zwierzak has found that α,α-dibromo-2,4-dichloroacetophenone (21) reacts with triethyl phosphite *via* bromophilic attack to give the postulated bromophosphonium enolate ion pair (22) which then goes on to yield the expected enol phosphate (23) as well as the ethoxy bromostyrene (24) as shown in Fig. 18.[31] Diethyl phosphite also reacts by a similar mechanism.[32]

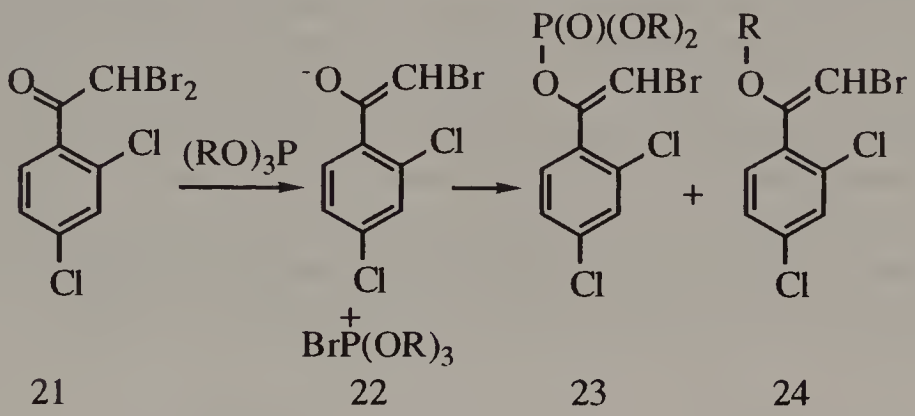
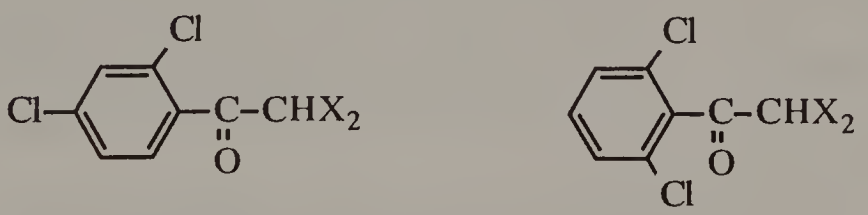


Fig. 18 - Reaction of α,α-dibromo-2,4-dichloroacetophenone with $(RO)_3P$

Zwierzak also found that α,α-dichloro-2,4-dichloroacetophenone (25) reacts with triethyl phosphite to give the enol phosphate much faster than does α,α-dichloro-2,6-dichloroacetophenone (26), shown in Fig. 19, which is sterically hindered at the carbonyl carbon. Therefore, he concluded that these haloketones react by the usual carbonyl addition mechanism.[10]

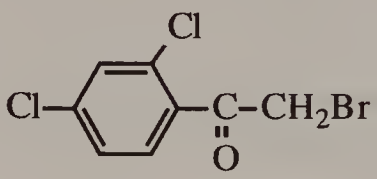


21 X = Br
26 X = Cl

25 X = Br
27 X = Cl

Fig. 19 - α,α-Dihaloacetophenones substituted on the ring

The corresponding α,α-dibromoketones (21) and (25) react with triethyl phosphite at comparable rates. In methanol, monodehalogenation to the α-bromoketone occurs from (21), (23), and 2,6-dichloro-α-bromoacetophenone (29), as shown in Fig. 20. The latter compound has a hindered carbonyl group which slows down carbonyl addition. α-Bromo-2,4-dichloroacetophenone (28), which does not have a hindered carbonyl, yields the enol phosphate. In summary, Zwierzak's work shows that the aprotic reactions of triethyl phosphite with α,α-dibromoketones yield the enol phosphates while the corresponding protic solvent reactions of α,α-dibromoketones and the aprotic reactions of hindered α-bromoketones with triethyl phosphite result in monodehalogenation to give respectively α-bromoketones or methyl ketones.



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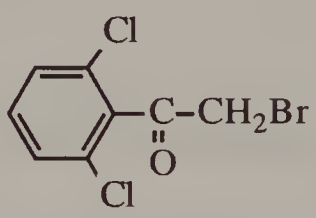


29

Fig. 20 - α-Bromo-2,4- and 2,6-dichloroacetophenones

Zwierzak concluded that these reactions could be rationalized by a mechanism showing nucleophilic attack on bromine by the phosphite, as shown in Fig. 21.[10] His data extend the previous work of Borowitz, *et al.*[9] and establishes nucleophilic attack on halogen as a second possible mechanism for enol phosphate formation, at least for α,α-dibromoketones and certain other hindered α-haloketones.

In the presence of protic solvents, usually alcohols or acetic acid, some dehalogenation and α-hydroxyphosphonate formation occurs in the reactions of trialkyl phosphites with α-haloketones, as noted above and shown in Fig. 22. The formation of α-hydroxyphosphonates, (4) or (30), most likely occurs by carbonyl addition

and is promoted by acid, as shown in Fig. 23. The dehalogenation reactions may occur by nucleophilic attack on halogen, as has been proven for the reactions of α-bromoketones with triphenylphosphine.[33]

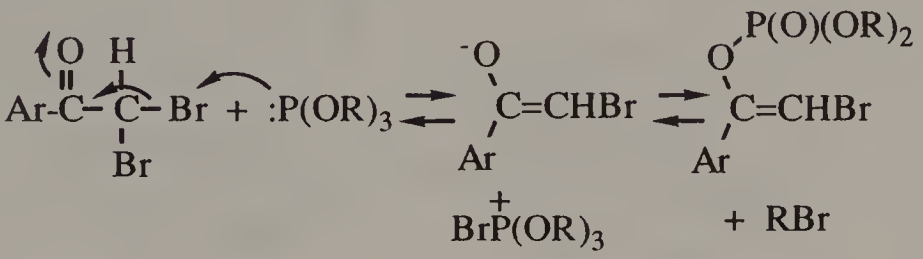


Fig. 21 - Enol phosphate formation from α,α-dibromoketones

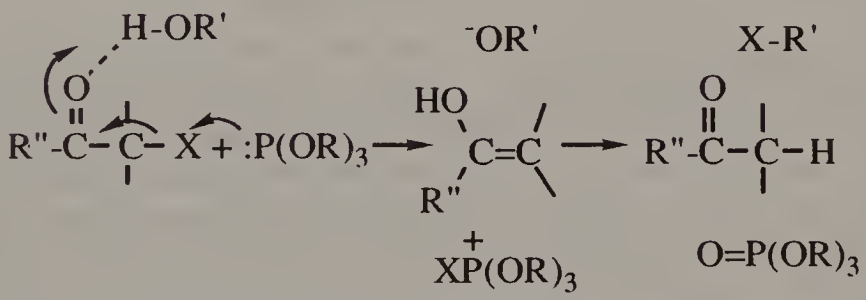


Fig. 22 - Dehalogenation of α-haloketones

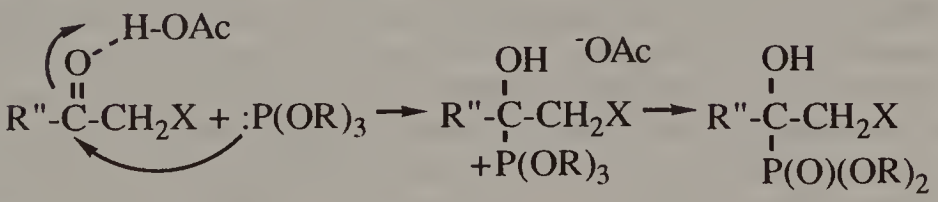


Fig. 23 - Mechanism of α-hydroxyphosphonate formation

The reaction of triethyl phosphite with excess chloral to give the phosphorane (10), a 2:1 adduct, supports the intermediacy of a "betaine" (31) which then reacts with a second molecule of chloral to yield (10), as shown in Fig. 24.

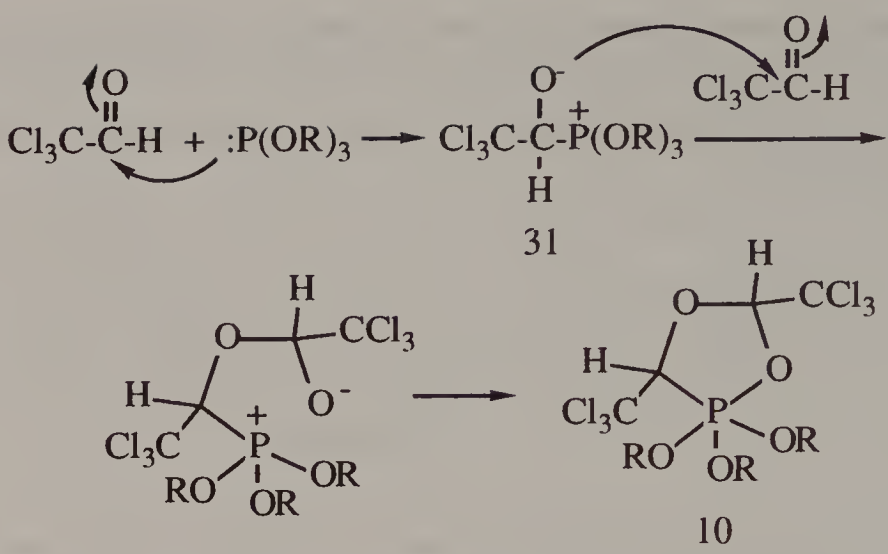


Fig. 24 - The reaction of chloral with a trialkyl phosphite

D. Physical Properties of Enol Phosphates

1. Geometric Isomerism

The Perkow reaction leads to a pair of isomeric enol phosphates in which there is often a predominant stereoisomer. In other cases only one of the two possible stereoisomers is formed. Thus, the Perkow reaction is stereospecific or at least stereoselective. Until the early 1970's there was no totally reliable method for determining the relative stereochemistry of trisubstituted or tetrasubstituted enol phosphates. Single crystal X-ray analysis was precluded since nearly all of the relevant cases were liquids. The use of proton NMR shifts by Royce, Webb, *et al.*[34] as well as the corrected NMR assignments by Borowitz, *et al.*[15] and similar observations by Gaydou[35] led to an important correlation. This research established that the NMR signal for the vinyl proton *cis* to the phosphoryl group always occurs at a lower field than that of the corresponding *trans* proton for either disubstituted or trisubstituted 1-phenyl enol phosphates, such as the *E,Z* isomer pairs (32) and (33) or (34) and (35), as shown in Fig. 25.

As a result of these and other NMR correlations, which are discussed below, Borowitz, *et al.* concluded that *E*-enol phosphates predominate in the Perkow reactions of α-haloaldehydes[15] and of α-chloroalkyl methyl ketones.[15] *Z*-Enol phosphates predominate in the Perkow reactions of α-bromoalkyl methyl ketones[15,35] and of

α-haloalkyl phenyl ketones.[15]

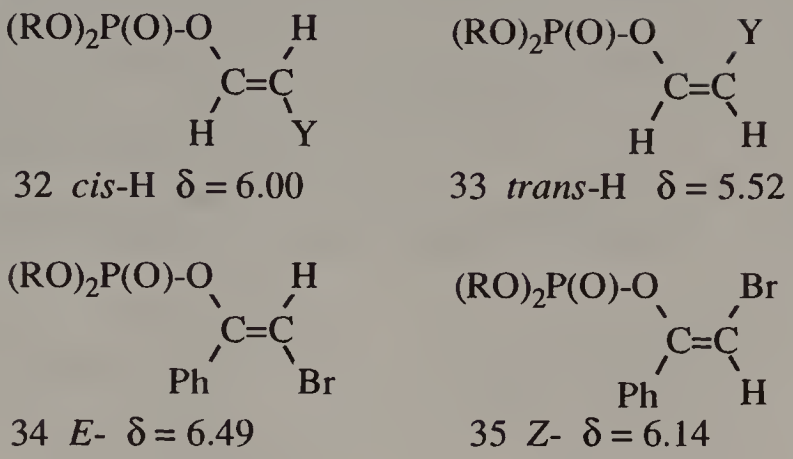


Fig. 25 - Assignment of enol phosphate stereochemistry by proton NMR shifts

All of these correlations were done on liquids. It was desirable to have confirmation of these observations by single crystal X-ray analysis on a suitable solid enol phosphate. Before any such structure was done, Borowitz, *et al.* prepared the crystalline diphenylphosphinate (36) from the reaction of α,α-dibromoacetophenone with ethyl diphenylphosphinite. It forms as the sole stereoisomer. It was correlated with the major enol phosphate stereoisomer (37) formed from α,α-dichloroacetophenone as well as with the bromo compound (35) formed from α,α-dibromoacetophenone. The phosphinate was shown to be the Z-isomer by an unpublished single crystal X-ray analysis done by Van der Veen.[36]

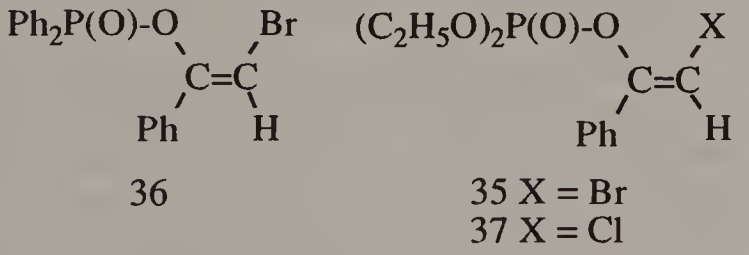
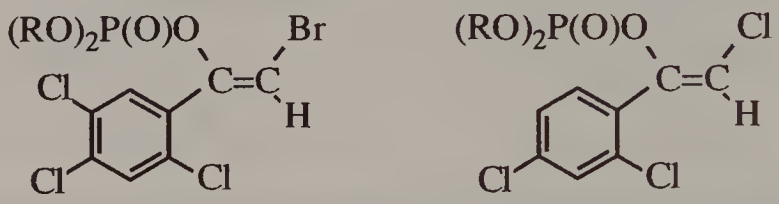


Fig. 26 - Correlation of stereochemistry of related structures

Zwierzak, *et al.* have shown that the enol phosphates bromfenvinphos (38) and methylbromfenvinphos (39), which are highly

effective insecticides, are formed in ratios of 95:5 for (38) and 100:0 for (39) from the reactions of triethyl phosphite or trimethyl phosphite with α,α-dibromo-2,4-dichloroacetophenone (21). Bromfenvinphos (38) and methylbromfenvinphos (39) have been shown to have the *Z*-configuration[37] by single crystal X-ray analysis on (39). The related chlorovinyl enol phosphate, stirofos or Gardona® (40), has also been shown to have the *Z*-configuration by X-ray analysis by Rohrbaugh and Jacobson.[38]



38 R = C_2H_5
39 R = CH_3

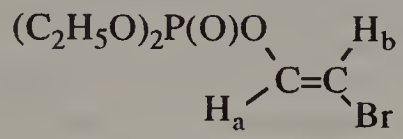
40 R = CH_3

Fig. 27 - Significant enol phosphate insecticides

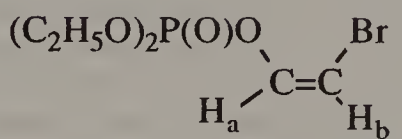
2. IR and NMR Spectral Data

Infrared spectral data on enol phosphates have been reviewed previously.[6] The distinguishing feature is the C=C double bond stretch which occurs between 1660-1640 cm^{-1} depending upon substituents. The carbonyl group in β-ketophosphonates, which also form from α-haloacetophenones, absorbs at *ca.* 1680 cm^{-1}. Proton NMR spectroscopy has been used to determine *E,Z* stereochemistry in enol phosphates and can be used to follow the course of Perkow reactions. In a number of *E,Z* di- or trisubstituted enol phosphate pairs, the isomer with a β-proton (H_b) *cis* to the phosphate group is deshielded relative to the *trans* proton isomer.[34] For the disubstituted cases, stereochemical assignments can be made more easily by using J_{HH} *trans* > J_{HH} *cis*. In disubstitued enol phosphates, such as (41) and (42), J_{PH} *trans* is > J_{PH} *cis*. However, the reverse is true for α-phenyl trisubstituted cases, such as (43) and (44), so that this proton NMR parameter is less reliable than the J_{HH} and β-proton absorption parameters which are discussed and illustrated below in Fig. 28. These methods for

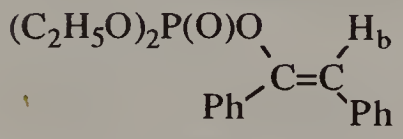
assigning *E,Z* stereochemistry are useful when both stereoisomers are present. If there is only one stereoisomer, then other methods may be more helpful for assigning *E,Z* stereochemistry. Boyce, *et al.*[34] used a modified model approach related to that of Tobey[39] to calculate the β-hydrogen NMR absorption for *E* and *Z* stereoisomeric enol phosphates.



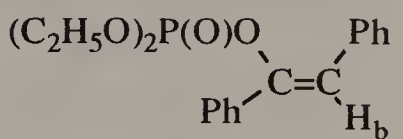
41 *E*- $\delta H_b = 6.00$
$J_{ab} = 11.4$ Hz
$J_{PHb} = 1.4$ Hz



42 *Z*- $\delta H_b = 5.52$
$J_{ab} = 4.1$ Hz
$J_{PHb} = 2.2$ Hz



43 *E*- $\delta H_b = 6.69$
calc. $\delta H_b = 6.66$
$J_{PHb} = 2.5$ Hz



44 *Z*- $\delta H_b = 6.33$
calc. $\delta H_b = 6.20$
$J_{PHb} = 1.0$ Hz

Fig. 28 - Enol phosphate stereochemistry *via* proton NMR correlations

Lanthanide induced shifts have also been used to establish the *E,Z* stereochemistry of enol phosphates and related enol phosphinates and phosphonates.[15] The uses of tris(dipivalomethanato)europium (III) [$Eu(DPM)_3$] in causing downfield proton NMR shifts in phosphates is well established.[40-43] It is generally agreed that the interaction involves coordination of the europium with the P-O bond.[39,42]. Application to *E* and *Z* stereoisomeric enol phosphates (45) and (46) is illustrated in Fig. 29. The following order of decreasing proton sensitivity, indicated as shift in Hz/mol of $Eu(DPM)_3$, is found: *gem*-vinyl-H > *cis-vic*-H > *trans-vic*-H. The sensitivity values do not differ greatly for the various groups on phosphorus for a given ethene.

The values for *cis-vic*-H range from 300-736 Hz/mol, with a

mean value of 503 Hz/mol. The corresponding values for *trans-vic*-H range from 75-280 Hz/mol, with a mean of 193 Hz/mol. These values have been correlated for a series of 18 enol phosphorylated compounds.[15] Although the exact position of the europium relative to the P-O group is unknown, making the angular term in the usual shift equations[40] difficult to evaluate, it seems reasonable to conclude that larger shifts are associated with the *vic*-vinyl protons that are *cis* to phosphate. The method can be extended to tetrasubstituted enol phosphates bearing methyl groups. In these cases methyls *cis* to phosphate have shifts of 292-322 Hz/mol. Therefore, they are more sensitive to complexing with $Eu(DPM)_3$ than those compounds in which the methyls are *trans* to the phosphate, where the shifts range from 108-112 Hz/mol.[15]

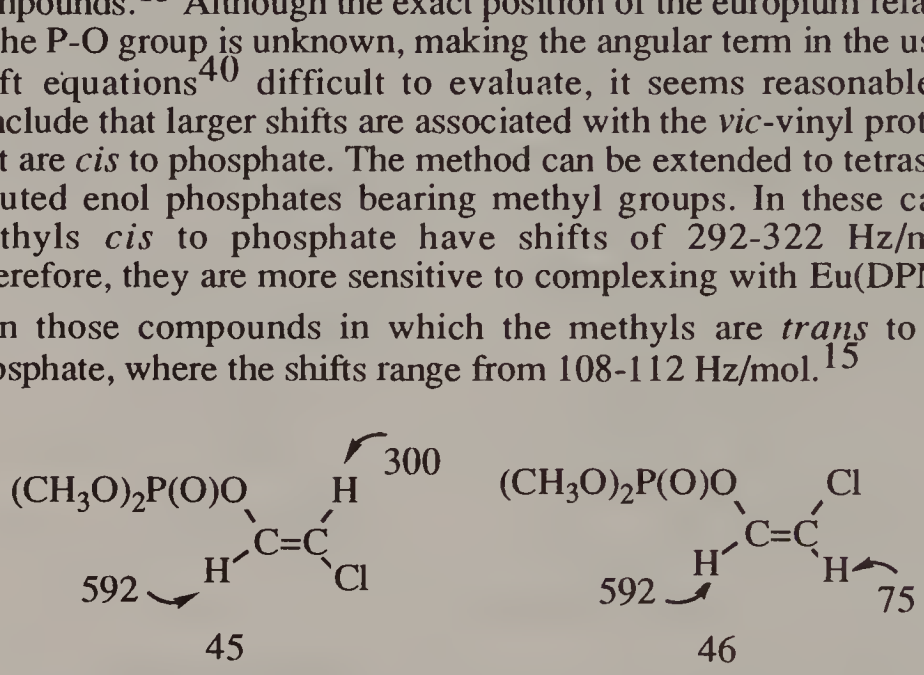


Fig. 29 - Enol phosphate stereochemistry using $Eu(DPM)_3$

E. Reactions of Enol Phosphates

1. Previously Reviewed Reactions

The halogenation, hydrogenation, monodealkylation, alcoholysis, hydrolysis to aldehydes or ketones, Diels-Alder dienophile reactions, polymerization, and ozonolysis of enol phosphates have been reviewed in great detail previously by Lichtenthaler.[6] This review will concentrate on newer uses and on those reactions of enol phosphates not reviewed in recent years.

2. Rearrangement to β-Ketophosphonates

Dialkyl enol phosphate derivatives of cyclic ketones such as (47) rearrange to β-ketophosphonates such as (48) upon treatment with lithium di-isopropylamide (LDA).[44] This reaction probably proceeds *via* cleavage of (47) with LDA to give an enolate phosphonium ion pair which then interacts to give the anion of (48) under equilibrium conditions. The reactions are quenched with

acetic acid. Cleavage of enol phosphates with strong bases such as phenyllithium or butyllithium to give lithium enolates which can then be C-alkylated has been previously reported.[45] The enol phosphates are made by Perkow reactions from the corresponding α-halocycloalkanones.

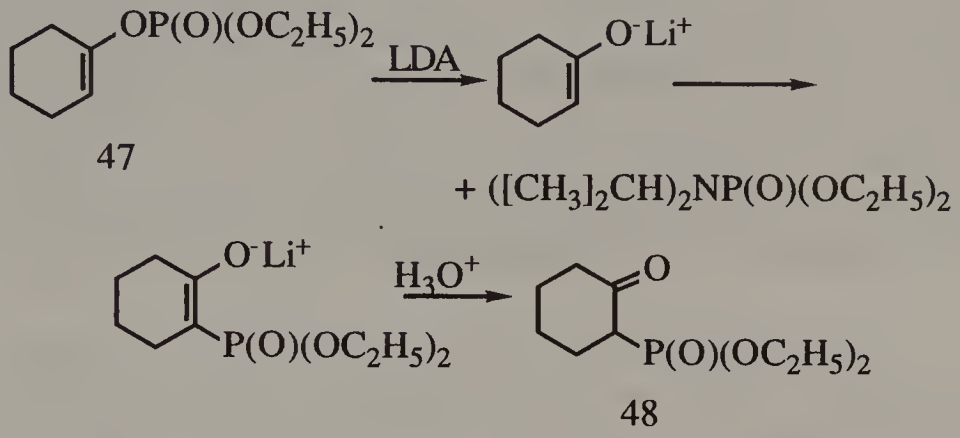


Fig. 30 - LDA mediated rearrangement of a cyclic enol phosphate to a ketophosphonate

Dialkyl enol phosphates (50) of lactones such as (49) give similar rearrangements to β-ketophosphonates (51) upon treatment with LDA at -100°.[46] The enol phosphates of lactones were made by: 1) treatment of lactones with LDA to give the lithium enolate and 2) *O*-phosphorylation of the enolate with a dialkyl chlorophosphoridate in THF-HMPA under kinetic conditions, or 3) a one step conversion of (49) to (51) without isolation of the intermediate enol phosphate.

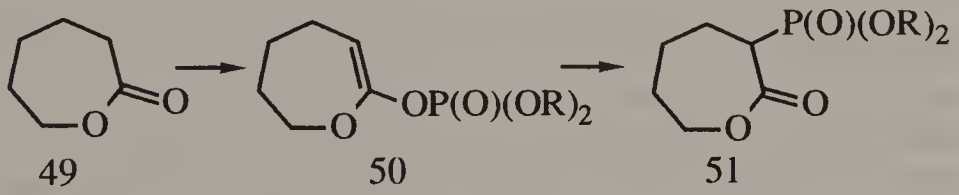
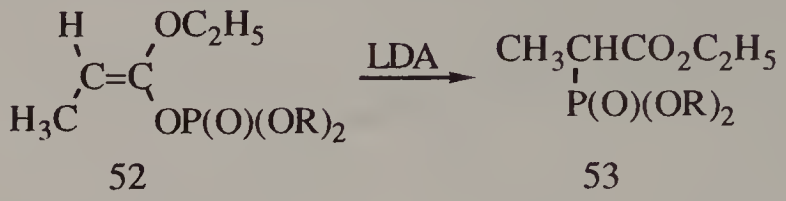


Fig. 31 - LDA mediated rearrangement of a lactone enol phosphate to an α-phosphonolactone

Similarly, several enol phosphates of acyclic esters (52) were rearranged to β-phosphonato esters (53) as shown in Fig. 32.

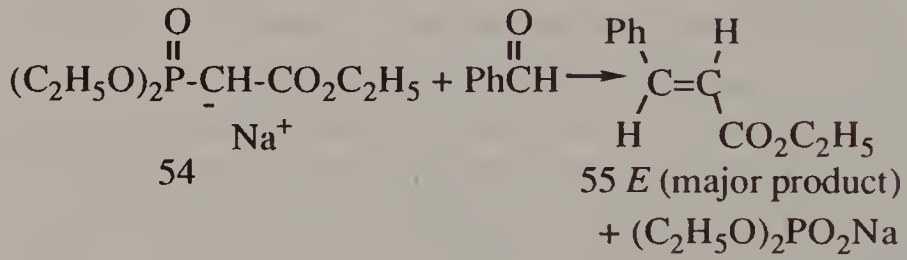
Isopropyl groups were necessary for good yields in these rearrangements.[46] This method may become an alternative to the Michaelis-Arbuzov reaction for the synthesis of at least some β-ketophosphonates.



52 53

Fig. 32 - LDA mediated rearrangement of an ester enol phosphate to an α-phosphonoester

β-Ketophosphonates are useful in a number of syntheses including the Wadsworth-Emmons reactions of their carbanions with aldehydes/ketones, or epoxides[47] to give alkenes (as shown in Fig. 33) or cyclopropanes. These reactions have been extensively reviewed.[47-49]



54

55 *E* (major product)
+ $(C_2H_5O)_2PO_2Na$

Fig. 33 - Wadsworth-Emmons reaction

The organophosphorus texts by Hudson,[50] Kirby and Warren,[51] and Walker[52] include some references to the literature on the Perkow and Michaelis-Arbuzov reactions up to 1972. The more recent Corbridge text[53] is a good general review of phosphorus chemistry. A comprehensive review on the Michaelis-Arbuzov reaction appeared in 1981 by Bhattacharya and Thygarajanan.[54]

3. Cleavage to Enolates

Enol phosphates such as (56) (Y = Z = OR), enol phosphinates (57) (Y = Z = Ph), and enol phosphonates (58) (Y = Ph, Z =

OR) react with methyllithium or butyllithium to give a lithium enolate which is then monoalkylated to (59) in 62-78% yield with various primary and secondary alkyl halides.[45] Some starting ketone is formed and some polyalkylation occurs, the latter especially with methyl iodide. Little or no dialkylation occurs with alkyl halides larger than ethyl. Butyllithium is the more efficient base. Enol phosphates give more starting ketone than do enol phosphinates, perhaps because of a side reaction involving displacement of the -OR group from phosphate by the alkyllithium. Phenyllithium or phenylmagnesium bromide give poorer alkylation yields as well as the undesired byproduct biphenyl. The method of forming enolates shown in Fig. 34 competes with the cleavage of enol trimethylsilyl ethers and the direct formation of enolates from ketones with LDA.[55,56]

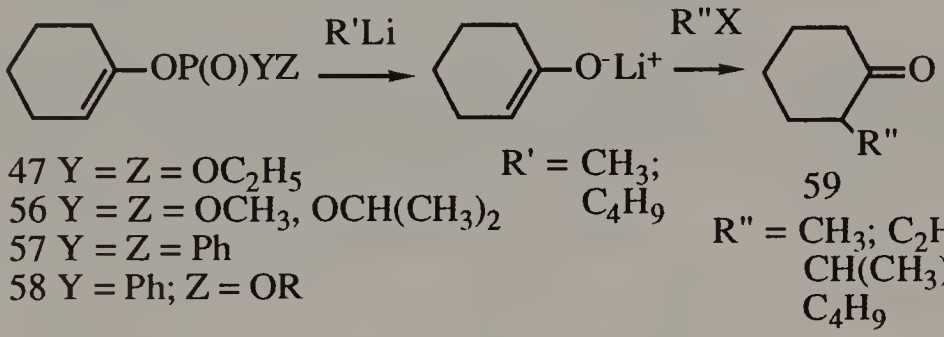


Fig. 34 - Cleavage and alkylation of enol phosphorylated species

4. Reductive Removal of Phosphate to Alkenes

Ireland reported that enones such as (60) could be converted to the less substitued alkene (62) *via* the intermediacy of the enol phosphate (61).[57] The sequence shown in Fig. 35 involves reduction of (60) with Li/NH_3(liq.) followed by phosphorylation of the resulting lithium enolate with diethyl phosphorochloridate to give (61), which is then treated with $Li/C_2H_5NH_2$/*t*-butyl alcohol. The reaction sequence can be done without isolation of (61). Applications to steroid conversions have been reported by Ireland[57] and by Kamata, *et al.*[58] A similar reduction of enol phosphates was also reported by Fetizon.[59]

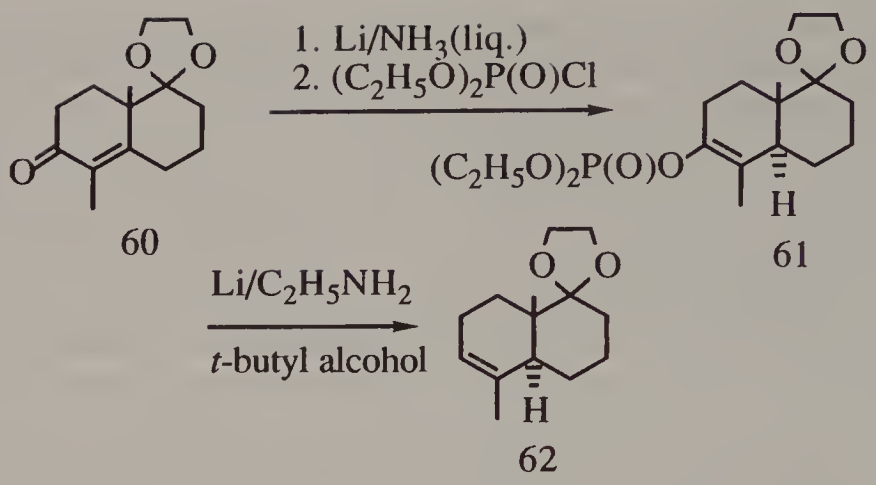


Fig. 35 - Conversion of ketones to alkenes *via* reduction of enol phosphates

Corey and Wright have utilized this reductive conversion of a diethyl phosphate group to an alkene in a synthesis of colneleic acid (65) *via* the enol ester (63) and its enol phosphate (64).[60]

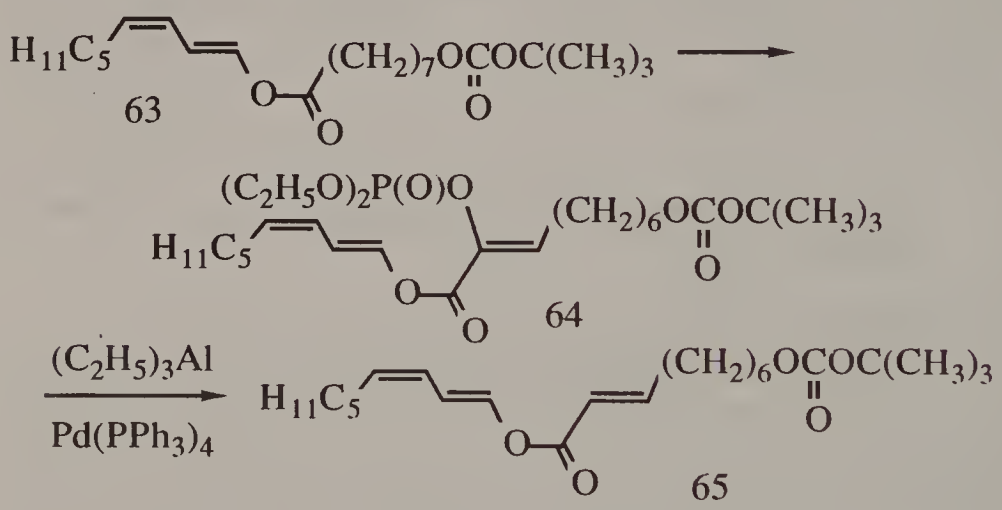


Fig. 36 - Corey's synthesis of colnelic acid

5. Organocuprate Induced Substitutions

The phosphate group in diphenyl enol phosphates can be replaced by an alkyl group through reaction with lithium di(*n*-butyl)cuprate (3 equivalents) in THF.[61] The less reactive lithium dimethylcuprate failed to react. Since the enol phosphates are made from ketones *via* the phosphorylation of enolates, as described in

Part IIC, or from α-haloketones *via* the Perkow reaction, these reactions represent a conversion of a ketone to an alkyl-substituted alkene. This is an important process in organic synthesis. In this manner the alkene (66) was prepared, as shown in Fig. 37.

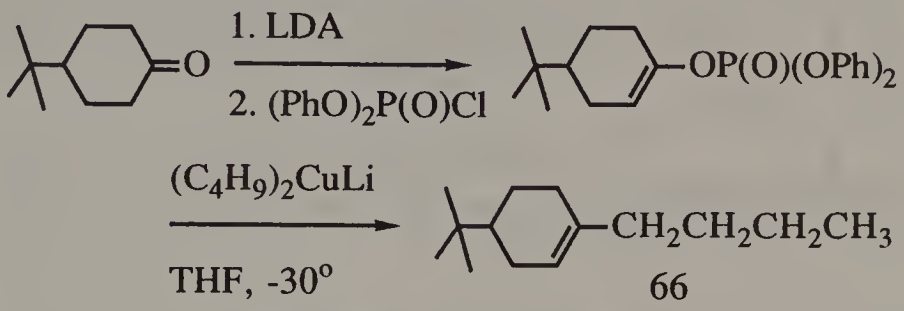


Fig. 37 - Synthesis of alkenes from ketones *via* coupling of R_2CuLi with enol diphenyl phosphate esters

More recently, Ishihara, *et al.* converted 2,2-difluoro diphenyl enol phosphates (67) into allyl and methyl or phenyl substituted allyl *gem*-difluoroalkanes (68) with lithium di-*n*-butylcuprate, as shown in Fig. 38.[62]

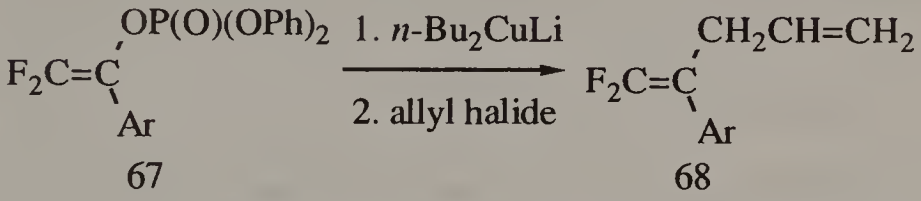


Fig. 38 - Conversion of enol phosphates into substituted allyl *gem*-difluoroalkenes

Claesson, *et al.* converted the dienyl phosphate (69) to the butylated diene (70) in good yield with either *n*-Bu_2CuLi or *n*-BuMgBr/Cu(I) salt.[63] Diethyl 2-butadienyl phosphate (71) reacts under similar conditions to give mixtures of isomeric alkylated allenes and 1,3-dienes, as shown in Fig. 39.

Takai, *et al.* reacted the enol phosphates (*Z*) and (*E*)-1-phenyl-1-propenyl diethyl phosphate (72) and (74) with trialkyl-aluminum and Pd(0) catalysts to give alkylated alkenes (73) and (75) stereospecifically and in high yields[64] as illustrated in Fig. 40. This synthesis can be combined with the formation of enol phosphates, *e.g.* (76), made from enolates, which are in turn

prepared *via* the 1,4-addition of *n*-Bu_2CuLi to enones, to finally yield alkenes such as (77),[64] shown in Fig. 41.

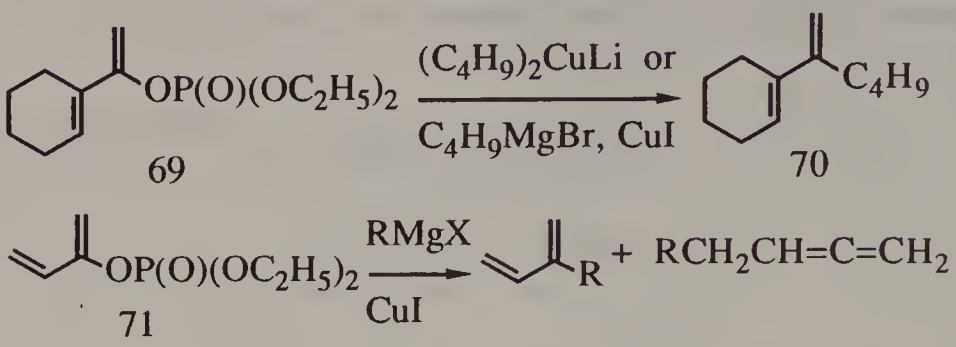


Fig. 39 - Conversion of dienyl phosphates to alkylated dienes and allenes

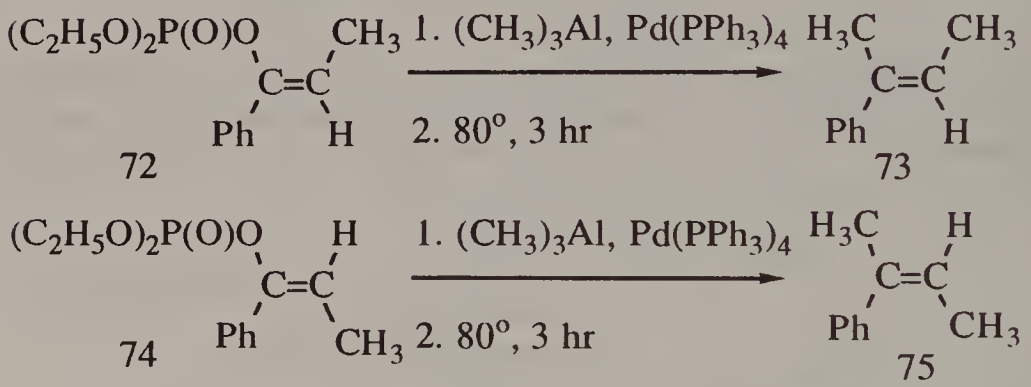


Fig. 40 - Conversion of enol phosphates to alkylated alkenes

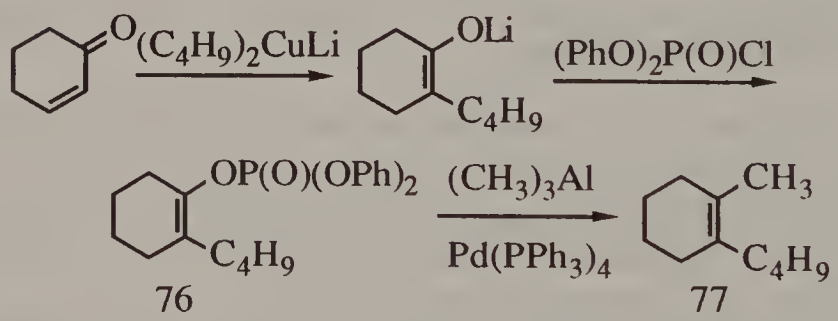


Fig. 41 - Conversion of enones to alkylated alkenes *via* enol phosphates

6. Other Reactions

Rosen, *et al.* found that diene (78) is a diene of unusual

stability. In Fig. 42 is shown how they prepared (78) by reacting 3,4-dichlorobutan-2-one with triethyl phosphite[65] as well as their more convenient preparation involving the reaction of the lithium enolate of methyl vinyl ketone with diethyl phosphorochloridate.[66]

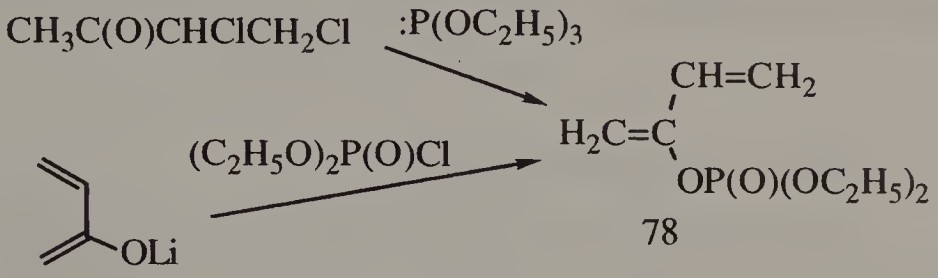


Fig. 42 - Preparations of diethyl 1,3-butadien-2-yl phosphate

The reaction of triethyl phosphite with 3,4-dichlorobutan-2-one to give (78) contrasts with the reaction of 3,4-dibromobutan-2-one with triethyl phosphite which gives methyl vinyl ketone as shown in Fig. 43. The latter reaction occurs by attack on bromine leading to *vic*-debromination.[67]

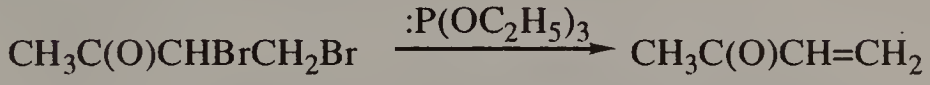


Fig. 43 - Reaction of $(RO)_3P$ with 3,4-dibromobutan-2-one to give methyl vinyl ketone

Diene (78) gives Diels-Alder reactions with maleic anhydride, with nitrosobenzene, and with methyl vinyl ketone. The last reaction gives a 2:1 mixture of the 1,3- and 1,5-cyclohexenyl adducts (79a) and (79b), shown in Fig. 44, which could not be separated.[65]

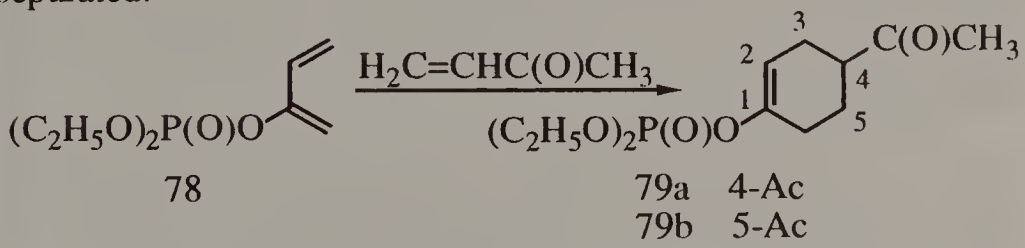


Fig. 44 - Diels-Alder reaction of diethyl 1,3-butadien-2-yl phosphate with methyl vinyl ketone

The reaction of 1,4-dibromo-2,3-butanedione (80) with two moles of triethyl phosphite gives the 2,3-diphosphate of 1,3-butadiene (81) *via* a double Perkow reaction, as shown in Fig. 45.[68]

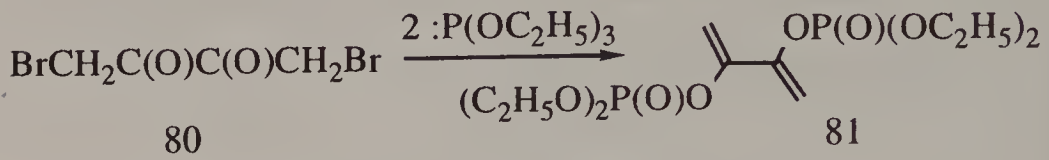


Fig. 45 - A double Perkow reaction

3-Chloro-2-[(diethoxyphosphoryl)oxy]-1-propene (82) is used by Welch in a "one-pot" annelation of cyclohexanone or cyclopentanone.[69] Thus, a cyclohexanone is converted to (84) as shown in Fig. 46 *via* enol phosphate (83).

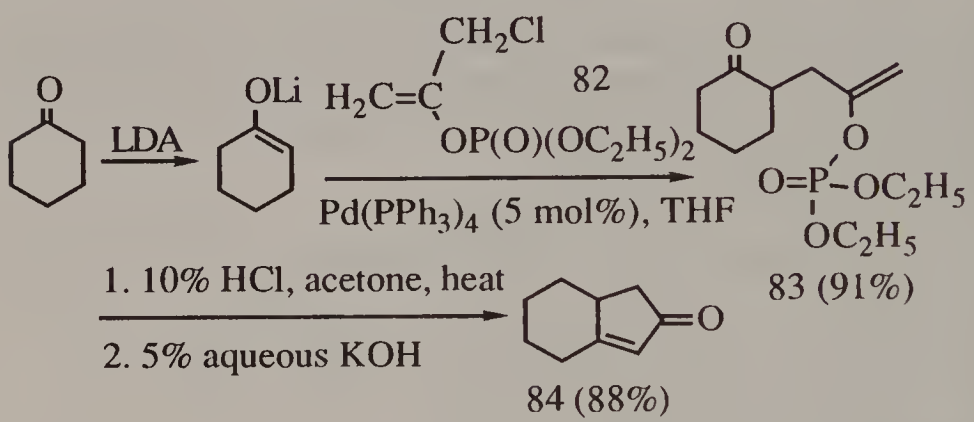
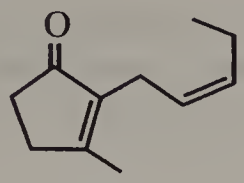


Fig. 46 - Welch's "one-pot" cyclohexanone annelation

Compound (82) is prepared from 1,3-dichloroacetone and triethyl phosphite. Other conversions of (82) lead to *cis*-jasmone (85) and to methylenomycin (86), as shown in Fig. 47, while related enol phosphate based electrophiles react with various nucleophiles to give other molecules of synthetic organic or biochemical interest.[70]

Enol phosphates are used in the syntheses of various members of the carbapenam family of antibiotics. For example, the azabicycloheptanedione (87) is enol-phosphorylated to give (88) which reacts with thiol (89) to yield an intermediate ester. The ester is then hydrogenolyzed to yield carbapenam (90).[71] Similar enol phosphates have been converted to useful intermediates for the synthesis of related carbapenam antibiotics shown in Fig. 48.[72,73]



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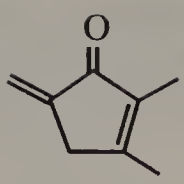


86

Fig. 47 - *cis*-Jasmone and methylenomycin

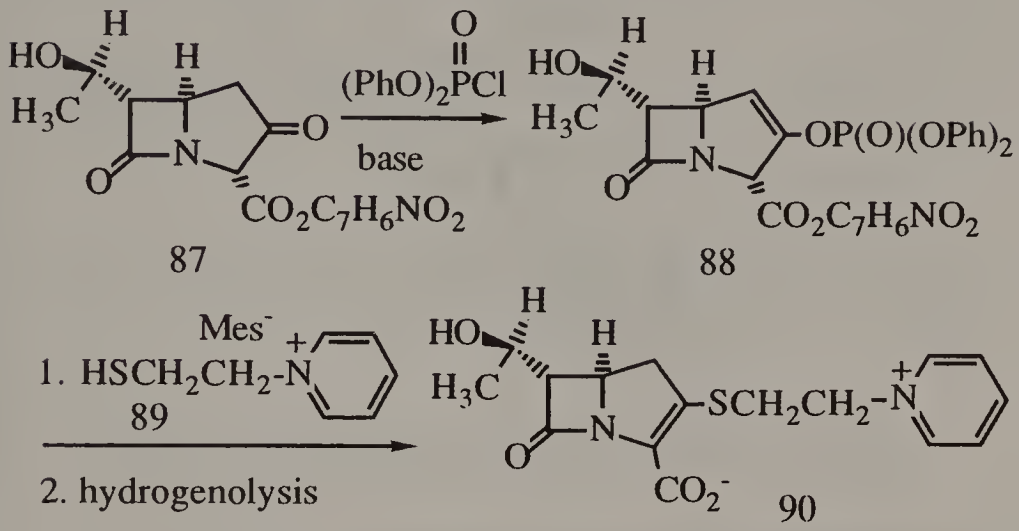


Fig. 48 - Carbapenam synthesis *via* an enol phosphate

Fugami, *et al.* cross-coupled substituted enol phosphates (91), as well as vinyl halides, sulfides, or trifluorosulfonates (triflates), with $(R_3Si)_3MnMgCH_3$ to give vinylsilanes (92), as shown in Fig. 49.[74]

$$R_1(R_4)C{=}C(R_2)OP(O)(OPh)_2 \xrightarrow{[(R_3)Si]_3MnMgCH_3} R_1(R_4)C{=}C(R_2)Si(R_3)$$

91 92

$R_1 = CH_3$, H, decyl, pentyl $R_2 = CH_3$, H, decyl, butyl, hexyl
$R_1R_2 = (CH_2)_4$, $(CH_2)_6$ $R_3 = (CH_3)_3$, $Ph(CH_3)_2$
R_4 = H, CH_3, decyl, Ph

Fig. 49 - Conversion of enol phosphates to vinylsilanes

Corey, *et al.* used the enol phosphate (93) to synthesize the

limonoid intermediate (94) and limonoid (95), as shown in Fig. 50. He developed a general preparative scheme *via* enol phosphates for the synthesis of limonoids, which are biosynthetically derived from triterpenes.[75]

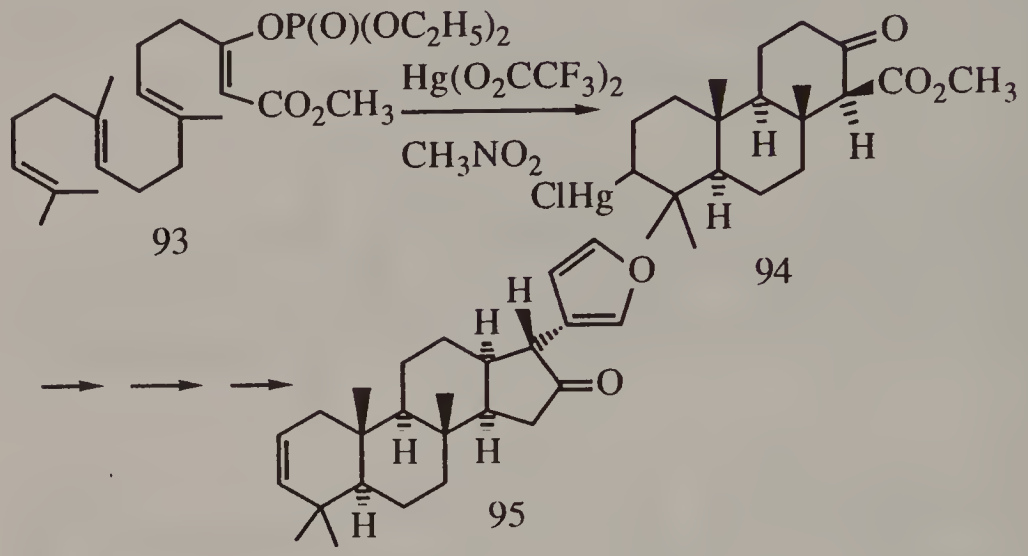


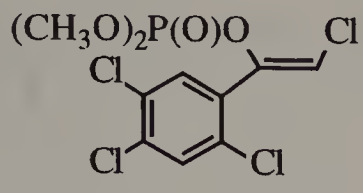
Fig. 50 - Corey's synthesis of a limonoid

F. Applications of Enol Phosphates

1. Insecticidal Properties

Foremost among the useful biological properties of enol phosphates is their insecticidal and pesticidal activity. While these properties will be reviewed in detail elsewhere, relevant structural, chemical, and synthetic features will be discussed here. There are several recent texts and reviews on phosphorus chemistry or insecticides which contain relevant material on enol phosphates.[76-78] Some of the more useful ones will be discussed.

Tetrachlorvinphos (Stirophos, Gardona®) (40) was shown to have the *Z* configuration by X-ray analysis[38] as previously mentioned. Mevinphos (Phosdrin®) (96) is a mixture of *Z* and *E* stereoisomers in which the *Z* isomer (*cis*) is found to be *ca.* 100 times more active.[76] It is prepared from methyl 3-chloroacetoacetate in reaction with trimethyl phosphite. The less toxic Clodrin® (97) used for control of ectoparasites on horses, cattle, sheep, and swine,[76] is similarly synthesized from the 1-phenylethoxy ester of 3-chloroacetoacetate, as shown in Fig. 51.



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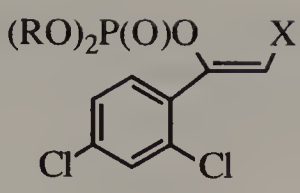

38 R = C_2H_5, X = Br
39 R = CH_3, X = Br
99 R = C_2H_5, X = Cl

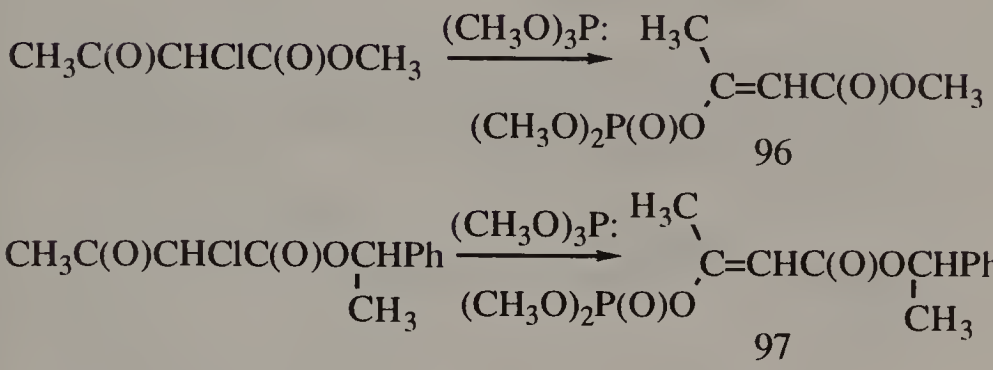

Fig. 51 - Structures and preparations of enol phosphate insecticides

Phosphamidon, 2-chloro-2-ethylcarbamyl-1-methylvinyl dimethyl phosphate (98), has a broad spectrum of activity against biting and sucking pests and spider mites.[76] The insecticide methylbromfenvinphos (39) was found to be the *Z* stereoisomer by single crystal X-ray analysis by Zwierzak[37] as previously discussed. Bromfenvinphos (38) and chlorfenvinphos (99) whose structures are shown in Fig. 51, and related insecticides have been synthesized by Zwierzak, *et al.*[79,80] In contrast to mevinphos (96) it is claimed that the *E* and *Z* isomers show no significant difference for a number of biological properties for insecticides such as bromfenvinphos (36) and chlorfenvinphos (99).[81] A cyclic enol phosphate, heptenophos (100) (Hostaquick®) is a systematic insecticide and acaricide (anti-tick and mite agent) with a short residual effect.[76] Its preparation is given in Fig. 52.

More recently, Zwierzak has synthesized enol phosphates containing α-carboalkoxy groups such as (101) and α-carbamoyl groups such as (102),[82] as shown in Fig. 53. Some of these compounds show fungicidal activity.

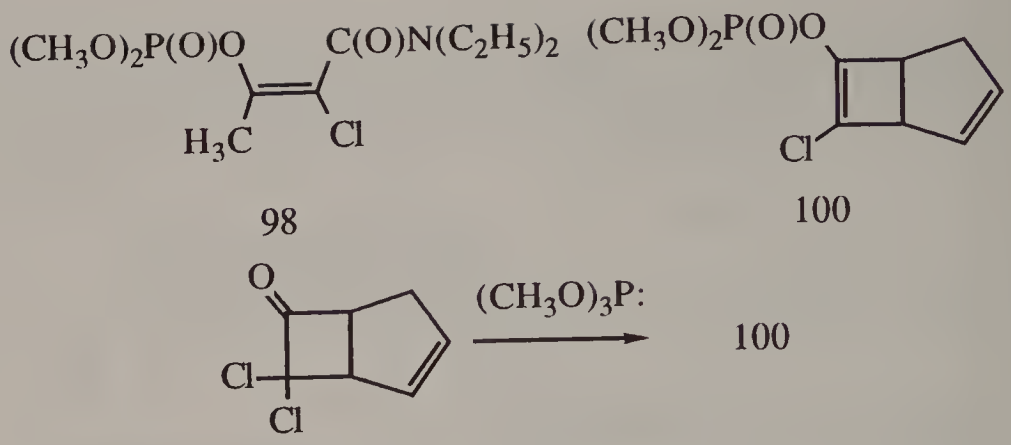

Fig. 52 - Structures of phosphamidon and heptenophos, and the synthesis of heptenophos

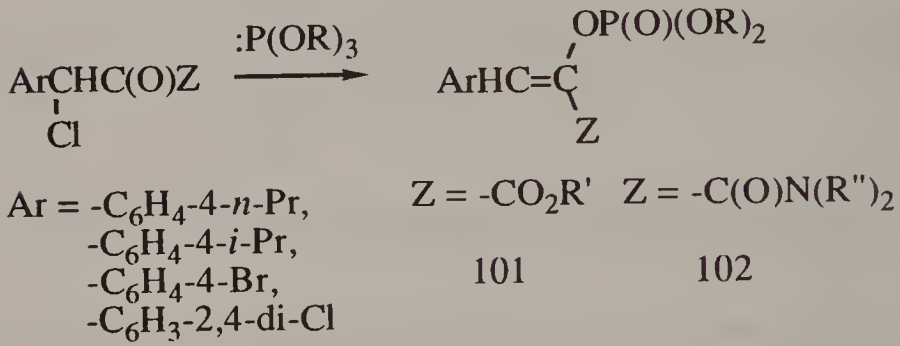

Fig. 53 - Synthesis of enol phosphate insecticides with α-carboalkoxy and α-carbamoyl groups

Malinowski, *et al.* concluded that the 2-carboalkoxy group in a series of dimethyl and diethyl enol phosphates (103) and (104), shown in Fig. 54, enhances insecticidal activity.[83] They compared fourteen compounds with such a group and eight compounds without it. The most effective insecticide and acaricide in their series is (105).

Two series of cyano-substituted ethyl thiopropyl enol phosphate insecticides (106) and (107) were synthesized by D'Silva[84] *via* phosphorylation of a precursor ketone. Some of the compounds were effective against the two spotted mite.

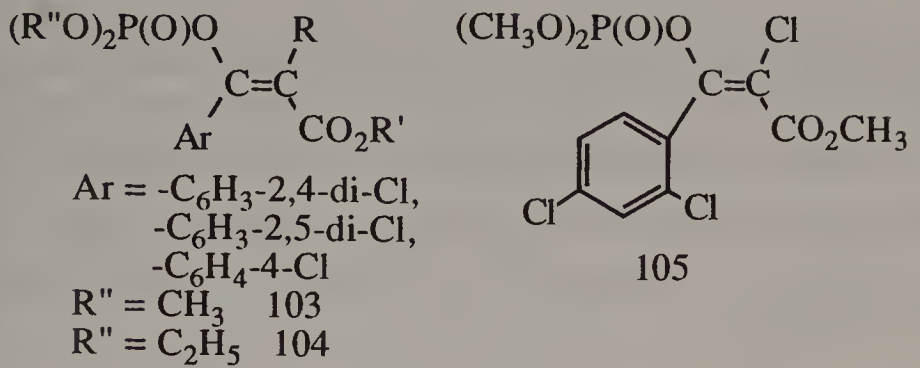

Fig. 54 - Enol phosphate insecticides with carboalkoxy and polychloroaryl groups

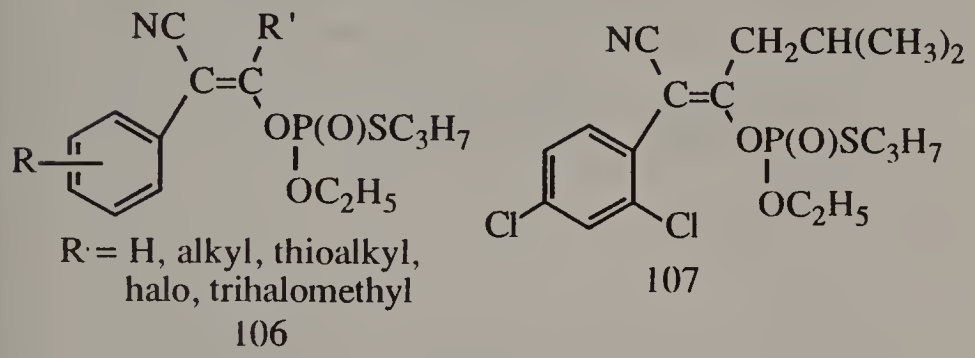

Fig. 55 - Cyano-substituted enol phosphate insecticides

2. Biological Properties

Phosphenol pyruvate, PEP [CA 2-propenoic acid, 2-(phosphonoxy)-, ion (1⁻), RN73-89-2] (108) is a well known high-energy phosphate which plays a vital role in a number of biological reactions. For example, PEP is involved in the conversion of ADP to ATP.[85a] The reaction of phosphoenol pyruvate with erythrose 4-phosphate (109) to give 3-deoxy-D-arabinoheptulosonic acid 7-phosphate (110) is the first step in the shikimic acid pathway for the biosynthesis of aromatic rings, as first delineated by Sprinson, Srinivasan, *et al.*[85b,86] as shown in Fig. 56.

Further along this pathway is the addition of phosphoenol pyruvate to shikimate 3-phosphate (111) to give 5-enolpyruvylshikimate 3-phosphate (112) as shown in Fig. 57.[85a,87] This is an enzymatic reaction which is postulated to occur by addition of the 5-hydroxyl group of the shikimate 3-phosphate to phosphoenol pyruvate, thus converting its C-3 carbon to a methyl group to give

the tetrahedral intermediate (113). This step is followed by elimination of phosphate to reform a double bond and yield (112).[87] In chemical reactions any addition-elimination reactions of a nucleophile with an α,β-unsaturated carbonyl compound such as phosphoenol pyruvate would have occurred at the carbon β to the carbonyl, not α as shown in the naturally occurring process in Figs. 57 and 58.

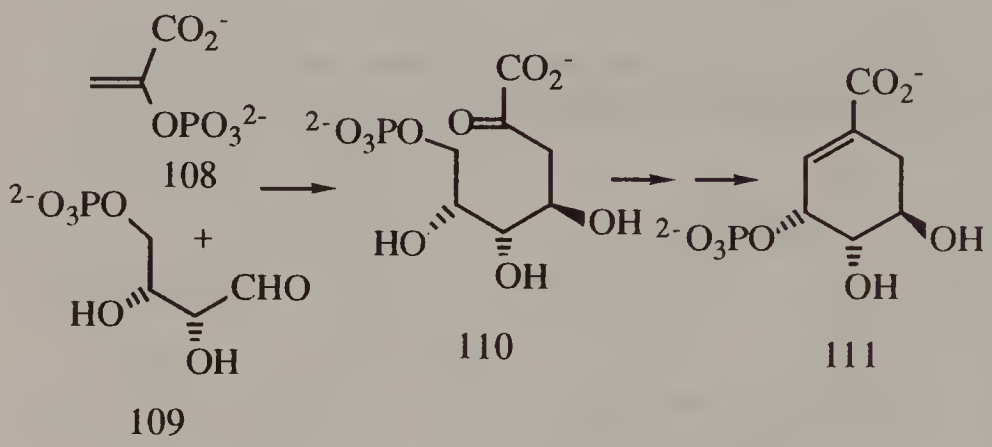

Fig. 56 - Biosynthesis of shikimate 3-phosphate

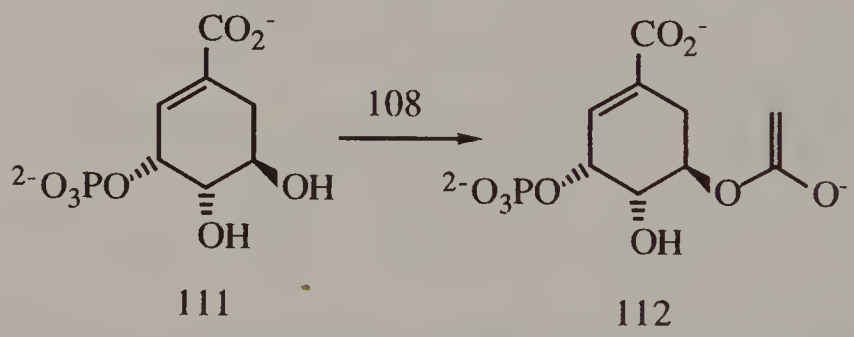

Fig. 57 - Biosynthesis of 5-enolpyruvylshikimate 3-phosphate

Early syntheses of phosphoenol pyruvate were reviewed by Lichtenthaler.[6] More recently, Hata synthesized the tri-sodium salt of phosphoenol pyruvate from pyruvic acid by application of a reaction that he developed in which dimethyl enol phosphates (114) are converted to bis(trimethylsilyl) enol phosphates (115) upon reaction with bromotrimethylsilane (TMSBr). In the phosphoenol pyruvate synthesis, the intermediate trimethylsilyl enol phosphate

(115) is hydrolyzed upon treatment with sodium ethoxide to the tri-sodium salt of (108).[88] Alternatively, Hata prepared (108) from the enol trimethylsilyl compound (116) upon bromination and treatment with dimethyl trimethylsilyl phosphite.

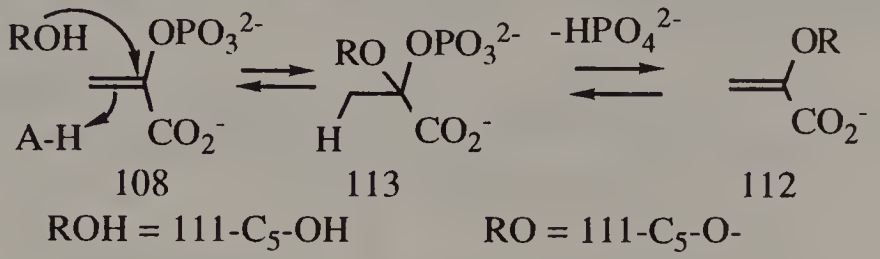

Fig. 58 - Knowles' proposed mechanism for biosynthesis of 5-enolpyruvylshikimate 3-phosphate

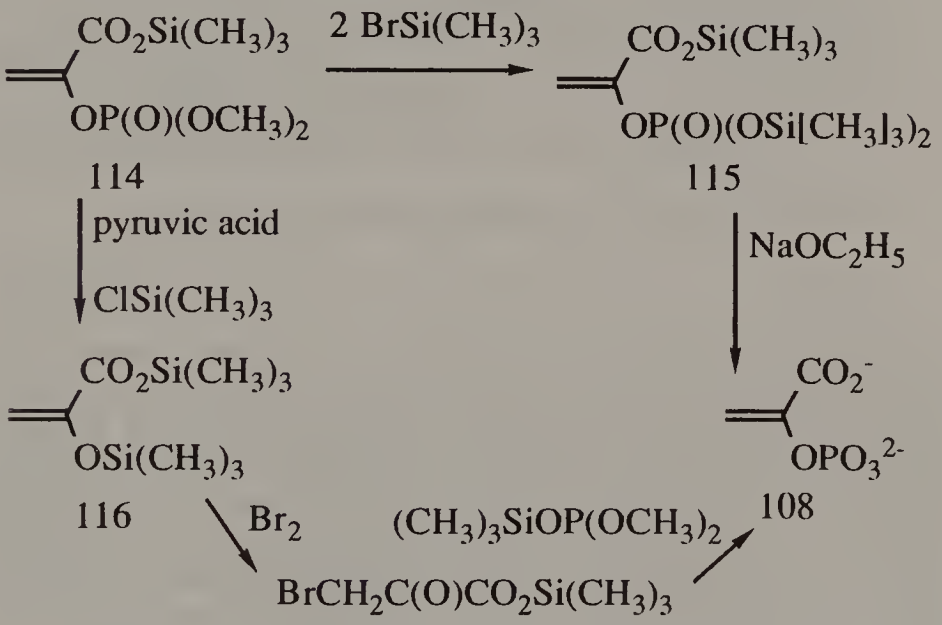

Fig. 59 - Hata's synthesis of phosphoenol pyruvate

Conditions for the separation of phosphoenol pyruvate from phosphate or acetyl phosphinate by liquid chromatography on a quaternary ammonium ion exchange column (Hamilton PRP-X100) using an aluminum-morin post-column reagent for indirect fluorometric detection have been determined.[89] The analysis of many other phosphous oxo-acid anions are included.

Kluger has synthesized phosphoenol pyruvamides (117) and (118) and has shown that their ethyl ester groups are hydrolyzed

10^4 times faster than is triethyl phosphite under comparable conditions.[90] These data indicate that participation occurs by the neighboring carboxamide group. The hydrolysis products (119)-(122), shown in Fig. 60, may be useful analogues of phosphoenol pyruvate in studies of enzyme mechanisms and in the design of inhibitors.

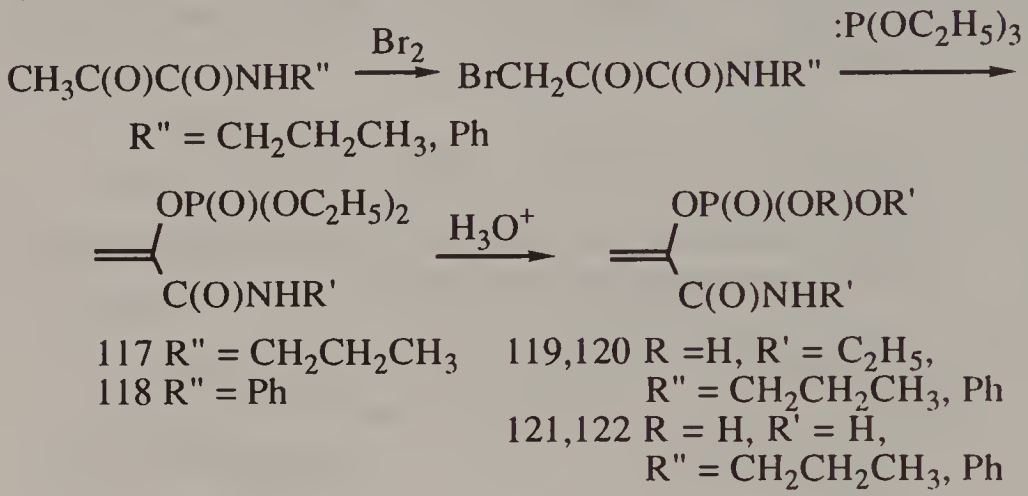

Fig. 60 - Hydrolysis of phosphoenol pyruvamides

Thiem, *et al.* developed a series of reactions which illustrate the viability of using α-acetoxyketones or α-tosyloxyketones in novel applications of the Perkow reaction. They constitute a clever application of the Perkow reaction which illustrates its continuing versatility and utility. In the first example shown in Fig. 61 a mixture of 1-deoxy-D-fructose (125) and 3-deoxy-D-*erythro*-hexulose (127) is prepared by the hydrolysis of the isomeric enol phosphates (124) and (126). The enol phosphates were prepared by a Perkow reaction using trimethyl phosphite on 1,3,4,5,6-penta-*O*-acetyl-D-fructose (123).[91]

More recently, Thiem has used similar Perkow reactions on uridines with α-tosyloxy groups at C-2' or C-3', such as (128) and (133). The sequence for the C-2' tosylate is illustrated in Fig. 62. The uridine derivative (128) is oxidized to the tosyloxyketone (129) which is then converted to the enol phosphate intermediate (130). Compound (130) is hydrolyzed under mildly basic conditions to prepare 5'-acetoxy-3'-deoxy-2'-ulose (131).[93] The C-3'-OTs uridine derivative (133) could not be cleanly converted to the corresponding 5'-acetoxy-2'-deoxy-3'-ulose (135).

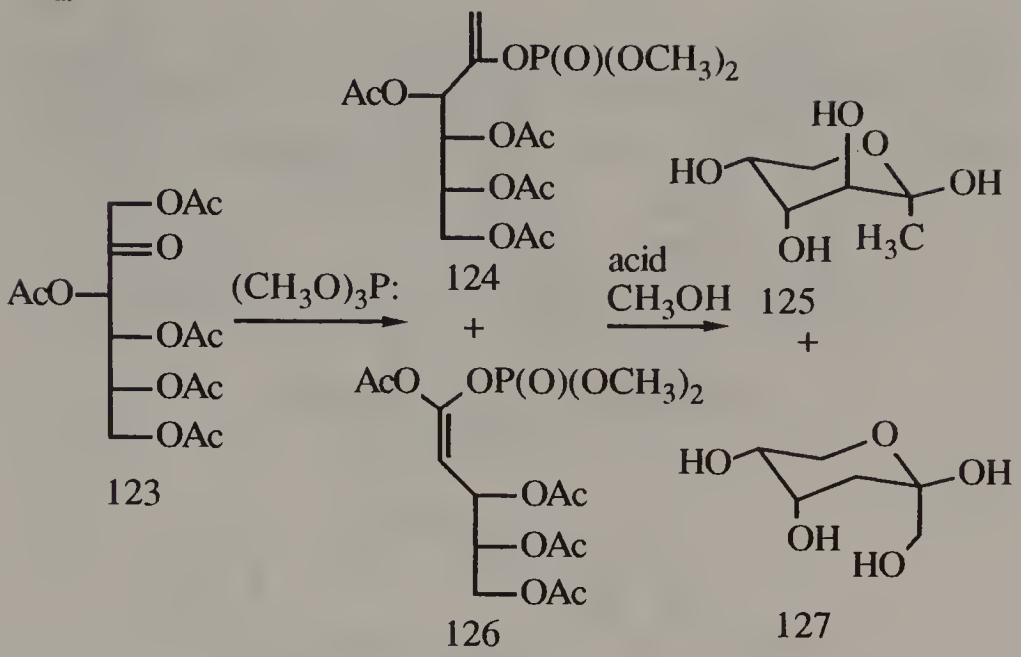

Fig. 61 - Thiem's synthesis of 1-deoxy-D-fructose and 3-deoxy-D-*erythro*-hexulose *via* enol phosphates

The 2'- and 3'-tosyloxy uridine derivatives (128) and (133), as well as the 2',3'-ditosyloxy uridine derivative (134) were prepared from 5'-acetoxyuridine (132) by treatment with *p*-toluenesulfonyl chloride, as shown in Fig. 63. They were separated by column chromatography to yield (128) as the major product.

Mitsuo, *et al.* found that 1-alkenyl and phenyl phosphate esters, such as (137), prepared from vinylene carbonates, such as (136), undergo smooth cleavage of the O-P linkage by a novel cesium fluoride catalyzed alcoholysis to give aldehydes such as deoxyaldose analogue (138) or ketones or phenols.[94] Other hydrolysis methods from either (136) or (137) were unsuccessful in preparing (138). Thus, 1 *N* HCl at 80° gives α,β-unsaturated aldehydes and not 2-deoxyaldoses. Alkali treatment gives a complicated mixture of products. Therefore, application of the cesium fluoride hydrolysis method provides a new route to deoxy sugar analogues as shown in Fig. 64.

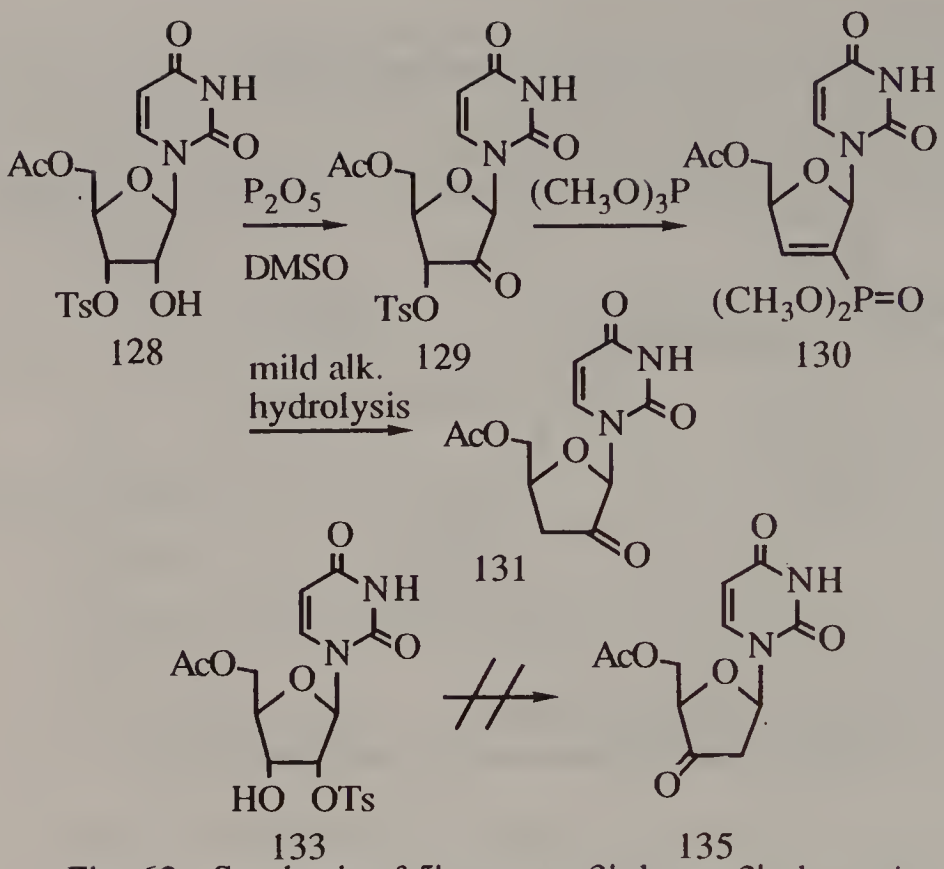

Fig. 62 - Synthesis of 5'-acetoxy-3'-deoxy-2'-ulose *via* enol phosphates

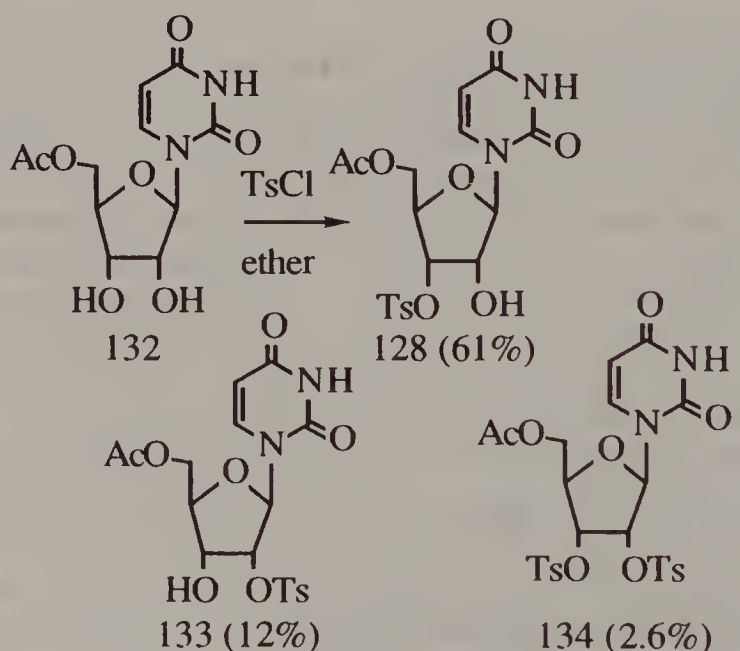

Fig. 63 - Synthesis of 5'-acetoxyuridine tosylates

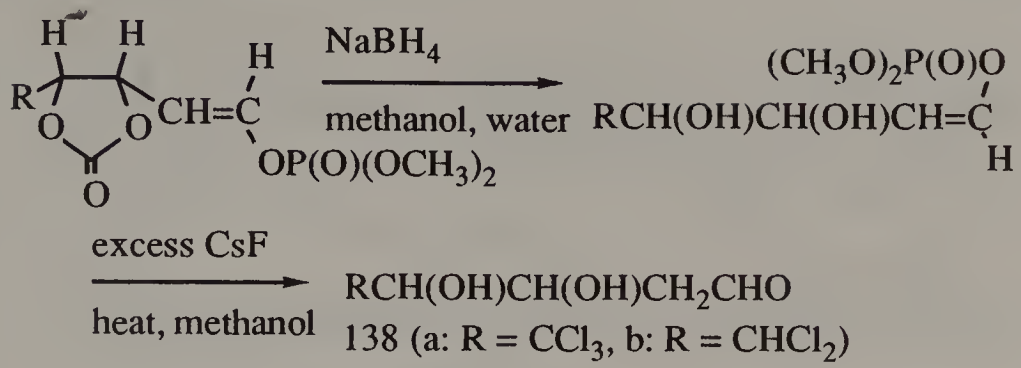

Fig. 64 - Synthesis of 2-deoxyaldose derivatives

Sauve, *et al.* converted N-acyldipeptides such as N-Ac-Leu-Phe (139) to difunctionalized enols.[95] One example employed malononitrile and 1,1'-carbonyldiimidazole (CDI) to give the difunctionalized enol (140). Phenyl phosphorodichloridate was used to transform the enols to the enol phosphates, such as the conversion of (140) to (141). The enol phosphates such as (141) were reacted with secondary amines, alcohols, or thiols to give the corresponding dipeptide derivatives, as shown in Fig. 65. For (141) these are enamines (142), enol ethers (143), and thioenol ethers (144). Phenyl phosphorodichloridate was found to be a uniquely effective enol activating reagent for these transformations. Other well known enol activating reagents such as DCC, $ClCO_2CH_3$-pyridine, PhCOCl-pyridine, Ph_3P-CCl_4, $SOCl_2$-pyridine were not succesful in these reactions.

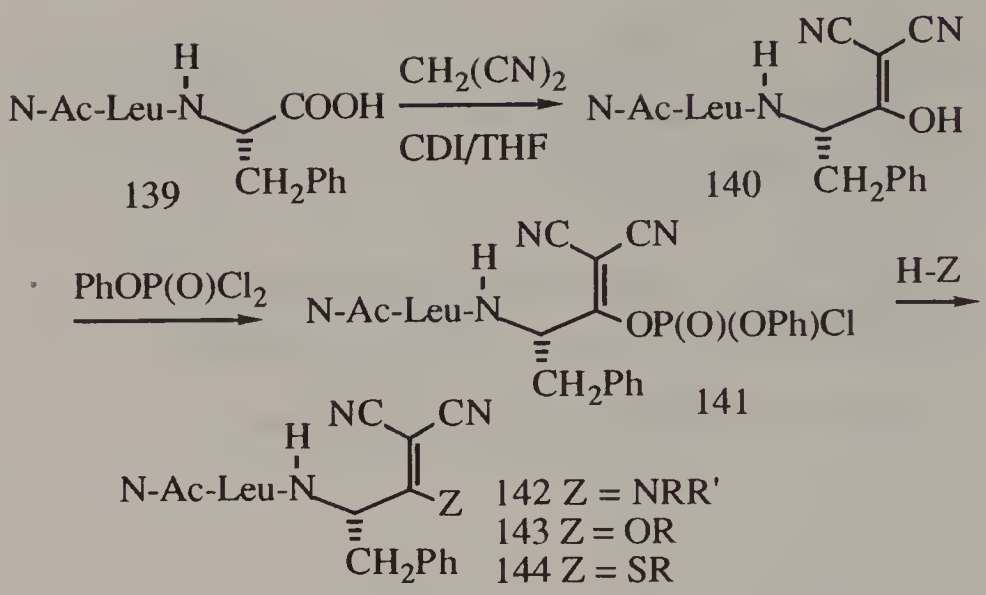

Fig 65 - Novel modifications of dipeptides

II. Reactions Related to the Perkow Reaction

A. Reactions of Phosphinites and Phosphonites with Mono- α-Halo- or α-Mesyloxycarbonyl or with α,α-Dihalocarbonyl Compounds to Give Keto or Enol Phosphorylated Products

The reactions of α-haloketones with tricovalent organophosphorus reagents afford systems in which the sites of reaction can be broadly correlated with hard and soft acid/base theory.[96-99] The relatively soft triphenylphosphine (TPP) reacts with α-bromo or α-chloroketones at the relatively soft carbon-halogen bonds to give ketophosphonium salts by S_N2 displacement of halide ion.[17,50-52,100] In the case of halocarbonyl systems bearing further electron-withdrawing α-substituents and/or having hindered carbonyls, enol phosphonium salts are formed *via* nucleophilic displacement by triphenylphosphine on halogen as shown in Fig. 66. This attack on such α-haloketones (145) leads to an enolate halophosphonium ion-pair (146) which then *O*-phosphorylates to give enol phosphonium salts (147).[50,101]

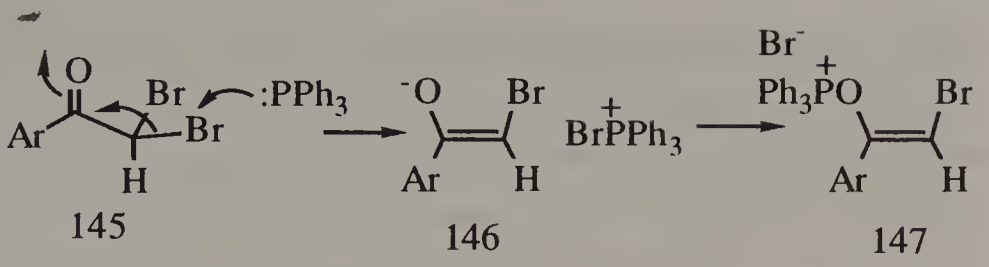

Fig. 66 - Mechanism of enol triphenylphosphonium bromide formation

Furthermore, α-bromoketones (148) are debrominated by triphenylphosphine in protic solvents (ROH, AcOH) as illustrated in Fig. 67. This debromination occurs by a pathway featuring proton or other acid coordination at carbonyl oxygen and attack of triphenylphosphine on bromine to yield the dehalogenated ketone (150) *via* the enol (149) or enolate (in the case of aromatic ketones with electron-withdrawing groups).[33]

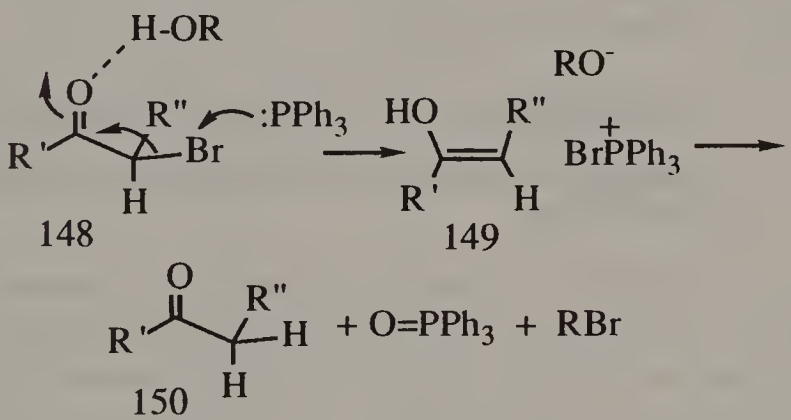

Fig. 67 - Mechanism of debromination of α-bromoketones with triphenylphosphine/ROH

The relatively harder trialkyl phosphites react with α-haloketones to give ketophosphonates or enol phosphates *via* the Perkow reaction, which involves addition of trialkyl phosphites to carbonyl carbon, a relatively hard center.[102] Production of ketophosphonates is usually a minor process except for primary α-bromoketones.

The behavior of alkyl diphenylphosphinites, Ph_2P-OR

(ADP), or dialkyl phenylphosphonites, $(RO)_2P\text{-}Ph$ (DAP), in reaction with α-haloketones are mechanistically in between those of triphenylphosphine and triethyl phosphite.[103] Ethyl diphenylphosphinite reacts with α-bromoacetophenone (151), Ar = Ph, at 25° in $CDCl_3$ to give the ketophosphine oxide (152) and enol phosphinate (153) in 2:1 product ratio. α-Chloro- or α-mesyloxyacetophenone (154) and (155) react to give only (153).[103]

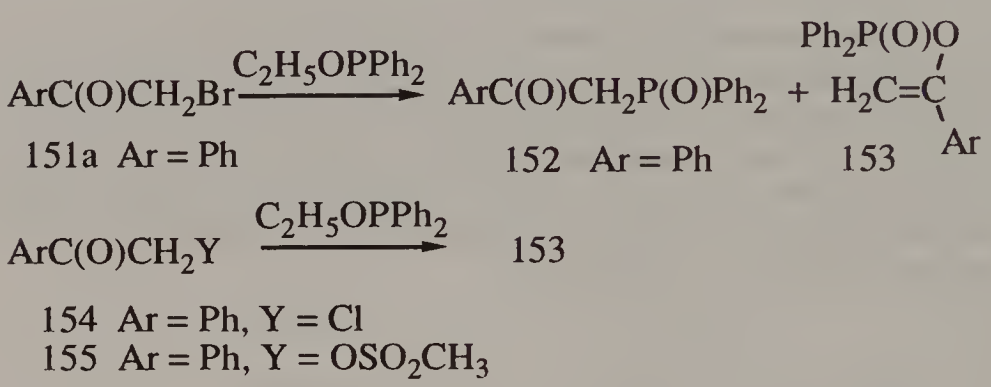

Fig. 68 - The reaction of ethyl diphenylphosphinite with α-bromoacetophenone to give ketophosphine oxide and enol phosphinate

As the electron density at carbonyl is increased by the addition of electron-donating groups on phenyl, the relative amount of ketophosphine oxide increases. Thus, *p*-methoxy-α-bromoacetophenone (151b) gives 94% of ketophosphine oxide and no enol phosphinate. Conversely, *p*-nitro-α-bromoacetophenone (151c) gives 94% of the enol phosphinate only. Similar effects are found for phenyl-substituted α-bromopropiophenones. Most other α-haloketones such as α-bromoisobutyrophenone (8), cyclic α-haloketones such as (7), α,α-dihaloketones such as (19) and (20), and α-halobenzyl phenyl ketones such as (6) give only enol phosphinates.

The presence of ethanol changes the reaction of chloroacetone (156) from giving mostly ketophosphine oxide (157) to giving 4:1 enol phosphinate (158)/keto phosphine oxide (157)

products, as shown in Fig. 69. Whether this can be used more generally to enahnce enol phosphinate formation is not yet known.

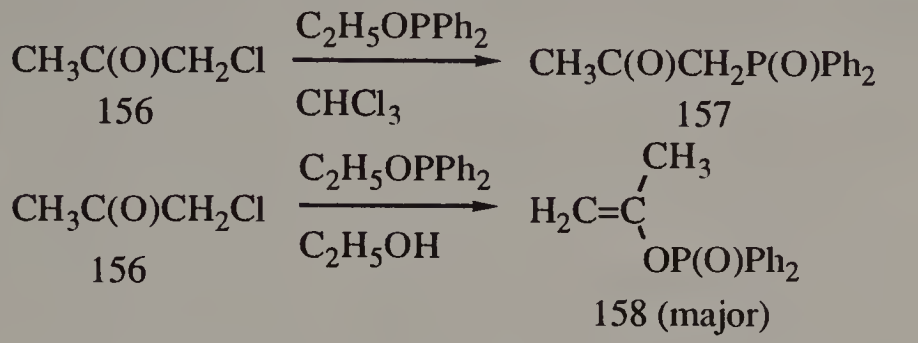

Fig. 69 - The effect of solvent on the ratio of enol/keto products

These studies suggest that ethyl diphenylphosphinite reacts in a similar manner to triphenylphosphine, *i.e.* it gives ketophosphine oxides by S_N2 displacement of halide ion and enol phosphinates by carbonyl addition, the Perkow reaction.[103] The same publication indicates that the rate of second-order reaction with *p*-methoxy-α-bromoacetophenone (151b) is in the order: Ph_2PO-*n*-Bu >> Ph-P(O-*n*-Bu)$_2$ > P(O-*n*-Bu)$_3$. Since these reactions give only ketophosphorylated products, which presumably occur by S_N2 reactions, the realtive carbophilicities of P(III) reagents is parallel to their S_N2 carbophilicities.

Reactions of $PhP(OR)_2$ were also investigated.[103] The results are similar to those for triethyl phosphite. Thus, α-chloroacetophenone (154) reacts with di-*n*-butyl phenylphosphonite to give *n*-butyl phenyl 1-phenylvinylphosphonate (159) in 92% yield as shown in Fig. 70.

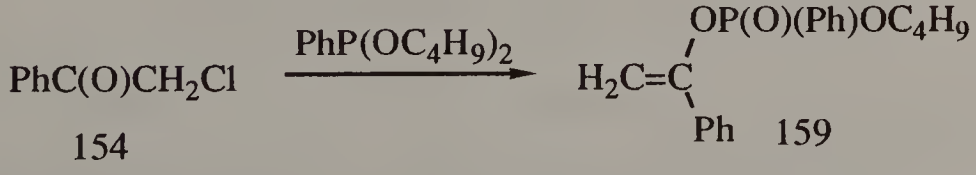

Fig. 70 - Reaction of α-chloroacetophenone to give enol-phosphorylated product

In summary, ethyl diphenylphosphonite can give enol phosphorylated products from α-haloketones in Perkow-type reactions. These products may be as useful or more useful than are enol phosphates since they do not contain -OR groups and thus should be more stable to hydrolysis, *etc.* The rearrangement of enol to ketophosphorylated compounds occurs much better with diphenylphosphinates then with dialkyl phosphates.[44,46]

Stork, *et al.* found that cleavage of the enol diphenylphosphinate (160) to give the desired enolate (161) occurs under milder conditions than are necessary for the corresponding phosphate. The liberated enolate (161) was then trapped with formaldehyde to give a prostaglandin precursor (162) as shown in Fig. 71. Mild conditions, including low reaction temperature, are necessary for the survival of this enolate which can otherwise β-eliminate the benzyloxy group.[104]

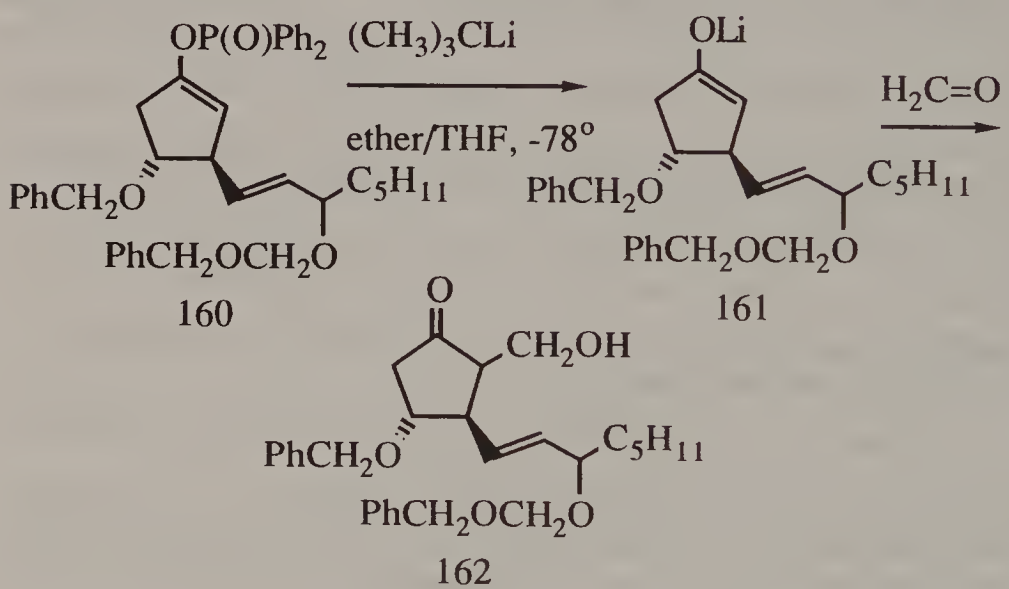

Fig. 71 - Generation of an enolate from an enol diphenylphosphinate in a prostaglandin synthesis

B. Reactions of Silyl Phosphites with α-Carbonyl Compounds

Hata has described several syntheses of trimethylsilyl-containing phosphites including tris(trimethylsilyl) phosphite (TTMSP) (163).[19,88,105] The most convenient synthesis of (163) involves treatment of phosphorous acid with chlorotrimethylsilane and

triethylamine to give a mixture of tris(trimethylsilyl) phosphite (163) and bis(trimethylsilyl) phosphite (164) as shown in Fig. 72. This mixture is treated with excess sodium to remove (164) and leave pure (163).

$$:P(OH)_3 \xrightarrow[(C_2H_5)_3N]{(CH_3)_3SiCl} \underset{163}{:P(OSi[CH_3]_3)_3} + \underset{164}{HP(O)(OSi[CH_3]_3)_2}$$

Fig. 72 - Synthesis of tris(trimethylsilyl) phosphite

Compound (163) is more reactive than is triethyl phosphite since the trimethylsiloxy group is electron-donating toward the phosphorus[88] in comparison with electron-withdrawing -OR groups in triethyl phosphite. The reactions of (163) with alkyl-substituted α-haloaldehydes or alkyl-substituted α-haloketones give neither β-ketophosphonates nor enol phosphates, but 1:1 carbonyl adducts[19] as already discussed in Part IC. α-Haloacetophenones react with (163) to give both enol phosphate (165) and β-ketophosphonates, presumably by direct S_N2 displacement of halide ion, as shown in Fig. 73.[19]

$$ArC(O)CH_2X \xrightarrow{163} \underset{165}{ArC(O)CH_2P(O)(OSi[CH_3]_3)_2} + \underset{166}{H_2C{=}C(Ar)OP(O)(OSi[CH_3]_3)_2}$$

151a Ar = Ph, X = Br
154 Ar = Ph, X = Cl

Fig. 73 - Reaction of tris(trimethylsilyl) phosphite with α-haloacetophenones

C. Other Methods of Synthesizing Enol or Keto-phosphorylated Species

The most useful alternative to the Perkow reaction for synthesizing enol phosphates is the phosphorylation of enolates.[6,44,45,57-60,66,75] Since either enolate of an unsymmetrical ketone can be synthesized *via* kinetic or equilibrium control deprotonation in many cases,[55,56] the two isomeric enol

phosphates can be prepared. In at least a few cases, the phosphorylation of enolates represents an improved method, that is, one with higher yields and/or greater convenience. Thus, the phosphorylation of enolates, as shown in Fig. 74, is often superior to the Perkow reaction for the preparation of enol phosphates.[6,66]

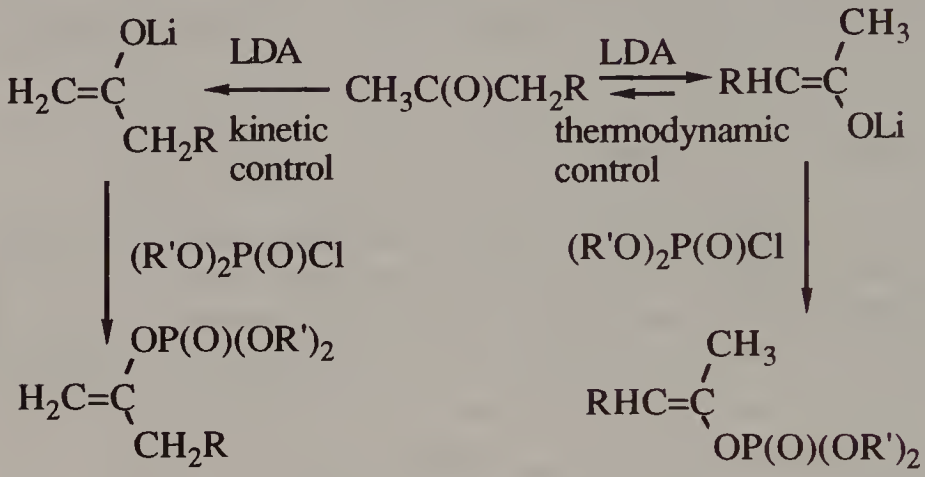

Fig. 74 - Formation and phosphorylation of enolates

The reactions of trialkyl phosphites with primary α-haloketones, such as α-chloroacetone (167) or α-chloroacetophenone (154), in methanol give 2-chloroalkyl-1-hydroxyphosphonates, (4) or (30) as the major product.[8,17,26] These products are also formed in the reactions of α-halocarbonyl compounds with dialkyl phosphites, as shown in Fig. 75.[6]

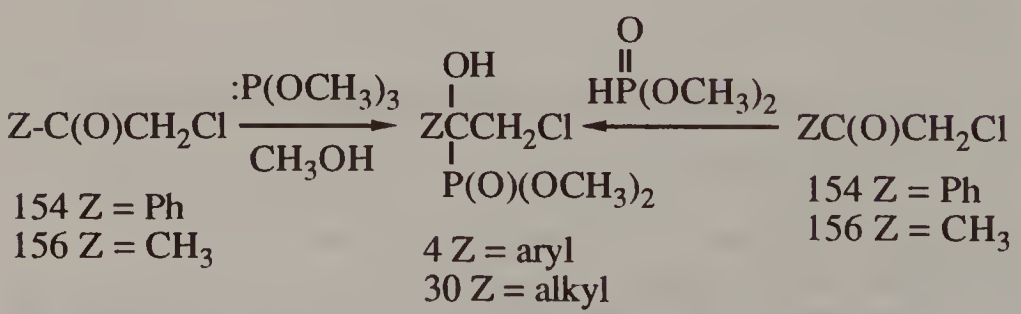

Fig. 75 - Preparation of 2-haloalkyl-1-hydroxyphosphonates

Haloalkyl-1-hydroxyphosphonates such as (30) and (167), upon treatment with base (HO^- and CH_3O^-) and gentle warming in

aqueous or alcoholic solution rearrange to enol phosphates (168),[2,6,51,106] as well as upon treatment with tri-*n*-butyltin methoxide.[19] In contrast, treatment of (167) with *n*-butyllithium gives epoxy phosphonates (169), as shown in Fig. 76.[19] Use of *t*-BuOK/*t*-BuOH gives (169) as the major product and (168) as the minor product.

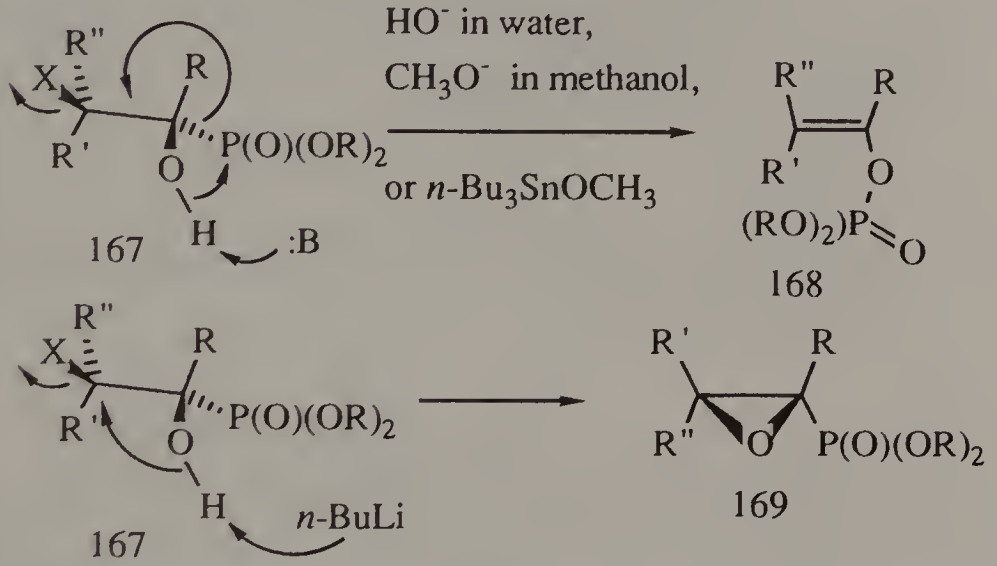

Fig. 76 - Rearrangements of 2-haloalkyl-1-hydroxyphosphonates

More recently Ishihara, *et al.* found that various α,α,α-chlorodifluoromethylketones (170) react with dialkyl or diaryl phosphites in $(C_2H_5)_3N$/THF at reflux to give the corresponding dialkyl or diaryl 1-substituted-2,2-difluoroethenyl phosphates (172) in good yield.[107] If these reaction are done at lower temperatures (0-20°), 1-hydroxyalkylphosphonates (171) form as shown in Fig. 77. They are converted to the enol phosphates (172) by treatment with triethylamine or sodium methoxide in THF at reflux.

Mitsuo, *et al.* found that vinylene carbonate telomers (173) react with trimethyl phosphite to lose carbon dioxide and give enol phosphates with one fewer cyclic carbonate unit (174) as shown in Fig. 78.[94] This novel synthesis of enol phosphates provides a new route to 2-deoxyaldoses (Part IF).

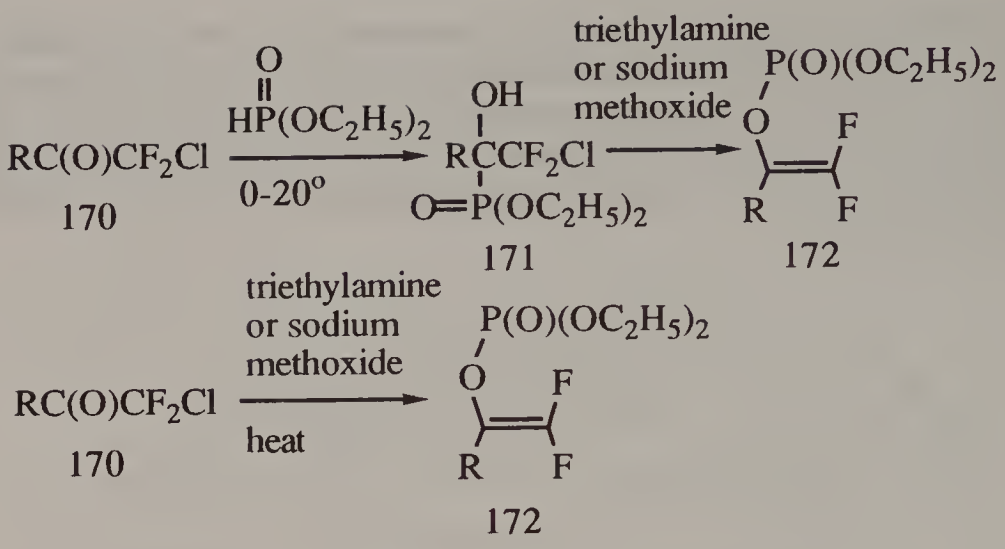

Fig. 77 - Reactionns of α,α,α-chlorodifluoromethyl ketones with dialkyl phosphites

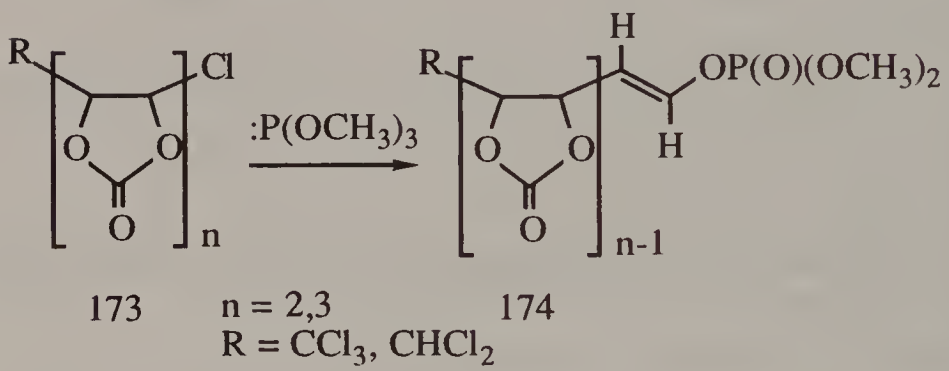

Fig. 78 - Synthesis of enol phosphates from vinylene carbonate telomers

Lichtenthaler has reviewed other, less general syntheses of enol phosphates.[6] These include: 1) catalytic addition of dialkyl hydrogen phosphates to disubstituted alkynes, and 2) mercuric ion catalyzed transesterification of vinyl acetate with phosphoric acid.

D. Reactions of Thiocarbonyl Compounds

Gaydou reported that α-chlorothioacetone (175) reacts with trimethyl or triethyl phosphite to give the tetrahedral intermediate (176) which leads to the episulfide (177) *via* a route *a* and to the thioenol phosphate (178) *via* route *b*.[108] He proposed the

mechanism shown in Fig. 79, which is related to that of the Perkow reaction.

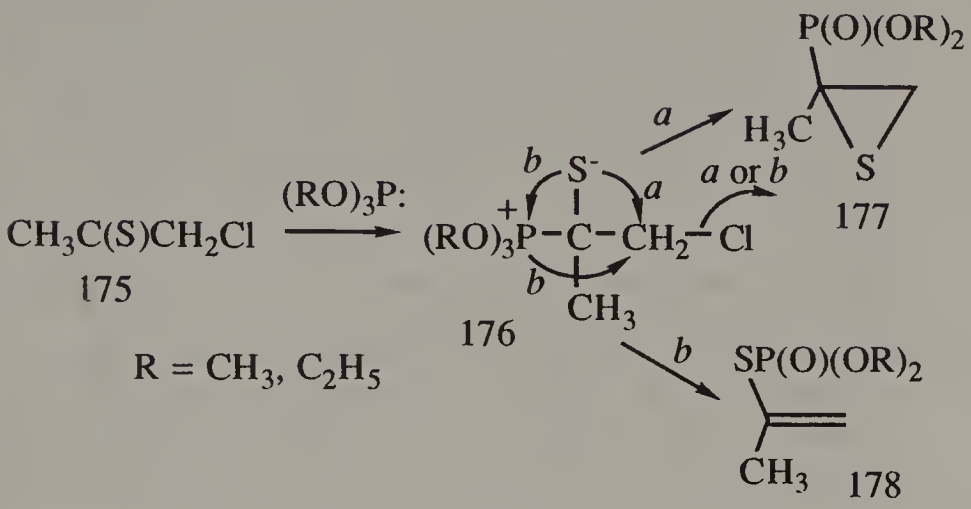

Fig. 79 - Reactions of α-chlorothioacetone with trialkyl phosphites

The promise of the Perkow reaction, first published by Perkow in 1952, continues to be fulfilled as shown by the wealth of research and applications to date. The search which produced the references cited in this Chapter covered the literature through October, 1990.

III. Bibliography

1. Michaelis, A., and Kaehne, R. (1898). About the behavior of alkyl iodides with so called phosphorus acid esters or with *O*-phosphines, *Ber.*, *31*: 1048.
2. Arbuzov, A.E. (1906). Reactions of alkyl halides with phosphites, *J. Russ. Phys. Chem. Soc.*, *38*: 687.
3. Arbuzov, B.A. (1964). Michaelis-Arbuzov and Perkow reactions, *Pure Appl. Chem.*, *9*: 307.
4. Perkow, E., Ullerich, K., and Meyer, F. (1952). New phosphoric ester with miotic activity, *Naturwissenschaften*, *39*: 353.
5. Whetstone, R.R., and Harman, D. (1960). Insecticidally active esters of phosphorus acids, *U.S. Patent 2,765,331*.
6. Lichtenthaler, F.W. (1961). The chemistry and properties of enol phosphates, *Chem. Rev.*, *61*: 607.
7. Borowitz, I.J., Anschel, M., and Firstenberg, S. (1967).

Organophosphorus chemistry. IV. The reactions of trialkyl phosphites with α-haloketones, *J. Org. Chem.*, *32*: 1723.
8. Keglevich, G., Petnehazy, I., Toke, L., and Hudson, H.R. (1987). Factors in the control of product composition in the reactions of trialkyl phosphites with α-halogenoacetophenones in alcoholic media, *Phosphorus and Sulfur*, *29*: 341.
9. Borowitz, I.J., Firstenberg, S., Casper, E.W.R., and Crouch, R. (1972). The monodebromination of α,α-dibromoketones by trialkyl phosphite-acetic acid or *via* enol phosphonium salts, *Phosphorus*, *1*: 301.
10. Mlotkowska, B., Majewski, P., Koziara, A., Zwierzak, A., and Sledzinski, B. (1981). Reactions of 2,4- and 2,6-dichlorophenacylidene halides with trialkyl phosphites in protic solvents. Direct evidence for the "enolate anion" pathway, *Pol. J. Chem.*, *55*: 631.
11. Gazizov, T.K., Sudarev, Y.I., Gol'dfarb, E.I., and Pudovik, A.N. (1975). Mechanism of the reaction of triethyl phosphite with chloral, *J. Gen. Chem. U.S.S.R.*, *46*: 924.
12. Allen, J.F., and Johnson, O.H. (1955). The synthesis of monovinyl esters of phosphorus(V) acids, *J. Am. Chem. Soc.*, *77*: 2871.
13. Kharasch, M.S., and Bengelsdorf, I.S. (1955). The reaction of triethyl phosphite with α-trichloromethyl carbonyl compounds, *J. Org. Chem.*, *20*: 1356.
14. Borowitz, I.J., Firstenberg, S., Borowitz, G.B., and Schuessler, D. (1972). On the kinetics and mechanism of the Perkow reaction, *J. Am. Chem. Soc.*, *94*: 1623.
15. Borowitz, I.J., Yee, K.C., and Crouch, R.K. (1973). Determination of stereochemistry in vinyl phosphorylated species by nuclear magnetic resonance shift reagents. Revised mechanistic pathways for the Perkow reaction, *J. Org. Chem.*, *38*: 1713.
16. Gaydou, E.M., Buono, G., and Freze, R. (1973). Enol phosphates. VI. Kinetic study of the Perkow reaction, *Bull. Soc. Chim. Fr.*, *7-8 (Part 2)*: 2284.
17. Chopard, P.A., Clark, V.M., Hudson, R.F., and Kirby, A.J. (1965). The mechanism of the reaction between trialkyl phosphites and α-halogenated ketones, *Tetrahedron*, *21*: 1961.
18. Arcoria, A., and Fisicella, S. (1971). Reaction kinetics of

triethyl phosphite with *p*-phenacyl chlorides, *Tetrahedron Lett.*: 3347.

19. Sekine, M., Okimoto, K., Yamada, K., and Hata, T. (1981). Silyl phosphites. 15. Reactions of silyl phosphites with α-halocarbonyl compounds. Elucidation of the mechanism of the Perkow reaction and related reactions with confirmed experiments, *J. Org. Chem.*, *46*: 2097.
20. Denney, D.B., and Wagner, Jr., F.A. (1973). Phosphite reactivity and the Perkow reaction, *Phosphorus*, *3*: 27.
21. Aksnes, G., and Aksnes, D. (1944). A kinetic study of Michaelis-Arbuzov reactions, *Acta Chem. Scand.*, *18*: 38.
22. Speziale, A.J., and Bissing, D.E. (1963). The reactions of phosphorus compounds. VIII. Kinetics and mechanism of the Wittig reaction, *J. Am. Chem. Soc.*, *85*: 3878.
23. Jencks, W.P. (1969). *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, (a) pp 480-497; (b) pp. 463-554.
24. Hudson, R.F., and Salvadori, G. (1966). Reactions entre les composes trivalent du phosphore et les derives α-halogenes de la trimethyl-2,4,6-acetophenone, *Helv. Chim. Acta*, *49*: 96.
25. Petnehazy, I., Szakal, G., Russ, K., and Toke, L. (1978). Kinetics of the Perkow reaction, *Acta Chim. Acad. Scient. Hung.*, *98*: 447.
26. Petnehazy, I., Kegelevich, G., Toke, L., and Hudson, H.R. (1988). Mechanism of the reaction of trialkyl phosphites with α-halogenoacetophenones in alcoholic solvents, *J. Chem. Soc., Perkin Trans. II*: 127.
27. Toke, L. Petnehazy, I., and Szakal, G. (1978). Reaction of trialkyl phosphites with α-halogenoketones. Mechanism of the Perkow and Arbuzov reactions, *J. Chem. Res. (S)*: 155.
28. Petnehazy, I., Szakal, G., Toke, L., Hudson, H.R., Powrozynk, L., and Cooksey, C.J. (1983). Quasiphosphonium intermediates - IV, *Tetrahedron*, *39*: 4229.
29. Toke, L., Petnehazy, I., Kegelevich, G., and Szakal, G. (1988). Reaction of trialkyl phosphites and α-haloketones in aprotic media (Perkow-Arbuzov reaction) and in protic solvents, *Periodica Polytechnica Chem. Eng.*, *32*: 101.
30. Gaydou, E.M., and Bianchini, J.P. (1975). Kinetics and mechanism of ketophosphonate formation from triethyl

phosphite and aryl substituted α-bromoacetophenones, *J. Chem. Soc., Chem. Commun.*: 541.
31. Koziara, A., Mlotkowska, B., Majewski, P., Sledzinski, B., and Zwierzak, A. (1981). Examination of byproducts formed upon reacting trialkyl phosphites with 2,4-dichlorophenacylidene bromide as a mechanistic probe of the Perkow reaction, *Pol. J. Chem.*, *55*: 399.
32. Zwierzak, A., Sledzinski, B., and Cieslak, L. (1974). The debromination of α-bromo derivatives of 2,4-dichloroacetophenone by diethyl phosphite, *Bull. de L'Acad. Polon. des Sciences (Ser. Chim.)*, *22*: 673.
33. Borowitz, I.J., Parnes, H., Lord, E., and Yee, K.C. (1972). Kinetic and mechanistic studies on the acid catalyzed debromination of α-bromoacetophenones and α-bromopropiophenones with triphenylphosphine in ethanol, *J. Am. Chem. Soc.*, *94*: 6817.
34. Boyce, C.B.C., Webb, S.B., Phillips, L., and Worthington, P.A. (1973). Determination of stereochemictry of vinyl phosphates from proton NMR chemical shifts, *J. Chem. Soc., Perkin Trans. I*: 2881.
35. Gaydou, E.M. (1972). Phosphates d'enols III - stereospecificite de la reaction de Perkow, *Tetrahedron Lett.*: 4473.
36. (a) A nearly completed X-ray crystal structure determination of (36) was done by J. Van Der Veen, deceased August 4, 1986. (b) This structure determination is being completed by P.W.R. Corfield.
37. Galdecki, Z., Glowka, M.L., and Zwierzak, A. (1979). Stereochemistry of the Perkow reaction. Crystal and molecular structure of *O*-[1-(2,4-dichlorophenyl)-2-bromovinyl] *O,O*-dimethyl phosphate, *Phosphorus and Sulfur*, *5*: 299.
38. Rohrbaugh, W.J., and Jacobson, R.A. (1978). Crystal and molecular structure of organophosphorus insecticides. 9. Stirofos, *J. Agric. Food Chem.*, *26*: 1120.
39. Tobey, S.W. (1969). Structure assignments in polysubstituted ethylenes by NMR, *J. Org. Chem.*, *34*: 1281.
40. Yee, K.C., and Bentrude, W.G. (1971). Six-membered ring phosphorus heterocycles. Use of europium shift reagents in the analysis of the PMR spectrum of *trans*-2-methyl-5-*t*-butyl-2-oxo-1,3,2-dioxaphosphorinane, *Tetrahedron Lett.*: 2275.

41. von Ammon, R., and Fischer, R.D. (1972). Shift reagents in NMR spectroscopy, *Angew. Chem., Int. Ed. Engl., 11*: 675.
42. Sanders, J.K.M., and Williams, D.H. (1971). Evidence for contact and pseudo-contact contributions in lanthanide induced ^{31}P NMR shifts, *Tetrahedron Lett.*: 2813.
43. Corfield, J.R., and Trippett, S. (1971). Assignment of configuration to 2,2,3,4,4-pentamethylphosphetan oxides using tris(dipivalomethanato)europium(III), *J. Chem. Soc., Chem. Commun.*: 721.
44. Calogeropoulou, T., Hammond, G.B., and Weimer, D.F. (1987). Synthesis of β-ketophosphonates from vinyl phosphates *via* a 1,3-phosphorus migration, *J. Org. Chem., 52*: 4185.
45. Borowitz, I.J., Casper, E.W.R., Crouch, R.K., and Yee, K.C. (1972). Formation and alkylation of lithium enolates from enol phosphorylated species, *J. Org. Chem., 37*: 3873.
46. Jackson, J.A., Hammond, G.B., and Weimer, D.F. (1989). Synthesis of α-phosphonolactones and esters through a vinyl phosphate-phosphonate rearrangement, *J. Org. Chem., 54*: 4750.
47. Wadsworth, Jr., W.S., and Emmons, W.D. (1961). The utility of phosphonate carbanions in olefin synthesis, *J. Am. Chem. Soc., 83*: 1733.
48. Johnson, A.W. (1966). *Ylid Chemistry*, Academic Press, New York, pp. 203-212.
49. Wadsworth, Jr., W.S. (1977). Synthetic applications of phosphoryl-stabilized anions, *Org. React., 25*: 73.
50. Hudson, R.F. (1965). *Structure and Mechanism in Organophosphorus Chemistry*, Academic Press, New York.
51. Kirby, A.J., and Warren, S.G. (1967). *The Organic Chemistry of Phosphorus*, Elsevier, Amsterdam.
52. Walker, B.J. (1972). *Organophosphorus Chemistry*, Penguin Books, Baltimore, Maryland.
53. Corbridge, D.E.C. (1985). *Phosphorus-Outline of Chemistry, Biochemistry, Technology*, Elsevier, Amsterdam.
54. Bhattacharya, A.K., and Thyagarajan, G. (1981). The Michaelis-Arbuzov rearrangement, *Chem. Rev., 81*: 415.
55. House, H.O. (1972). *Modern Synthetic Reactions (2nd. Ed.)*, Benjamin, Menlo Park, California, pp. 546-570 and

references therein.
56. Carey, F.A., and Sundberg, R.J. (1983). *Advanced Organic Chemistry (2nd. Ed. Part B)*, Plenum Press, New York, pp. 10-26 and references therein.
57. Ireland, R.E., and Pfister, G. (1969). A new method for the synthesis of structurally specific olefins from enolate anions, *Tetrahedron Lett.*: 2145.
58. Kamata, S., Haga, N., Matsui, T., and Nagata, W. (1986). Synthesis of Δ^{11} and Δ^{6} steroids, *Synthesis*: 588.
59. Fetizon, M., Jurion, M., and Nguyen, T.A. (1969). A new synthesis of Δ^{2} steroids, *J. Chem. Soc., Chem. Commun.*: 112.
60. Corey, E.J., and Wright, S.W. (1990). Total synthesis of colneleic acid, *J. Org. Chem.*, *55*: 1670.
61. Blaszczak, L., Winkler, J., and O'Kuhn, S. (1976). A new synthesis of olefins from ketones *via* coupling of lithium dialkylcuprates with diphenyl phosphate esters, *Tetrahedron Lett.*: 4405.
62. Ishihara, T., Yamana, M., and Ando, T. (1983). Organocuprate-induced substitution of the enol oxygen moiety in 2,2-difluoro enol phosphates with alkyl halides: a novel route to *gem*-difluoroolefins from chlorodifluoromethyl ketones, *Tetrahedron Lett.*, *24*: 5657.
63. Claesson, A., Quader, A., and Sahlberg, C. (1983). Allenes and acetylenes. XXVI. Organocuprate reactions of 1,3-alkadien-2-yl phosphates. A new approach to the synthesis of allenes, *Tetrahedron Lett.*, *24*: 1297.
64. Takai, K., Sato, M., and Nozaki, H. (1984). Cross-coupling between enol phosphates and organoaluminum compounds in the presence of palladium(0) catalyst, *Bull. Chem. Soc. Jpn.*, *57*: 108.
65. (a) Kienzle, F., and Rosen, P. (1979). The synthesis and reactions of dialkyl 1-vinylvinyl phosphates, *Helv. Chim. Acta*, *62*: 442; (b) Burri, K.F., Kienzle, F., and Rosen, P. (1977). *U.S. Patent 4,025,584.*
66. Burri, K.F., Kienzle, F., and Rosen, P. (1978). 4-(*O,O*-Dialkyl phosphoryloxy)cyclohex-4-ene-1,2-carboxylic anhydride, *U.S. Patent 4,077,985.*
67. Schroeder, J.P., Braxton Tew, L., and Peters, V.M. (1970). Dehalogenation of vicinal dibromoalkanes with triethyl phosphite, *J. Org. Chem.*, *35*: 3181.

68. Honig, M.L., and Sheer, M.L. (1973). A double Perkow reaction. 1,3-Butadiene-2,3-diol bis(dialkyl phosphate), *J. Org. Chem.*, *38*: 3434.
69. Welch, S.C., Assercq, J.M., and Loh, J.P. (1986). A new reagent for a "one-pot" cyclopentenone annelation, *Tetrahedron Lett.*, *27*: 1115.
70. Welch, S.C., Assercq, J.M. Loh, J.P., and Glase, S.A. (1987). 3-Chloro-2-[(diethoxyphosphoryl)oxy]-1-propene: a new reagent for a "one-pot" cyclopentenone annelation. Synthesis of desoxyallethrolone, *cis*-jasmone, and methyl-eneomycin B, *J. Org. Chem.*, *52*: 1440.
71. Dextraze, P. (1984). Carbapenam derivatives and their intermediate products. *German Patent DE 3,408,347.*
72. Grabowski, E., and Hughes, D.L. (1990). Process for preparing 2-(aminoalkylthio)carbapenams, *U.S. Patent 4,894,450.*
73. Fuentes, L.M. (1989). Process for preparing bis(substi-tutedphenyl)phosphorohalidates useful in the synthesis of carbapenam antibiotics, *U.S. Patent 4,845,251.*
74. Fugami, K., Oshima, K., Utimoto, K., and Nozaki, H. (1986). New syntheses of vinylsilanes and allylsilanes by cross-coupling of $(R_3Si)_3MnMgMe$ with alkenyl and allylic compounds, *Tetrahedron Lett.*, *27*: 2161.
75. Corey, E.J., Reid, J.G., Myers, A.G., and Hahl, R.W. (1987). Simple synthetic route to the limonoid system, *J. Am. Chem. Soc.*, *109*: 918.
76. Fest, C., and Schmidt, K.J. (1983). *Chemistry of Pesticides* (Buchel, K.H., ed., Holmwood, G., trans.), J. Wiley, New York, pp. 48-125.
77. Maier, T., and Heubach, G. (1983). *Pesticide Chemistry Vol. 1* (Miyamoto, J., and Kearney, P.C., eds.), Pergamon Press, Oxford, pp. 45-54.
78. Toy, A.D.F., and Walsh, E.N. (1987). *Phosphorus Chemistry in Everyday Living, 2nd. Ed.*, Amer. Chem. Soc. Monograph, Washington D.C., pp. 313-314.
79. Zwierzak, A., Sledzinski, B., and Cieslak, L. (1974). Some aspects of new insecticidally bromovinyl phosphates, *Proc. Instit. Indust. Org. Chem. Tech. Univ. Lodz*, *6*: 85.
80. Zwierzak, A., Sledzinski, B., and Cieslak, L. (1974). Synthesis of bromfenvinphos, *Proc. Instit. Indust. Org. Chem. Tech. Univ. Lodz*, *6*: 115.
81. Kolodynski, J., Ulaczewski, S., and Witek, S. (1983).

Comparison of biological activity among stereoisomers of enol phosphate insecticides. Mechanism of their action, *Rocz. Nauk Roln., Ser. E, 10*: 210.

82. Bodalski, R., Mikolajczyk, J., Zwierzak, A., Wroblewski, A., Markowicz, W., Koszuk, J., Kluba, M., and Brylikowska-Piotrowicz, J. (1983). Synthesis of new enol phosphates displaying biological activity, *J. Environ. Sci. Health B18 (4&5)*: 579.
83. Malinowski, J., and Kroczynski, J. (1980). Chemical structure and activity of selected groups of enol phosphates with respect to arthropods, *Pestycydy (Warsaw), 3*: 17.
84. D'Silva, T.D.J. (1984). Pesticidal cyano enol phosphates, *U.S. Patent 4,469,688 A*.
85. Zubay, G. (1988). *Biochemistry (2nd. Ed.)*, Macmillan, New York, (a) p. 456; (b) p. 780.
86. Srinivasan, P.R., Katagiri, M., and Sprinson, D.B. (1955). The enzymatic synthesis of shikimic acid from D-erythrose-4-phosphate and phosphoenol pyruvate, *J. Am. Chem. Soc., 77*: 4943.
87. Knowles, J.R. (1983). Chorismate mutase: an enzyme-catalyzed pericyclic reaction, *The Robert A. Welch Foundation Conferences on Chemical Research. XXVII*, Houston, Texas, pp. 149-165 and references therein.
88. Hata, T., and Sekine, M. (1980). Silyl and stannyl esters of phosphorus oxyacids-intermediates for the synthesis of phosphate derivatives of biological interest, *Phosphorus Chemistry Directed Toward Biology*, Stec, W.J., ed.., Pergamon Press, Oxford, pp. 197-212.
89. Meek, S.E., and Pietrzyk, D.J. (1988). Liquid chromaographic separation of phosphorus oxo-acids and other anions with post-column indirect fluorescence detection by aluminum-morin, *Anal. Chem., 60*: 1397.
90. Kluger, R., Chow, J.F., and Croke, J.J. (1984). Phosphoenol pyruvamides. Amide-phosphate interactions in analogues of phosphoenol pyruvate, *J. Am. Chem. Soc., 106*: 4017.
91. Thiem, J., Rasch, D., and Paulsen, H. (1976). Phosphorus containing carbohydrates. XV. Perkow reaction with α-acyloxyketo sugars for the synthesis of enol phosphates and their reactions, *Ber., 109*: 3588.
92. Thiem, J., and Rasch, D. (1976). Synthesis of deoxysugars by Perkow reactions. A new preparation of methyl 4,6-*O*-

benzylidene-2-deoxy-α-D-*erythro*-hexapyranosid-3-ulose, *Synthesis*: 481.
93. Thiem, J., and Rasch, D. (1985). Synthesis and Perkow reaction of uridine derivatives, *Nucleos. Nucleotid.*, *4*: 487.
94. Mitsuo, N., Abe, Y., Takizawa, T., and Kuneida, T. (1980). Telomers and oligomers of vinylene carbonate. Part XIV. Synthetic route to 2-deoxyaldoses by fluoride-catalyzed solvolysis of enol phosphate esters, *Chem. Pharm. Bull.*, *28*: 1327.
95. Sauve, G., Le Berre, N., and Zacharie, B. (1990). Novel modifications of peptides: simple syntheses of difunctionalized enamines, enol ethers, and thioenol ethers from carboxylic acids *via* acylimidazole and enol phosphate intermediates, *J. Org. Chem.*, *55*: 3002.
96. Pearson, R.G., and Songstad, J. (1967). Application of the principle of hard and soft acids and bases to organic chemistry, *J. Am. Chem. Soc.*, *89*: 1827.
97. Ho, T.L. (1977). *Hard and Soft Acids and Bases Principle in Organic Chemistry*, Academic Press, New York.
98. Pearson, R.G. (1989). Absolute electronegativity and hardness. Applications to organic chemistry, *J. Org. Chem.*, *54*: 1423.
99. Pearson, R.G. (1990). Hard and soft acids and bases - the evolution of a chemical concept, *Coord. Chem. Rev.*, *100*: 403.
100. Borowitz, I.J., and Parnes, H. (1967). Kinetics and mechanism of the reaction of triphenylphosphine with α-haloacetophenones, *J. Org. Chem.*, *32*: 3560.
101. Borowitz, I.J., Kirby, K.C., Rusek, P.E., and Casper, E.W.R. (1971). On the mechanism and chirality of enol and ketophosphonium salt formation from the reactions of α-haloketones or α,α-dihaloketones with tertiary phosphines, *J. Org. Chem.*, *36*: 88.
102. Pearson, R., private communication: confirms that phosphites should be harder than phosphines by analogy to calculations on PF_3 *vs.* trimethylphosphine.
103. Borowitz, I.J., and Crouch, R.K. (1973). Comparative reactions of phosphinites, phosphonites, and phosphites with α-haloketones. Further aspects of the Perkow reaction, *Phosphorus*, *2*: 209.

104. Stork, G., and Isobe, M. (1975). A general approach to prostaglandins *via* methylenecyclopentanones. Total synthesis of *rac*-prostaglandin F_{2a}, *J. Am. Chem. Soc.*, *97*: 4745.
105. Sekine, M.T., Nakajima, M., and Hata, T. (1981). Silyl phosphites. 16. Mechanism of the Perkow reaction and the Kukhtin-Ramirez reaction. Elucidation by means of a new type of phosphoryl rearrangement utilizing silyl phosphites, *J. Org. Chem.*, *46*: 4030.
106. Sledzinski, B., and Zwierzak, A. (1977). Stereochemical studies of the reactions between diethyl phosphite and its structural analogs with 2,4-dichlorophenacylidene chloride, *Organika*: 1.
107. Ishihara, T., Yamana, M., Maekawa, T., Kuroboshi, M., and Ando, T. (1988). Selective preparation of 1-substituted 2,2-difluoroethenyl phosphates or 1-hydroxyalkane phosphonates through the reaction of chlorodifluoromethyl ketones with dialkyl or diaryl phosphites, *J. Fluorine Chem.*, *38*: 263.
108. Gaydou, E., Peiffer, G., and Guillemont, A. (1971). Extension de la reaction de Perkow aux composes thiocarbonyl α-halogenes, *Tetrahedron Lett.*: 239.

CHAPTER 4

NONHYDROLYTIC CLEAVAGE OF PHOSPHORUS ESTERS

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I. Introduction

The synthesis of structurally complex organophosphorus compounds (and phosphate partial esters) often requires the removal of ester linkages from phosphorus acid sites while numerous other reactive functionalities are also present. In such syntheses the use of acidic or basic catalyzed hydrolysis is thus at times precluded, and other selective methods of ester removal are needed. It is the intent of this Chapter to present a survey of various methods of selective phosphorus ester cleavage which are of use in these situations. The range of available approaches for phosphorus ester cleavage are reviewed, and exemplary procedures are noted.

II. Hydrogenolysis

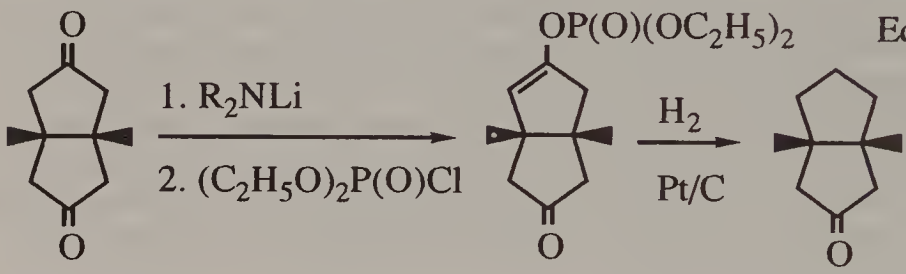
The use of catalytic hydrogenolysis for the selective cleavage of particular phosphorus esters is not new. Numerous early examples of the use of catalytic hydrogenolysis of simple phenyl esters selectively over other phosphorus ester functions and in the presence of a varitey of hydrolytically labile functionalities are available, particularly for the synthesis of phosphate (alkyl) esters which are biological metabolites.[1-5] In certain instances the use of *p*-nitrophenyl esters rather than unsubstituted phenyl provides a more facile overall experimental procedure.[6,7] More recently the hydrogenolysis of phenyl phosphonate esters has been used in the preparation of phosphonic acid analogues of α-amino acids[8] and nucleoside diphosphate carbohydrates,[9] as noted in Chapter 11.

These hydrogenolyses of phenyl esters proceed well using Adams' catalyst (PtO_2), but not palladium based catalysts. Palladium catalysts, such as palladium on charcoal, *are* of use for the hydrogenolysis of benzyl esters of phosphorus acids. This utility was demonstrated in some early syntheses of alkyl phosphate esters[10,11] and more recently in the synthesis of phosphonic acid

analogues and derivatives of α-amino acids.[12,13]

Differences in the relative activities of platinum and palladium catalysts and the lack of activity for alkyl group cleavage has proven useful in the selective removal of protecting benzyl and phenyl groups in numerous syntheses. Of particularl note is the lack of reactivity of phosphorus phenyl esters in the presence of palladium catalysts.[14-17] The selective hydrogenolysis procedure has proven useful in the purification and isolation of monoalkyl esters of phosphonic acids.[18]

Vinylic esters of phosphorus acids also undergo facile hydrogenolysis in the presence of Adams' catalyst. This reaction has been used to advantage in the two-step reduction of a ketone function to a methylene group, as shown in Eqn. 1.[19,20]



Eqn. 1

77 %

The mechanism of hydrogenolysis of phenyl and vinylic esters of phosphorus acids over Adams' catalyst has been investigated.[21,22] The cleavage of both types of esters proceed by initial hydrogenolysis of the C-O bond followed by reduction of the resulting hydrocarbon fragment. When an olefinic linkage is farther removed than the vinylic position, immediate reduction competes with migration into a position subject to hydrogenolysis. Thus, partial hydrogenolysis of diethyl 5-pent-1-enyl phosphate occurs.[22]

III. Cleavage of Benzyl or Aryl Esters with Metals

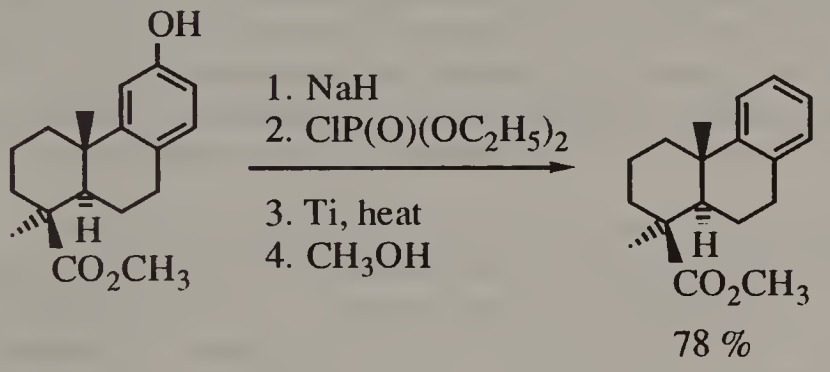
Benzyl and aryl esters of phosphorus esters undergo cleavage of the C-O bond upon treatment with active metals. This approach has been used both for the preparation of alkyl phosphate esters and the deoxygenation of phenols.

Treatment of a dibenzyl alkyl phosphate ester intermediate with sodium in liquid ammonia has been used in the synthesis of pantethine 4'-phosphate for the determination of the structure of

coenzyme A.[23] The use of the same reagent has been demonstrated to be of use in the preparation of aromatic hydrocarbons from phenols[24] and in deoxygenations leading to a series of piscicidal compounds.[25] Sodium amalgam has also been used to accomplish the same type of conversion.[26]

The mechanism of cleavage of aromatic esters of phosphorus acids by electron donating species has been investigated.[27] The reaction takes different pathways depending on the nature of the reducing species. With high concentrations of more powerful reducing agents (sodium in liquid ammonia) C-O bond cleavage dominates. However, with lower concentrations of a less powerful reducing agent, such as sodium naphthalene, P-O bond cleavage occurs.

Another facile two-step approach for the deoxygenation of phenols proceeding in excellent yield involves the use of freshly generated titanium.[28] An example is shown in Eqn. 2.



Eqn. 2

78 %

IV. Electrochemical Cleavage of Esters

The electrochemical cleavage of tribenzyl phosphate to form dibenzyl phosphate has been accomplished in 85% yield.[29] The benzyl ester linkage is removed at a potential (2.87 V relative to SCE) which allows selective removal in the presence of a *N*-carbobenzyloxy function. Thus the approach is seen to be of use in syntheses of phosphonopeptides.

The electrochemical removal of aromatic and vinylic ester linkages has also been noted.[30] With aromatic esters, the C-O bond is cleaved in good yield to form the aromatic hydrocarbon.

V. Ester Cleavage with Alkali Metal Halides

It was early observed that metal halides could be used for the cleavage of benzyl esters of phosphoric acid. A single benzylic ester linkage can be removed selectively from dibenzylic alkyl

phosphates, or from tribenzylic phosphates using sodium iodide or barium iodide.[31] A similar mono-debenzylation was observed with lithium chloride, and a second debenzylation could be accomplished using sodium bromide after conversion of the initial salt to the free acid form.[32] Through the use of this approach with lithium chloride in 2-ethoxyethanol, monobenzyl phosphate could be synthesized in good yield.[33] The removal of a single benzyl ester from each of the two phosphorus sites in tetrabenzyl pyrophosphate was also reported using sodium iodide or calcium iodide.[34]

The selective cleavage of a single benzylic ester linkage of phosphate triesters using alkali metal halides has been used in numerous syntheses. Among these are the synthesis of cortisone-21 phosphate,[11] asymmetrically substituted lecithins,[29,35] and cyclic nucleotides.[36]

In later efforts the cleavage of a single methyl ester from dimethyl phosphates and dimethyl phosphoramides was reported using sodium halides in acetone or acetonitrile.[37-39] Further, a general didealkylation of phosphonate diesters was reported using sodium iodide in dimethylformamide at elevated temperatures.[40] This latter procedure was used for the preparation of the salts of numerous phosphonic acid analogues of natural phosphates.

VI. Alkyl Ester Cleavage with Halogenating Agents

Various halogenating agents have been used for the direct conversion of esters of phosphorus acids to their acid chlorides. The removal of a single alkyl ester from a fully esterified phosphate or phosphonate in the presence of additional reactive functional groups has been reported using phosphorus pentachloride.[41-43] An example of this type of conversion is shown in Eqn. 3.

Eqn. 3

$$(C_2H_5O)_2P(O)(CH_2)_3CO_2C_2H_5 \xrightarrow{PCl_5} C_2H_5OP(O)(Cl)(CH_2)_3CO_2C_2H_5$$

81%

Upon continued exposure to an excess of the phosphorus pentachloride, conversion of a phosphonate diester to the diacid chloride can be accomplished.[44]

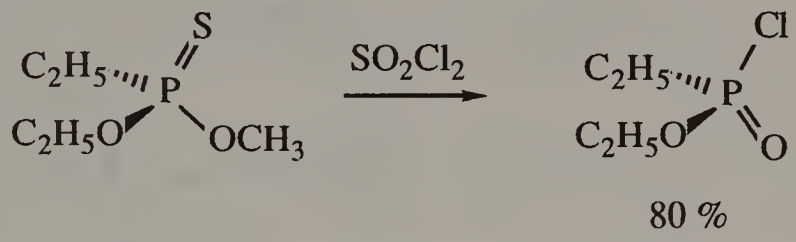
Thionyl chloride reacts preferentially with methyl esters as compared to vinylic esters in the presence of tetramethylammonium

chloride to generate phosphoryl dichlorides, as shown in Eqn. 4.[45]

$$Cl_2C{=}CHOP(OCH_3)_2 \xrightarrow[(CH_3)_4NCl]{SOCl_2} Cl_2C{=}CHOPCl_2 \quad \text{90 \%} \qquad \text{Eqn. 4}$$

Thionyl chloride and phosgene have both been shown to be of use for the removal of both alkyl esters of dialkyl phosphonates to form the phosphonyl dichlorides.[46,47] In some instances the intermediate mono-chloride-mono-ester can be isolated. With mixed esters of thiophosphonic acids, alkyl groups are removed preferentially from the sulfur using either of these reagents.[44]

The reactions of chlorine and sulfuryl chloride with esters of thiophosphate, thiophosphonates, and thiophosphinates have been examined.[48-51] Whether the sulfur is contained as P=S or in an ester linkage, elemental sulfur is formed along with with phosphoryl chloride. With stereogenic phosphorus, the reaction proceeds with retention of configuration at phosphorus, as shown in Eqn. 5.[49] Depending on the substituents at phosphorus, at alternative reaction to form sulfenyl chlorides can occur.



Eqn. 5

80 %

The use of phosphorus oxychloride with phosphonate diesters results in partial mono- and diester cleavage.[52] Obtaining either product in pure form is difficult *via* this procedure. An alternative approach for the conversion of a single ester linkage to the acid chloride involves the treatment of the diester with triphenylphosphinedichloride.[53] An example is shown in Eqn. 6.

$$CH_3P(O)(OCH_3)_2 \xrightarrow[CHCl_3]{(C_6H_5)_3PCl_2} CH_3P(O)OCH_3 \quad | \quad Cl \quad 90\ \% \qquad \text{Eqn. 6}$$

Phosphonyl dichlorides are readily obtained in the pure state

by treatment of the silyl esters of phosphonic acids with phosphorus pentachloride.[54] The formation of silyl esters from alkyl ester is treated extensively in the next section.

VII. Reactions of Silyl Halides with Phosphorus Esters

Alkyl phosphate, phosphonate, and phosphinate esters undergo facile transesterification reactions with silyl halides to form the corresponding silyl esters of the phosphorus acids and alkyl halides. The resulting silyl esters are then subject to cleavage by protic solvents under extremely mild conditions to yield the free phosphorus acids. Overall, the equivalent of hydrolysis of the phosphorus alkyl ester is accomplished, but under conditions much milder than could be used directly with the parent ester.

The seminal work on this process was performed by Rabinowitz[55] who treated a series of dialkyl phosphonates with an excess of trimethylchlorosilane to generate the intermediate bis(trimethylsilyl) esters, and worked-up the reaction by the addition of water or alcohol. The reaction proceeds as illustrated in Fig. 1.

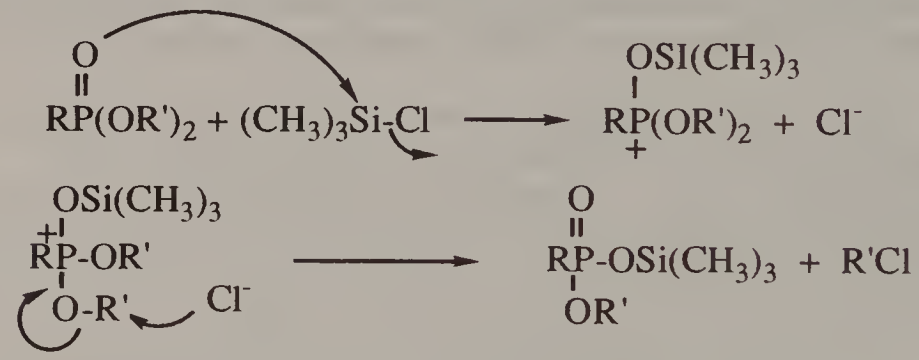


Fig. 1 - Reaction of a dialkyl ester of a phosphonic acid with trimethylchlorosilane followed by work-up with a protic solvent

Water or simple alcohols serve well in the cleavage of the silyl ester linkages, generating a new Si-O bond in the by-product.

For the transesterification steps, the reaction proceeds most

rapidly with methyl esters, and significantly slower with more highly substituted alkyl esters. Aryl esters do not react, and oxy esters react faster than do thiolo esters.[56,57] The particular rapidity of reaction of methyl esters has led to the development of a method for the synthesis of phosphate monoesters.[58] The stereochemistry of the final step of the process, the silyl ester displacement, has been investigated using silyl ester linkages stereogenic at silicon.[59] The reactions of phosphonic and phosphinic silyl esters with water or simple alcohols has thus been shown to proceed predominantly with retention of configuration at silicon.

The general success of the use of trimethylchlorosilane as an agent for the generation of free phosphonic acids from the diesters in the presence of other reactive functional groups[59,60] has led to the development of silyl esters of trivalent phosphorus acids for use in the Michaelis-Arbuzov and other reactions forming the C-P bond. The use of such reagents allows the direct facile formation of the free phosphorus acid after C-P bond generation. The preparation and use of these reagents have been reviewed here (Chapter 7) and elsewhere.[61-64]

The use of trimethylchlorosilane for the cleavage of alkyl ester linkages of dialkyl phosphonates suffers from certain difficulties. In particular, a significant excess of the reagent is required with long reaction times. It has been found that the related reagent, trimethylbromosilane provides the same overall result but with a limited amount of reagent and much shorter reaction times.[65] This reagent has proven to be of use in the dealkylation of numerous types of sensitive dialkyl phosphonates,[66-68] and unsymmetrical phosphates,[57] particularly those related to biological materials.[57,69-74]

Trimethyliodosilane has also been used numerous times to accomplish the ester cleavage of dialkyl phosphonates.[75-82] However, the use of trimethyliodosilane is also attendant with some experimental difficulties. In addition to the increased reactivity of trimethyliodosilane with other functionalities compared to the bromo- and chloro- derivatives, side-reactions occur with the generation of iodine which must be removed from the reaction mixture. An alternative approach uses trimethylchlorosilane in the presence of sodium iodide.[83] This latter method has found use for a variety of systems.[54,84-89] Facilitated reaction has also been reported using trimethylchlorosilane in the presence of catalytic amounts of ammonium chloride and hexamethyldisilazine.[90]

VIII. Pyrolysis of Alkyl Esters

The pyrolysis of alkyl ester linkages from phosphonates has been noted to occur in a facile manner.[91] The decomposition proceeds at lower temperatures and more rapidly with increased branching at the α- and β-positions of the alkyl group. Thus, the order of ease of ester pyrolysis is:

s-Bu > *i*-Pr > *n*-Pr > Et.

The thermal decomposition of the *i*-Pr ester linkage has been used synthetically for the generation of free phosphonic acids *in lieu* of hydrolytic or hydrogenolytic methods.[92]

t-Butyl esters, while not investigated in the early efforts with phosphonates, have been observed to undergo extremely facile thermolysis to generate the free phosphorus acid site with *t*-butyl dialkyl phosphates.[93] In fact, the difficulty in using the *t*-butyl linkage synthetically for the masking of a phosphorus acid site is its extremely facile decomposition.

The thermolysis of alkyl esters of diphenylphosphinic has been investigated and found to lead to olefin formation in nearly quantitative yield.[94] The olefin product distribution indicates that the reaction proceeds *via* a cyclic activated complex rather than a carbocation, and is presumed to involve a concerted elimination.

IX. Other Methods of Ester Cleavage

A. β-Eliminations

Two β-elimination type reactions are noted which are useful as ester cleavage reactions with phosphate and other phosphorus esters. The presence of an electron-withdrawing group, such as a cynao group, at the β-position of an alkyl ester linkage activates the β-hydrogen for removal by base. Treatment of such esters with barium hydroxide leads to the formation of acrylonitrile and the salt of the phosphorus acid, as shown in Fig. 2.[95]

When a halogen is present at the β-position of the ester linkage, treatment with sodium metal results in elimination of an alkene and formation of the sodium salt of the phosphorus acid, as shown in Fig. 3.[96]

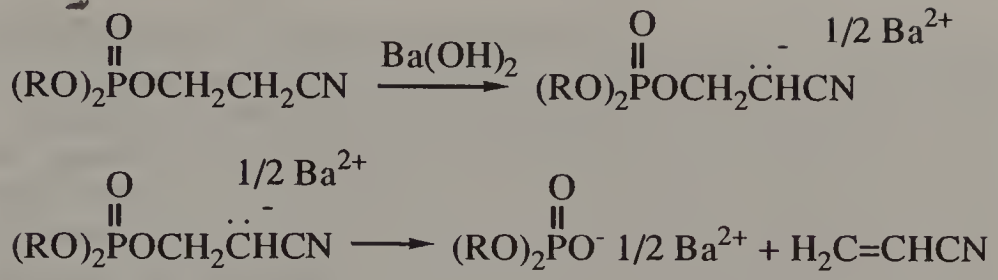


Fig. 2 - Cleavage of a β-cyanoester linkage with base

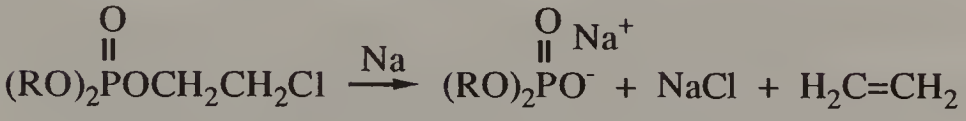


Fig. 3 - Cleavage of a β-chloroester linkage with sodium

B. Displacements of Phosphorus from Carbon

Nucleophilic reagents have been used for direct attack at the α-carbon of phosphorus esters to accomplish a displacement of the phosphorus acid anion. In early work *N*-methylmorpholine was used for the cleavage of benzyl groups from phosphate esters. The quaternary ammonium salt was formed of the mono-debenzylated phosphate.[97] Only benzyl esters could be cleaved in this manner, and only a single benzyl ester was removed from tribenzyl phosphate. Following this work, a series of primary alkyl esters of aryltrichloromethylphosphinic acids were dealkylated using primary or secondary amines.[98] The alkylated amine salts were formed.

With dimethylesters of thiophosphonic acids, it was shown that a single methyl ester linkage could be cleaved by treatment with triethylamine, forming the tetramethylammonium salt of the resulting phosphonate monoester.[99] It was shown that methyl ester linkages could be cleaved selectively using *t*-butylamine, forming the methyl-*t*-butylammonium salt of the parent acid.[100] The selective demethylation reaction by amines was used in the synthesis of a series of unsymmetrical dithiopyrophosphates.[101]

Other nucleophiles, such as triphenylsilyllithium[102] and lithium propanethiolate[103] have also been used for the removal of a single primary or methyl ester linkage from phosphate and phosphonate tri- and diesters. Alkylation of the silicon and sulfur sites respectively occurs in these reactions. In other work

alcohols,[104] phenols,[104] and formic acid[105] effect direct displacement of phosphorus acid anions from carbon alkyl esters with attendant formation of ethers and formate esters respectively.

Selective dealkylation of secondary ester linkages of phosphates and phosphonates occurs under anhydrous conditions using sulfate cation exchange resins.[106] With mixed alkyl esters of phenylphosphonic acid, treatment with Amberlite 200C in benzene medium gives yields of greater than 90% of the monoester product in which a secondary alkyl ester linkage had been removed.

X. Experimental Procedures

A. Cleavage of a Diaryl Alkyl Phosphate to the Alkyl Phosphate Monoester by Catalytic Hydrogenation

(-)-Menthyl dihydrogen phosphate[7] - A solution of (+)-menthyl bis(*p*-nitrophenyl) phosphate (500 mg, 1.05 mmol) in ethanol (100 mL) containing concentrated hydrochloric acid (0.5 mL) is subjected to hydrogenation at atmospheric pressure over platinum oxide catalyst (100 mg). Hydrogen uptake is monitored over a period of 4 hr, after which time the reaction is determined to have gone to completion. The catalyst is removed by filtration and the filtrate is concentrated under reduced pressure. The residue is extracted with water and the remaining syrup is recrystallized from water to yield the (-)-menthyl dihydrogen phosphate (253 mg, 95%) of mp 83-84°.

B. Cleavage of an Aryl Dialkyl Phosphate to the Aromatic Hydrocarbon Using Titanium

p-Cymene[28] - Anhydrous titanium trichloride (0.467 g, 3.03 mmol) is stirred in dry tetrahydrofuran (20 mL) and potassium metal cut in small pieces (0.359 g, 9.21 mg-atoms) is added under argon. The slurry is stirred at reflux until no trace of unreacted potassium is visible. 2-Methyl-5-isopropylphenyl diethyl phosphate (1.264 g, 4.42 mmol) is added, and the mixture is stirred while heating to reflux for 8 hr. The reaction mixture is cooled to 5° and methanol (2 mL) is added. The mixture is filtered through a slug of Celite/silica gel (4:1 w/w) and the filtrate is concentrated under reduced pressure. The residue is distilled to yield *p*-cymene (0.550 g, 93%) of bp 175-177°.

C. Conversion of a Dialkyl Phosphonate to the Alkyl

Phosphonyl Chloride Using PCl_5

Ethyl 4-(*P*-chloro-*P*-ethoxyphosphinoyl)butanoate[43] - To a solution of ethyl 4-(diethoxyphosphinoyl)butanoate (50 g, 0.2 mol) in carbon tetrachloride (500 mL) is added in small portions over a period of 3 hr at 40° phosphorus pentachloride (41.3 g, 0.2 mol). After completion of the addition the mixture is evaporated under reduced pressure and the residue is vacuum distilled to yield the ethyl 4-(*P*-chloro-*P*-ethoxyphosphinoyl)butanoate (39.7 g, 81%) of bp 118°/0.1 Torr.

D. Cleavage of a Dialkyl Phosphonate to the Phosphonic Acid Using Bromotrimethylsilane

Anilinium hydrogen cyanomethylphosphonate[66] - To diethyl cyanomethylphosphonate (1.7 g, 10 mmol) in the absence of solvent is added dropwise with stirring over a period of 1 hr bromotrimethylsilane (3.0 g, 20 mmol). The volatile materials are evaporated under reduced pressure and the residual material is dissolved in ether (50 mL) and the solution is extracted with water (3 x 30 mL). The combined aqueous solution is neutralized by the addition of aniline and concentrated to dryness under reduced pressure to give a solid. The solid is recrystallized from a mixture of methanol/acetone (1:5 v/v) to yield the anilinium hydrogen cyanomethylphosphonate (2.0 g, 97%) of mp 172-174°.

E. Cleavage of a Dialkyl Phosphonate to the Phosphonic Acid Using Chlorotrimethylsilane and Lithium Iodide

Anilinium hydrogen ethoxycarbonylmethylphosphonate[84] - Chlorotrimethylsilane (5.22 g, 48 mmol) is added slowly to a stirred mixture of diethyl ethoxycarbonylmethylphosphonate (4.48 g, 20 mmol) and anhydrous lithium iodide (6.42 g, 48 mmol) in carbon tetrachloride (22,4 mL) under an argon atmosphere at room temperature. The reaction mixture is heated to 50° for 30 min with vigorous stirring. The solid is then filtered and the filtrate is evaporated under reduced pressure. The residue is dissolved in water (20 mL), washed with diethyl ether (4 x 25 mL). and lyophilized to give a solid material. The solid is treated with ethanol (3.5 mL), aniline (3.72 g, 40 mmol) and diethyl ether (60 mL) resulting in the formation of a pale yellow precipitate which is recrystallized from ethanol/ethyl acetate/ diethyl ether to yield the anilinium hydrogen ethoxycarbonylmethylphosphonate (4.74 g,

91%) of mp 133-135°.

XI. Bibliography

1. Baer, E., and Fischer, H.O.L. (1943). Glyceraldehyde 1,3-diphosphate (dimeric), *J. Biol. Chem.*, *150*: 213.
2. Baer, E., and Stanacev, H.C. (1956). Phosphorylethanolamine, *Can. J. Chem.*, *34*: 436.
3. Bevan, T.H., Malkin, T., and Tiplady, J.M. (1957). A new synthesis of phosphatidylserine and the preparation of serine and 2-aminoethyl ("ethanolamine") phosphate esters, *J. Chem. Soc.*: 3086.
4. Ballou, C.E., and Fischer, H.O.L. (1956). The synthesis of dihydroxyacetone phosphate, *J. Am. Chem. Soc.*, *78*: 1659.
5. Maurukas, J., and Holland, C.V. (1961). An improved synthesis of glycerylphosphorylcholine, *J. Org. Chem.*, *26*: 608.
6. Moffatt, J.G., and Khorana, H.G. (1957). Carbodiimides. VII. Tetra-*p*-nitrophenyl pyrophosphate, a new phosphorylating agent, *J. Am. Chem. Soc.*, *79*: 3741.
7. Tagaki, W., and Hashizume, T. (1961). Synthesis and properties of isomeric menthyl phosphates. Organophosphorus compounds. III, *J. Org. Chem.*, *26*: 3038.
8. Lejczak, B., Kafarski, P., and Szewczyk, J. (1982). Transesterification of diphenyl phosphonates using the potassium fluoride/crown ether/alcohol system; Part 2. The use of diphenyl 1-aminoalkanephosphonates in phosphonopeptide synthesis, *Synthesis*: 412.
9. Vaghefi, M.M., Bernacki, R.J., Hennen, W.J., and Robins, R.K. (1987). Synthesis of certain nucleoside methylenediphosphonate sugars as potential inhibitors of glycosyltransferases, *J. Med. Chem.*, *30*: 1391.
10. Miyano, M., and Funahashi, S. (1955). Synthesis of organic phosphorus compounds. I. *p*-Substituted benzyl esters, *J. Am. Chem. Soc.*, *77*: 3522.
11. Cutler, F.A., Conbere, J.P., Lukes, R.M., Fisher, J.F., Mertel, H.E., Hirschmann, R., Chemerda, J.M., Sarett, L.H., and Pfister, K. (1958). Synthesis of cortisone-21 phosphate, *J. Am. Chem. Soc.*, *80*: 6300.
12. Kametani, T., Kigasawa, K., Hiiragi, M., Wakisaka, K., Haga, S., Sugi, H., Tanigawa, K., Suzuki, Y., Fukawa, K., Irino, O., Saita, O., and Yamabe, S. (1981). Studies on the synthesis of chemotherapeutics. Part XI. Synthesis and

antibacterial activities of phosphonopeptides, *Heterocycles*, *16*: 1205.
13. Elliott, R.L., Marks, N., Berg, M.J., and Portoghese, P.S. (1985). Synthesis and biological evaluation of phosphonamidate peptide inhibitors of enkephalinase and angiotensin-converting enzyme, *J. Med. Chem.*, *28*: 1208.
14. Ballou, C.E., and Fischer, H.O.L. (1955). The synthesis of D-glyceraldehyde-3-phosphate, *J. Am. Chem. Soc.*, *77*: 3329.
15. Baer, E., Buchnea, D., and Stancer, H.C. (1959). Synthesis of L-α-glyceryl-L-serine, *J. Am. Chem. Soc.*, *81*: 2166.
16. Engle, T.W., Zon, G., and Egan, W. (1982). ^{31}P NMR kinetic studies of the intra- and intermolecular alkylation chemistry of phosphoramide mustard and cognate *N*-phosphorylated derivatives of *N,N*-bis(2-chloroethyl)amine, *J. Med. Chem.*, *25*: 1347.
17. Yamauchi, K., Ohtsuki, S., and Kinoshita, M. (1984). Synthesis of peptide analogues containing (2-aminoethyl)-phosphonic acid (ciliatine), *J. Org. Chem.*, *49*: 1158.
18. Plenat, F., Ibrahim, S., and Cristau, H.J. (1988). An improved access to phosphonic acids and their mono- and diesters, *Synthesis*: 912.
19. Coates, R.M., Shah, S.K., and Mason, R.W. (1979). Synthesis of gymnomitrol, *J. Am. Chem. Soc.*, *101*: 6767.
20. Coates, R.M., Shah, S.K., and Mason, R.W. (1982). Stereoselective total synthesis of (±)-gymnomitrol *via* reduction-alkylation of α-cyano ketones, *J. Am. Chem. Soc.*, *104*: 2198.
21. Jung, A., and Engel, R. (1975). Catalytic hydrogenolysis-reduction of aryl phosphate esters, *J. Org. Chem.*, *40*: 244.
22. Jung, A., and Engel, R. (1975). Hydrogenolysis of unsaturated phosphate esters, *J. Org. Chem.*, *40*: 3652.
23. Baddiley, J., Thain, E.M., Novelli, G.D., and Lipmann, F. (1953). Structure of coenzyme A, *Nature*, *171*: 76.
24. Pelletier, S.W., and Locke, D.M. (1958). Reduction of polycyclic phenols to hydrocarbons, *J. Org. Chem.*, *23*: 131.
25. Ishii, H., Ishikawa, T., Chen, I.-S., and Lu, S.-T. (1982). New phenyl propanoids having weak piscicidal action and the related compound: wutaiensol, wutaieensal, wutai-aldehyde, and methyl dmethoxywutaiensate, *Tetrahedron*

Lett., *23*: 4345.
26. Welch, S.C., and Kabay, M.C. (1985). Reductive dephosphorylation of (Z)-bis(diethoxyphosphinyl)stilbene to diphenylacetylene, *J. Org. Chem.*, *50*: 136.
27. Shafer, S.J., Closson, W.D., van Dijk, J.M.F., Piepers, O., and Buck, H.M. (1977). On the mechanism of reductive cleavage of aryl phosphates, *J. Am. Chem. Soc.*, *99*: 5118.
28. Welch, S.C., and Walters, M.E. (1978). Reduction of aryl diethyl phosphates with titanium metal: a method for deoxygenation of phenols, *J. Org. Chem.*, *43*: 4797.
29. Mel'nik, S.Y., Mairanovskii, V.G., Miropol'skaya, M.A., and Samokhvalov, G.I. (1968). Studies in the complex lipid field synthesis of (α-stearoyl-β-oleoyl)phosphatidyl-*N*-(glycyl)ethanolamine using electrochemical cleavage of *N*-carbobenzoxy- and *O*-benzyl protective groups, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *38*: 1445.
30. Shono, T., Matsumura, Y., Tsubata, K., and Sugihara, Y. (1979). Electroreductive elimination of phenolic hydroxyl groups and a new synthesis of olivetol, *J. Org. Chem.*, *44*: 4508.
31. Zervas, L., and Dilaris, I. (1955). Dealkylation and debenzylation of triesters of phosphoric acid. Phosphorylation of hydroxy and amino compounds, *J. Am. Chem. Soc.*, *77*: 5354.
32. Miyano, M. (1955). Synthesis of organic phosphorus compounds. II. Exhaustive debenzylation reactions, *J. Am. Chem. Soc.*, *77*: 3524.
33. Smith, M., Moffatt, J.G., and Khorana, H.G. (1958). Carbodiimides. VIII. Observations on the reactions of carbodiimides with acids and some new applications in the synthesis of phosphoric acid esters, *J. Am. Chem. Soc.*, *80*: 6204.
34. Cremlyn, R.J.W., Kenner, G.W., Mather, J., and Todd, A. (1958). Studies on phosphorylation. Part XVI. Iodides as debenzylating and dealkylating agents, *J. Chem. Soc.*: 528.
35. de Haas, G.H., and van Deenen, L.L.M. (1960). Synthesis of a "mixed-acid" α-lecithin, *Tetrahedron Lett.*: 1.
36. Engels, J., and Hoftiezer, J. (1977). Synthese und Eigenschaften von Uridin-3',5'-cyclophosphat-estern, *Ber.*, *110*: 2019.
37. Goldstein, J.A. (1977). *N*-Alkyl (aryl) sulfonylphosphor-

amidate monoesters, *J. Org. Chem.*, *42*: 2466.
38. Petnehazy, L., Szakal, G., and Toke, L. (1983). Mono-Entalkylierung von Phosphonsaure- und Phosphorsaure-estern mittels Halogenid-Ionen unter Phasentransfer-Bedingungen, *Synthesis*: 453.
39. Moschidis, M. (1988). Synthesis of a phosphono analogue of cardiolipin and study of its silicic acid column chromatographic behaviour, *Chem. Phys. Lipids*, *46*: 253.
40. Moffatt, J.G., and Jones, G.H. (1970). Process for the di-dealkylation of phosphonate esters, *U.S. Patent 3,524,846*.
41. Gozman, I.I. (1968). Some new derivatives of 2-butene-2,3-diol cyclophosphoric acid, *Izv. Akad. Nauk S.S.S.R.*: 2362.
42. Yurchenko, R.I., Klepa, T.I., Bobrova, O.B., Yurchenko, A.G., and Pinchuk, A.M. (1981). Phosphorylated adamantanes. II. Adamantyl esters of phosphorous acid in an Arbuzov reaction, *Zh. Obshch. Khim.*, *51*: 786.
43. Hewitt, D.G., and Teese, M.W. (1984). Organophosphorus chemistry. IV. Synthesis and reactions of 2-ethoxy-6-oxo-1,2-azaphosphinane 2-oxide, *Aust. J. Chem.*, *37*: 1631.
44. Pelchowicz, Z. (1961). Organic phosphorus compounds. Part I. The reaction of dialkyl methylphosphonates and methylphosphonothioates with inorganic acid chlorides, *J. Chem. Soc.*: 238.
45. Colby, T.H. (1972). Dihalovinyl phosphorodichloridates, *Ger. Offen. 2,140,298*.
46. Wojtowicz, J.A. (1989). Making methylphosphonic dichloride from dimethyl methylphosphonate and thionyl chloride or phosgene in the presence of metal halide catalysts, *U.S. Patent 4,871,486*.
47. Maier, L. (1990). Organic phosphorus compounds. 90. A convenient one-step synthesis of alkyl- and arylphosphonyl dichlorides, *Phosphorus Sulfur*, *47*: 465.
48. Michalski, J., and Skowronska, A. (1958). Reactions of thiono-esters of phosphorus with halogens and sulphuryl chloride, *Chem. Ind. (London)*: 1199.
49. Michalski, J., Mikolajczak, J., and Skowronska, A. (1978). Chemistry of thiono- and selenophosphoranes. A mechanistic study of chlorination reactions of phosphorus thiono esters >P(S)OR: reactive intermediates and stereochemistry, *J. Am. Chem. Soc.*, *100*: 5386.
50. Krawiecka, B., Michalski, J., and Wojna-Tadeusiak, E. (1986). Reaction of thiolo and seleno esters of phosphorus

acids with halogens. 1. Stereochemical and ^{31}P NMR studies of *S*-methyl *tert*-butylphenylphosphinothioate with elemental chlorine and sulfuryl chloride, *J. Org. Chem.*, *51*: 4201.

51. Skowronska, A., Dembinski, R., Gwara, J., and Michalski, J. (1988). Chlorination reactions of phosphorus thionoesters >P(S)OSiMe$_3$; general synthesis of compounds containing >P(O)SCl functional group, *Phosphorus Sulfur*, *39*: 119.
52. Maier, L. (1973). Organic phosphorus compounds. 59. A new method for the synthesis of phosphonic dichlorides, *Helv. Chim. Acta*, *56*: 492.
53. Ylagan, L., Benjamin, A., Gupta, A., and Engel, R. (1988). Organophosphorus chemistry. Ester-chloride conversion under mild conditions at phosphorus, *Synth. Commun.*, *18*: 285.
54. Morita, T., Okamoto, Y., and Sakurai, H. (1980). A mild and facile synthesis of alkyl- and alkylphosphonyl dichlorides under neutral conditions. Reaction of bis(trimethylsilyl) phosphonates with phosphorus(V) chloride, *Chem. Lett.*: 910.
55. Rabinowitz, R. (1963). The reactions of phosphonic acid esters with acid chlorides. A very mild hydrolytic route, *J. Org. Chem.*, *28*: 2975.
56. Borecka, B., Chojnowski, J., Cypryk, M., Michalski, J., and Zielinska, J. (1979). Synthetic and mechanistic aspects of the reaction of trialkylsilylhalides with thio and seleno esters of phosphorus, *J. Organomet. Chem.*, *171*: 17.
57. Hata, T., Yamada, K., Futatsugi, T., and Sekine, M. (1979). Facile synthesis of unesterified enolphosphates, *Synthesis*: 189.
58. Bittman, R., Rosenthal, A.F., and Vargas, L.A. (1984). Synthesis of phospholipids *via* dimethylphosphoryl chloride, *Chem. Phys. Lipids*, *34*: 201.
59. Wozniak, L., Cypryk, M., Chojnowski, J., and Lanneau, G. (1989). Optically active silyl esters of phosphorus. II. Stereochemistry of reactions with nucleophiles, *Tetrahedron*, *45*: 4403.
60. Sarin, V., Tropp, B.E., and Engel, R. (1977). Isosteres of natural phosphates. 7. The preparation of 5-carboxy-4-hydroxy-4-methylpentyl-1-phosphonic acid, *Tetrahedron Lett.*: 351.
61. Rudinskas, A.J., Hullar, T.L., and Salvador, R.L. (1977).

Phosphonic acid chemistry. 2. Studies on the Arbuzov reaction of 1-bromo-4,4-diethoxy-2-butyne and Rabinowitch method of dealkylation of phosphonate diesters using chloro- and bromotrimethylsilane, *J. Org. Chem.*, *42*: 2771.

62. Engel, R. (1988). *Synthesis of carbon-phosphorus bonds*, CRC Press, Boca Raton, FL.
63. Engel, R. (1988). Phosphorus addition at sp^2 carbon, *Org. React.*, *36*: 175.
64. Wozniak, L., and Chojnowski, J. (1989). Silyl esters of phosphorus - common intermediates in synthesis, *Tetrahedron*, *45*: 2465.
65. McKenna, C.E., Higa, M.T., Cheung, N.H., and McKenna, M.-C. (1977). The facile dealkylation of phosphonic acid dialkyl esters by bromotrimethylsilane, *Tetrahedron Lett.*: 155.
66. Morita, T., Okamoto, Y., and Sakurai, H. (1978). The preparation of phosphonic acids having labile functional groups, *Bull. Chem. Soc. Jpn.*, *51*: 2169.
67. Chojnowski, J., Cypryk, M., and Michalski, J. (1978). The selective displacement of *O*-alkyl by trialkylsilyl in some derivatives of acids of phosphorus, *Synthesis*: 777.
68. Kozhushko, B.N., Lomakina, A.V., Paliichuk, Y.A., and Shokol, V.A. (1983). Optically active α-phosphorylated benzyl isocyanates, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *53*: 1768.
69. Davidson, R.M., and Kenyon, G.L. (1980). Analogues of phosphoenolpyruvate. 4. Syntheses of some new vinyl- and methylene-substituted phosphonate derivatives, *J. Org. Chem.*, *45*: 2698.
70. Lalinde, N., Tropp, B.E., and Engel, R. (1983). Isosteres of natural phosphates. 10. Synthesis of analogues related to glycerol 3-phosphate, *Tetrahedron*, *39*: 2369.
71. Padyukova, N.S., Karpeisky, M.Y., Kolobushkina, L.I., and Mikhailov, N. (1987). A new scheme for the synthesis of 5'- nucleotide phosphonate analogs, *Tetrahedron Lett.*, *28*: 3623.
72. Burton, D.J., and Sprague, L.G. (1988). Preparation of difluorophosphonoacetic acid and its derivatives, *J. Org. Chem.*, *53*: 1523.
73. Chambers, R.D., Jaouhari, R., and O'Hagan, D. (1988). Synthesis of a difluoromethylenephosphonate analogue of glycerol-3-phosphate. A substrate for NADH linked

glycerol-3-phosphate dehydrogenase, *J. Chem. Soc., Chem. Commun.*: 1169.
74. Chambers, R.D., Jaouhari, R., and O'Hagan, D. (1989). Fluorine in enzyme chemistry. Part 2. The preparation of difluoromethylenephosphonate analogues of glycolytic phosphates. Approaching an isosteric and isoelectronic phosphate mimic, *Tetrahedron, 45*: 5101.
75. Zygmunt, J., Kafarski, P., and Mastalerz, P. (1978). Preparation of oxoalkanephosphonic acids, *Synthesis*: 609.
76. Blackburn, G.M., and Ingleson, D. (1978). Specific dealkylation of phosphonate esters using iodotrimethylsilane, *J. Chem. Soc., Chem. Commun.*: 870.
77. Blackburn, G.M., and Ingleson, D. (1980). The dealkylation of phosphate and phosphonate esters by iodotrimethylsilane; a mild and selective procedure, *J. Chem. Soc., Perkin Trans. I*: 1150.
78. Shames, S.L., and Byers, L.D. (1981). Effect of phosphono substituents on acyl transfer reactions, *J. Am. Chem. Soc., 103*: 6177.
79. Shames, S.L., and Byers, L.D. (1981). Acyl substituent effects on rates of acyl transfer to thiolate, hydroxide, and oxy dianions, *J. Am. Chem. Soc., 103*: 6170.
80. Loewus, D.I., and Eckstein, F. (1983). Symmetrical monothiopyrophosphate, *J. Am. Chem. Soc., 105*: 3287.
81. Burton, D.J., Sprague, L.G., Pietrzyk, D.J., and Edelmuth, S.H. (1984). A safe, facile synthesis of difluorophosphonoacetic acid, *J. Org. Chem., 49*: 3437.
82. Vo-Quang, Y., Carbiato, D., Vo-Quang, L., Lacoste, A.-M., Neuzil, E., and Le Goffic, F. (1986). (β-Chloro-α-aminoethyl)phosphonic acids as inhibitors of alanine racemase and D-alanine:D-alanine ligase, *J. Med. Chem., 29*: 148.
83. Morita, T., Okamoto, Y., and Sakurai, H. (1978). A convenient dealkylation of dialkyl phosphonates by chlorotrimethylsilane in the presence of sodium iodide, *Tetrahedron Lett.*: 2523.
84. Machida, Y., Nomoto, S., and Saito, I. (1979). A useful method for the dealkylation of dialkyl phosphonates, *Synth. Commun., 9*: 97.
85. Morita, T., Okamoto, Y., and Sakurai, H. (1981). Dealkylation reaction of acetals, phosphonate, and phosphate esters with chlorotrimethylsilane/metal halide reagent in acetonitrile,

and its application to the synthesis of phosphonic acids and vinyl phosphates, *Bull. Chem. Soc. Jpn.*, *54*: 267.
86. Hakimelahi, G.H., and Just, G. (1982). The synthesis of 4-decarboxy-4-phosphono-*O*-2-isooxazephems, -isopenams and -isooxacephems containing phosphorus at the 3-position, *Helv. Chim. Acta*, *65*: 1359.
87. Maruyama, T., Taira, Z., Horikawa, M., Sato, Y., and Honjo, M. (1983). Synthesis of uracil-5- and adenine-8-phosphonic acids, *Tetrahedron Lett.*, *24*: 2571.
88. Mlotkowska, B., and Markowska, A. (1984). Thiophosphatidsaureester mit C-S-P-Bindung, *Ann.*: 1.
89. Griengl, H., Hayden, W., Penn, G., De Clerq, E., and Rosenwirth, B. (1988). Phosphonoformate and phosphonoacetate derivatives of 5-substituted 2'-deoxyuridines: synthesis and antiviral activity, *J. Med. Chem.*, *31*: 1831.
90. Issleib, K., Balszuweit, A., and Stiebitz, B. (1987). Eine neue einfache Methode zur Entalkylierung von Phosphon- und Phosphinsaureestern, *Z. anorg. allgem. Chem.*, *546*: 147.
91. Canavan, A.E., Dowden, B.F., and Eaborn, C. (1962). The thermal decomposition of dialkyl alkylphosphonates: a new route to alkylphosphonic acids, *J. Chem. Soc.*: 331.
92. Gupta, A., Sacks, K., Khan, S., Tropp, B.E., and Engel, R. (1980). An improved synthesis of vinylic phosphonates from ketones, *Synth. Commun.*, *10*: 299.
93. Jung, A., and Engel, R. unpublished results of this laboratory.
94. Berlin, K.D., and Austin, T.H. (1965). The pyrolysis of alkyl diphenylphosphinates, *J. Org. Chem.*, *30*: 2745.
95. Witzel, H., Mirbach, H., and Dimroth, K. (1960). Synthese von Phosphorsaure-monoestern durch β-Eliminationaus β-Cyanoathyl-phosphaten, *Angew. Chem.*, *72*: 751.
96. Dimroth, K., and Botta, A. (1960). Spaltung von β-Chlorathylestern der Phosphorsaure mit Natrium, *Angew. Chem.*, *72*: 751.
97. Baddiley, J., Clark, V.M., Michalski, J., and Todd, A.R. (1949). Studies on phosphorylation. Part V. The reaction of tertiary bases with esters of phosphorous, phosphoric, and pyrophosphoric acids. A new method of selective debenzylation, *J. Chem. Soc.*: 815.
98. Kharrasova, F.M., Kamai, G.K., Sultanova, R.B., and

Shagidullin, R.R. (1967). Reaction of aryltrichloromethylphosphinic esters with amines, *J. Gen. Chem. U.S.S.R., Engl. Transl., 37*: 2410.
99. Thuong, N.T., and Chabrier, J.-P. (1970). Contribution a l'etude de l'isomerisation des sels des acides thiophosphoriques et thiophosphoniques, *Bull. Soc. Chim. Fr.*: 780.
100. Gray, M.D.M., and Smith, D.J.H. (1980). Selective demethylation of phosphorus esters, *Tetrahedron Lett.*: 859.
101. Lopusinski, A., Michalski, J., and Potrzebowski, M. (1986). Reaction of dialkoxythiophosphoranesulfenyl chlorides with dialkyl phosphites. New stereoselective route to the unsymmetrical tetraalkyl dithiopyrophosphates. Preparation of diastereoisomeric 2-trimethylsiloxy-4-methyl-1,2,3-dioxaphosphorinanes, *Phosphorus Sulfur, 28*: 299.
102. Gilman, H., and Gaj, B.J. (1961). Alkylation of triphenylsilyllithium with trialkyl phosphates, *J. Org. Chem., 26*: 2471.
103. Giannousis, P.P., and Bartlett, P.A. (1987). Phosphorus amino acid analogues as inhibitors of leucine aminopeptidase, *J. Med. Chem., 30*: 1603.
104. Frank, A.W. (1964). Stability of the carbon-phosphorus bond in trichloromethylphosphonate esters. Ether formation in reactions with alcohols and phenols, *J. Org. Chem., 29*: 3706.
105. Lukszo, J., Kowalik, J., and Mastalerz, P. (1978). Advantages of using di(*p*-methylbenzyl) hydrogen phosphite in synthesis of aminophosphonates from aldimines, *Chem. Letters*: 1103.
106. Nitta, Y., and Arakawa, Y. (1986). The selective dealkylation of mixed esters of phosphoric acid and phenylphosphonic acid using cation exchange resin, *Chem. Pharm. Bull., 34*: 3121.

CHAPTER 5

THE REDUCTION OF QUINQUEVALENT PHOSPHORUS TO THE TRIVALENT STATE

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I. Introduction

The major approaches for the formation of carbon to phosphorus bonds involve one of two fundamental types of reaction: the attack of a phosphorus acid derivative (generally a halide or an ester) by an organometallic reagent, or the nucleophilic attack by a trivalent phosphorus site on an electrophilic carbon site. Both of these approaches are attendant with difficulties and limitations. While the organometallic route maintains the original coordination state of the phosphorus reagent, yields are often low and reaction conditions are not convenient. With the nucleophilic attack of phosphorus on electrophilic carbon, aside from the common limitations associated with nucleophilic substitution reactions, the coordination state of the phosphorus is increased. In reaction using a phosphine as the nucleophile, a phosphonium ion with tetracoordination forms. In reactions involving derivatives of trivalent phosphorus acids, a quinquevalent phosphorus results.

A further major difficulty arises with the use of the nucleophilic phosphorus route when more than one bond to carbon is to be introduced at a given phosphorus site, particularly when the two attached carbon-bound groups are not the same. Once a single carbon-phosphorus bond has been introduced, the phosphorus site is no longer suitably disposed for the introduction of a second one. One approach to overcoming this difficulty involves the use of successive attacks by nucleophilic phosphorus on electrophilic carbon, with an intervening reduction of the quinquevalent phosphorus site to the trivalent state.

Several approaches have been developed to accomplish this type of reduction. These include the reaction with a variety of silyl reagents, hydrides, atom transfer reagents, electropositive metals, among others. In this Chapter we will survey the major approaches to the accomplishment of the reduction of quinquevalent

phosphorus to the trivalent state, providing experimental details for those methods of general utility.

II. Hydride Reductions

A. Reduction of Phosphoryl Compounds to Phosphines

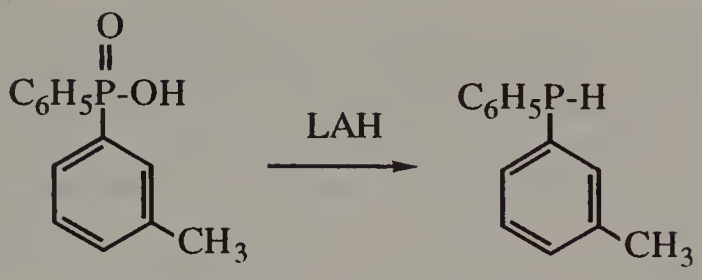
The use of lithium aluminum hydride (LAH) for the conversion of halophosphines to phosphines has been reported in several instances.[1-3] An example is shown in Eqn. 1.[3]

$$(CH_3)_3CPCl_2 \xrightarrow[\text{diglyme}]{LiAlH_4} (CH_3)_3CPH_2 \quad 86\% \qquad \text{Eqn. 1}$$

While this type of reaction does *not* involve a change in the coordination at phosphorus, it does point the way for the use of LAH in the reduction of phosphonyl chlorides to phosphonous acids. After meeting failure in the use of a wide range of common reducing agents for the direct reduction of phosphonic acids to the corresponding phosphonous acids, conversion of the free acid to the corresponding phosphonyl dichloride was accomplished by standard procedures. That resultant acid chloride underwent rapid reduction to phenylphosphine with LAH in ether, as shown in Eqn. 2.[4] Once the primary phosphine has been generated, controlled oxidation leads to the phosphinous and phosphonus acids. This approach has been used successfully as well with other phosphonyl dichlorides.[5,6]

$$C_6H_5P(O)(OH)_2 \xrightarrow{PCl_5} C_6H_5P(O)Cl_2 \xrightarrow[\text{ether}]{LAH} C_6H_5PH_2 \quad 55\% \qquad \text{Eqn. 2}$$

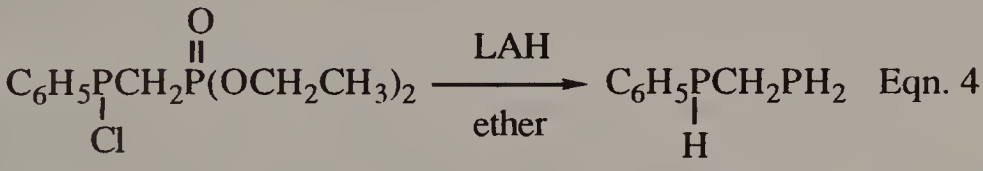
While free phosphonic and phosphinic acids are also subject to reduction to their respective primary and secondary phosphines,[7-9] as illustrated in Eqn. 3,[7] the corresponding reactions proceed in better yield using the chlorides.[4,9]



Eqn. 3

44%

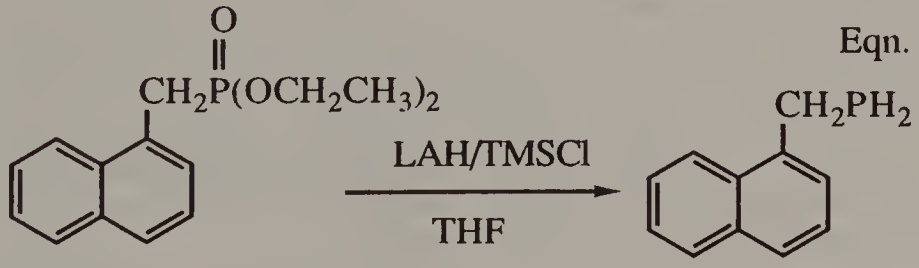
The reduction of phosphonate and phosphinate esters to the respective primary and secondary phosphines has also been accomplished in reasonable yield using LAH in diethyl ether and other ether solvents.[9-20] Of special interest are those examples in which diphosphines are formed,[12,14-18] one of which is shown in Eqn. 4.[12] In this particular reaction a compound containing both chlorophosphine and phosphonate diester linkages is reduced to a diphosphine.



Eqn. 4

34%

The reduction of a phosphonate diester to a primary phosphine has also been accomplished using a mixture of LAH and trimethylchlorosilane in tetrahydrofuran (THF).[21] This reagent mixture presumably generates the more powerful reducing agent $LiCl\text{-}AlH_3$. An example is shown in Eqn. 5.



Eqn. 5

76%

Interestingly, while phosphinic acids, phosphinic chlorides, and phosphinates all undergo reduction and displacement of the electronegative substituent from phosphorus when treated with LAH, phosphinamides undergo reduction but retain the nitrogen-phosphorus bond. Moreover, using a phosphinamide with a stereogenic phosphorus, optical activity due to the phosphorus center is maintained in the trivalent phosphorus amide.[22] In this latter regard the phosphinamides are distinctly different from phosphine oxides, which undergo not only reduction with LAH but also racemization about stereogenic phosphorus.[23,24] It has been demonstrated that the racemization process occurs much more rapidly than does reduction, being virtually complete before significant reduction to the phosphine has occurred.[24]

Vinylic phosphonate diesters are reduced to the primary vinylphosphines by treatment with dichloroalane, prepared from lithium aluminum hydride and aluminum chloride.[25]

The reaction of dialkylboranes with phosphinic acids yields the corresponding secondary phosphines, and with phosphate triesters gives phosphine (PH_3). However, phosphoric acid and free phosphonic acids are not reduced by this reagent.[26]

The reduction of tertiary phosphine oxides to the parent tertiary phosphines is also easily accomplished using LAH.[10,27-29] Similarly, aluminum hydride,[30] calcium aluminum hydride,[28] dialkylboranes,[26,31] sodium hydride,[30] and calcium hydride[32] have been used to accomplish the reduction of tertiary phosphine oxides to tertiary phosphines. While the dialkylborane route provides the best yield of tertiary phosphine from the corresponding oxide, the reaction conditions are less convenient for laboratory work than the other methods.

Asymmetric induction by reduction of racemic tertiary phosphine oxides, stereogenic at phosphorus, using chiral hydride reagents has been attempted. In studies with racemic phospholene oxides using poly[(*S*)-phenylethylamino]alane, the optical purity of the phosphine product varied greatly with the reaction conditions.[33] In later studies using (*S*)-2-(anilinomethyl)-pyrrolidone and acyclic racemic phosphine oxides, the degree of asymmetric induction was low (<7%).[34]

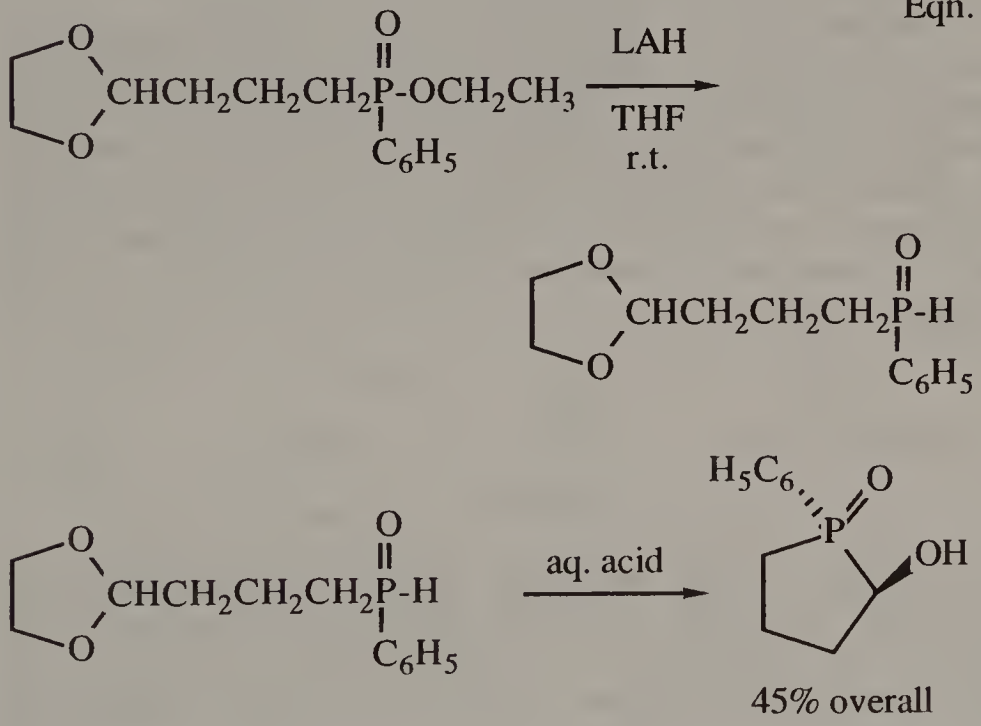
A direct approach to the accomplishment of a synthetic goal stated previously in the Introduction, reduction of a phosphoryl function for further introduction of carbon-phosphorus bonds, has

been reported.[35] The use of sodium bis(2-methoxyethoxy)-aluminum hydride in the presence of alkyl halides allows direct synthesis of tertiary phosphines from phosphonate diesters.

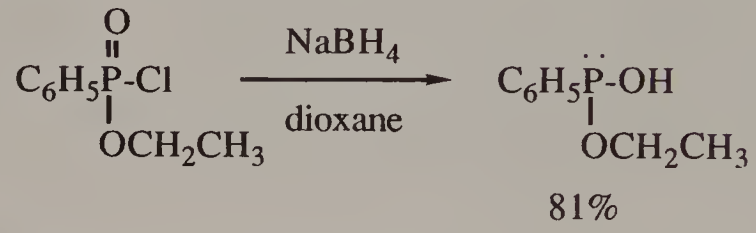
B. Reductions of Phosphoryl Compounds to Trivalent Oxyacids

While the reduction of phosphonate and phosphinate esters to their respective primary and secondary phosphines can be accomplished by heating with LAH in an ether solvent, the process can be interrupted at the intermediate phosphine oxide stage. Maintenance of the reaction mixture at room temperature or below allows isolation of a product in which the ester linkage has been displaced but the phosphoryl oxygen is retained.[35-37] Given the tautomeric equilibrium of quinquevalent and trivalent phosphorus acid forms, this serves the purpose of providing a phosphorus center capable of further alkylation to a tertiary phosphine oxide. An example of this procedure wherein a Pudovik reaction is used for the generation of the tertiary phosphine oxide is shown in Eqn. 6.[35]

Eqn. 6



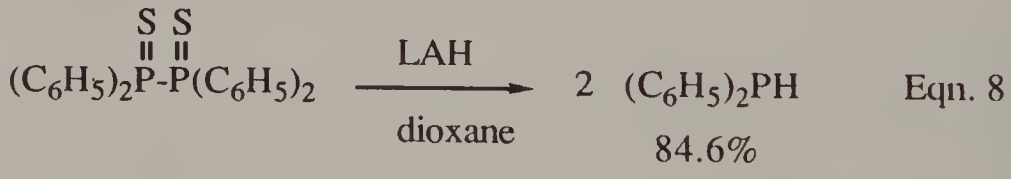
Limited reduction of derivatives of phosphoric and phosphonic acids,[38] and of thiophosphonic acids[39] to phosphorous, phosphonous and thiophosphonous acids respectively is also possible using sodium borohydride. With the acid chloride derivatives of phosphoric or phosphonic acids, reduction is performed with a dispersion of the reducing agent in dioxane, as shown in Eqn. 7.[38] Thiophosphonic acids are converted to the mixed (O) anhydride using trifluoromethanesulfonic anhydride prior to reduction in ethanol solution. When an optically active thiophosphonic acid is used which is stereogenic at phosphorus, reduction occurs with inversion of configuration at phosphorus.[39]



Eqn. 7

C. Reductions of Thiophosphoryl Compounds

Several reports have been made of the reduction of phosphine sulfides to phosphines using LAH.[40-42] The primary work was reported by Issleib and Tzschzch in which fully substituted diphosphine disulfides were reduced to secondary phosphines.[41] An example of this process is shown in Eqn. 8. It is notable that the phosphorus-phosphorus bond is cleaved in this reaction along with reduction of the two phosphine sulfide linkages.



Eqn. 8

When a tertiary phosphine sulfide is used in which the phosphorus is a stereogenic site, the reaction proceeds with retention of configuration for the generation of the tertiary phosphine.[42] Yields of up to 78% have been reported with optical purities of greater than 70%.

D. Reductions of Phosphonium Salts

Quaternary phosphonium salts also undergo reduction with LAH involving the cleavage of a carbon-phosphorus bond. With mixed aryl/alkyl quaternary phosphonium bromides, an aryl carbon-phosphorus bond undergoes preferential cleavage to yield the phosphine in moderate yield, as shown in Eqn. 9.[43] In a study using a series of mixed aryl/benzyl/vinylic diphosphines, it was found that the facilities for cleavage of each of the three types of carbon-phosphorus bonds were competitive.[44] Benzyl groups are cleaved from phosphorus preferentially to other alkyl groups.[45]

Eqn. 9

$$CH_3CH_2CH_2CH_2\overset{+}{P}(C_6H_5)_3\ Br^- \xrightarrow[THF]{LAH} CH_3CH_2CH_2CH_2P(C_6H_5)_2 \quad 54\%$$

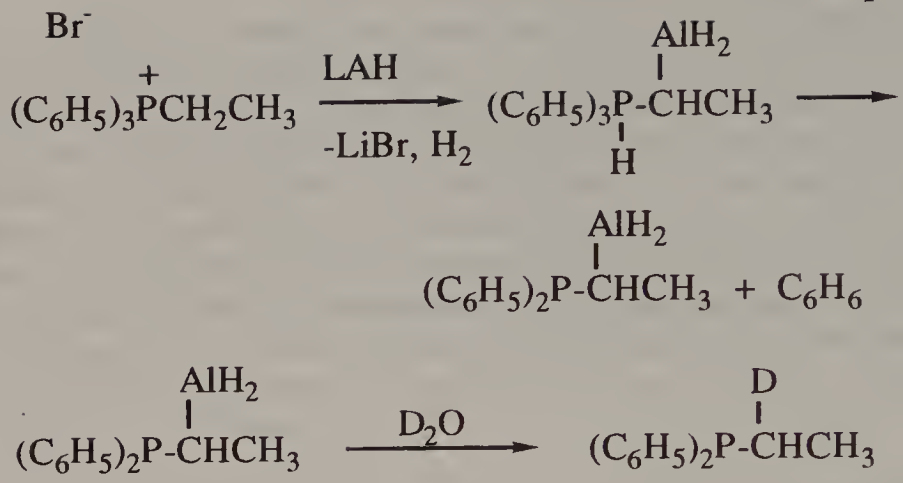
E. Reductions of Phosphinealkylidenes

Triarylphosphinealkylidenes (Wittig reagents) also undergo reduction/cleavage when treated with LAH. The reaction, first reported by Saunders and Burchman,[46] was further studied by Gough and Trippett,[43] and mechanistic investigations were reported by Makhaev and Borisov.[47] The reaction involves cleavage of an aryl ring from phosphorus as the arene, producing the free diarylalkylphosphine in moderate to good yield. An example is shown in Eqn. 10.[47]

$$(C_6H_5)_3P{=}CH_2 \xrightarrow[\text{aq. work-up}]{\text{LAH/dioxane}} (C_6H_5)_2PCH_3 + C_6H_6 \quad 79\% \qquad \text{Eqn. 10}$$

The reductions of quaternary phosphonium salts and triarylphosphinealkylidenes are mechanistically related. The reaction presumably involves addition of the tetrahydroaluminate across the ylide, followed by elision of the arene forming an intermediate alkylaluminum species which yields the diarylalkylphosphine upon aqueous work-up, as shown in Eqn. 11.[47]

Eqn. 11



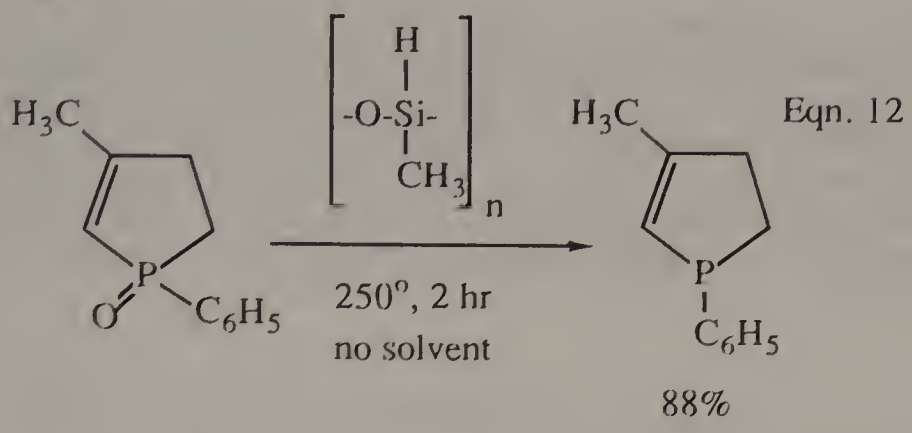
F. Reductions of Dihalophosphoranes

Tertiary phosphine oxides readily undergo conversion to the dihalophosphoranes upon reaction with either phosphorus pentachloride[48] or phosgene.[49] Once the phosphoryl oxygen has been removed in this manner, the quinquevalent phosphorus is subject to facile reduction using lithium aluminum hydride.[48,50]

III. Silane Reductions

A. Introduction

Initially mediocre yields in the reduction of tertiary phosphine oxides to tertiary phosphines using hydride reagents prompted the investigation of other reagents to accomplish this conversion.[32] Significantly improved yields were obtained upon heating the tertiary phosphine oxide with methylpolysiloxane, phenylsilane, diphenylsilane, or triphenylsilane. Methylpolysiloxane was found to be particularly useful when certain other functionalities, such as a free amino group, were present.[51] Further synthetic applications of the phenylsilanes have been described for the preparation of cyclic phosphines,[52,53] and tertiary phosphines containing as well a secondary amine function.[53] A typical example using methylpolysiloxane is shown in Eqn. 12.[32]



Eqn. 12

Similarly, these reagents also proved to be of use for the preparation of primary phosphines from the corresponding dialkyl phosphonates, and secondary phosphines from phosphinic acids and their derivatives.[55] An example of the preparation of dibutylphosphine using diphenylsilane is shown in Eqn. 13.

Eqn. 13

$$(CH_3CH_2CH_2CH_2)_2\overset{\overset{O}{\|}}{P}\text{-Cl} \xrightarrow[250^\circ,\ 3\ hr]{(C_6H_5)_2SiH_2} (CH_3CH_2CH_2CH_2)_2PH$$

In this early work employing silicon centered reagents, the use of trichlorosilane was also explored as a reducing agent.[55] The yields with trichlorosilane were overall significantly lower than with methylpolysiolxane or the phenylsilanes. However, trichlorosilane and hexachlorodisilane, because of the relatively mild conditions under which they can be used, have become standard reagents for accomplishing the reduction of quinquevalent to trivalent phosphorus. In the following sections we will survey this use of these silyl halide reagents.

B. Reductions with Halosilanes

1. Trichlorosilane

Subsequent to the initial investigations using trichlorosilane mentioned previously, modifications in the reaction conditions were found to result in the reduction of tertiary phosphine oxides to

tertiary phosphines in high yield.[56] Either the use of a two-equivalent amount of the trichlorosilane, or the addition of an equivalent amount of a tertiary amine, such as pyridine or triethylamine, allows the reagent to be used for high-yield reduction. This provides a greatly simplified method for the reduction of tertiary phosphine oxides to the tertiary phosphine. An example is shown in Eqn. 14 in which triethylamine is used as an adjunct.[56]

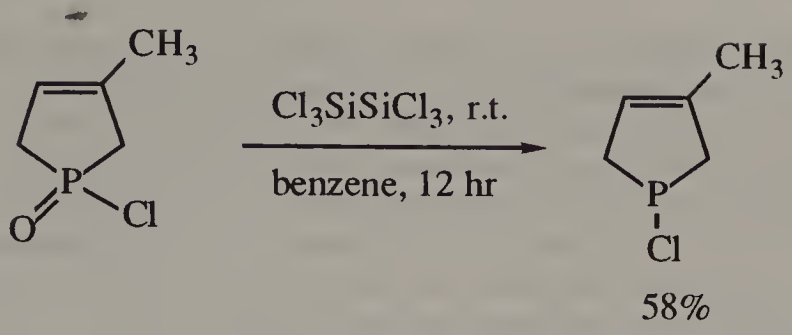
Eqn. 14

$$(CH_3CH_2CH_2CH_2)_3P{=}O \xrightarrow[(CH_3CH_2)_3N \\ \text{heat, 2 hr}]{Cl_3SiH,\ C_6H_6} (CH_3CH_2CH_2CH_2)_3P \quad 92\%$$

Following efforts demonstrated the versatility of the trichlorosilane reduction system, not only for monofunctional phosphine oxides,[57] but also in the presence of other sensitive functional groups, such as ethers,[29,30,58] alkynes,[59] and ketones.[60] This approach has also been of use in the synthesis of substituted phosphetanes,[61,63] diazaphospholenes,[63] phospholanes,[64] phospholes,[65-69] and phosphorines[68,70] in good yield from the corresponding oxides.

2. Hexachlorodisilane

In addition to compounds containing the Si-H bond, those with a Si-Si linkage were also found to be of use in the reduction of phosphine oxides to phosphines. Initially, a series of perchloropolysilanes were reported to be of use for this conversion, although the simplest and most readily available, hexachlorodisilane, has been the material exploited for synthetic purposes.[60] In addition to its use with acyclic phosphine oxides,[71-73] hexachlorodisilane has been used in the preparation of phosphatanes,[74] phospholenes,[75] and polyphosphines[76] from the corresponding oxides. It is also useful for desulfurization of phosphine sulfides to generate the phosphines.[77,78] An example of the use of this reagent with a 1-chlorophospholene oxide (the acid chloride of a phosphinic acid) is illustrated in Eqn. 15.[75]



58%

Eqn. 15

C. Stereochemistry

The stereochemistry of the silane reduction has been investigated with several reagent systems and a variety of substrates. There have been reported variable results, depending on both the reagent system and the nature of the substrate.

Initial studies using trichlorosilane indicated the reduction to be stereoselective, albeit with different stereochemical outcomes depending on the reaction conditions used.[79] Using trichlorosilane alone, the reaction proceeded with predominantly retention (net 33-87%) of configuration at phosphorus. However, when base was used with the trichlorosilane, the stereochemical outcome depended on the specific base used; retention of configuration at phosphorus predominated when pyridine or *N*,*N*-diethylaniline was used (net 55-83%), but inversion occurred when triethylamine was the base (net 70-93%). Similar results dependent on the reaction conditions have been obtained in other efforts using trichlorosilane in conjunction with triethylamine[61,63,64] and pyridine.[80,81] One effort using trichlorosilane in the absence of any added base produced non-stereospecific reduction, actually a result of induced equilibration about the resultant phosphorus center owing to the presence of free hydrogen chloride in the reaction system.[82]

Further investigation of the reaction using added base with the trichlorosilane indicated that the stereochemical course depended on the *strength* of the base used.[82] For all tertiary amines, initial complex formation occurs with trichlorosilane. However, for the *stronger* bases such as triethylamine, the initial complex rapidly undergoes decomposition forming a mixture of chlorosilane species and triethylammonium ion.[72,83] With a weaker base, such as pyridine, the complex with trichlorosilane is stable in solution at the temperature used.

Reductions involving the pyridine complex of trichlorosilane are postulated to involve the attack of silicon on the phosphoryl oxygen to form a hexacoordinated silicon intermediate, which then breaks down to a phosphine, as shown in Fig. 1.[80] The tertiary phosphine thus generated forms with retention of configuration at phosphorus. This route is precluded for those reactions in which triethylamine is used as the adjunct reagent, owing to the fact that neither trichlorosilane nor a simple complex of it is present.

When a phosphine oxide bearing the phosphorus in an angle-contracted ring is reduced using the trichlorosilane alone, the stereochemical outcome is not readily predicted. Depending on the compound used, retention or inversion of configuration about phosphorus may result.[80,84] These complications are avoided using the pyridine-trichlorosilane complex.

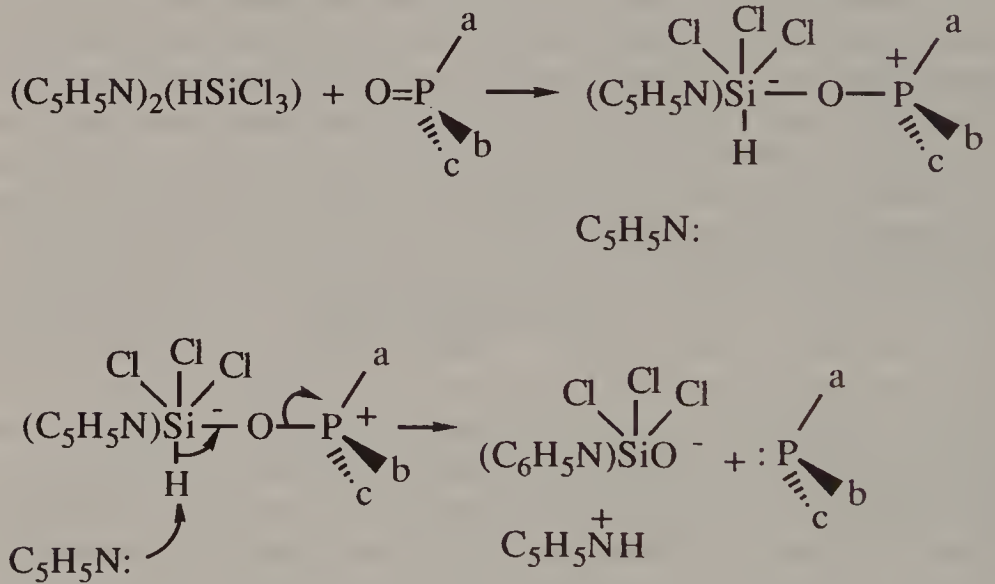


Fig. 1 - Reduction of a phosphine oxide with retention of configuration at phosphorus using trichlorosilane-pyridine

Reduction of quinquevalent phosphorus to phosphines using hexachlorodisilane also exhibits different stereochemical characteristics depending on the quinquevalent phosphorus species involved. With acyclic phosphine oxides, reduction is reported to occur stereoselectively with predominant *inversion* of configuration at phosphorus.[72,85,86] However, with phosphetane oxides[74] and with acyclic phosphine sulfides[77] reaction occurs with *retention* of

configuration at phosphorus.

Chiral alkoxycarbonylphosphonate diesters have been reported to undergo cleavage and reduction to dialkyl phosphites with retention of configuration at stereogenic phosphrus using trimethylchlorosilane in the presence of acetylacetone and zinc powder.[87]

Reductions of phosphine oxides using phenylsilane have been reported to proceed stereoselectively with retention of configuration at phosphorus,[52,53,63,88,89] although the reduction of phosphetane oxides has been reported to proceed non-stereospecifically with this reagent.[90]

If stereochemistry is *not* a matter of concern in the reduction of a particular phosphine oxide to the correpsonding phosphine, a convenient approach involves the use of a mixture of silyl reagents. The use of the high boiling residue from the industrial preparation of methylchlorosilanes has been proposed as an inexpensive and convenient reagent for this reduction.[91]

IV. Abstraction Reactions

A. Thiophosphoryl Sulfur Abstractions by Phosphorus Reagents

In some instances the reduction of a quinquevalent phosphine sulfide *via* abstraction of sulfur using another lower valent phosphorus reagent has been found to be of synthetic utility. Several diphosphines, of utility as chelating agents, were prepared from the corresponding diphosphine disulfides by treatment with a 15% excess of tributylphosphine, tributylphosphine sulfide being formed as the reaction by-product.[92] An example is shown in Eqn. 16.

Eqn. 16

$$(CH_3)_2P(S)CH_2CH_2P(S)(CH_3)_2 \xrightarrow[245^\circ]{(C_4H_9)_3P} (CH_3)_2PCH_2CH_2P(CH_3)_2 \quad 78\%$$

This reaction, which is really an equilibrium between reduced and oxidized forms of two phosphine species, is pushed to the desired end by distillation of the target material from the reaction mixture.

This approach has been used for the desulfurization of a variety of thiophosphoryl halides using as the sulfur abstraction reagent tributylphosphine,[93] phenyldichlorophosphine,[94] and triphenyl phosphite.[95] Yields in the range 60-85% are common using a small (15%) excess of the sulfur abstraction agent.

An attempt was made to accomplish stereospecific sulfur abstraction from a chiral ester of a dithiophosphinic acid using tribuylphosphine.[96] Although the sulfur abstraction reaction went to completion in 1 hour at 170°, or 12 hours at 90°, the isolated product was racemic. The racemization of the product phosphine occurred presumably *via* thermal inversion at the reaction temperatures used.

A desulfurization of a tertiary aromatic phosphine sulfide has been reported upon treatment with acid, in the presence or absence of additional triphenylphospine.[97]

B. Abstraction of Halogen from Halogenated Phosphoranes

As noted previously, upon reaction with phosphorus pentachloride or phosgene, tertiary phosphine oxides are readily converted to dichlorophosphoranes.[48,49,98] Several reagents have been found to serve functionally as abstractors of the elements of a halogen molecule from these materials to generate the free tertiary phosphine. With more highly halogenated phosphoranes, halophosphines are generated.

Initial efforts in this regard were performed upon alkyltetrachlorophosphoranes, generated in the reaction of phosphorus pentachloride with alkenes, and used elemental phosphorus in the presence of small amounts of iodine as the reducing agent.[99,100] Although the formation of the alkyltetrachlorophosphoranes proceeded in only relatively low yields, the halogen abstraction step was quite efficient. An example is shown in Eqn. 17.[99]

$$C_6H_5PCl_4 \xrightarrow[I_2,\ 0\text{-}20^\circ,\ CS_2]{P} C_6H_5PCl_2 \qquad \text{Eqn. 17}$$

95%

This approach using elemental phosphorus abstraction of the

elements of a halogen molecule from halophosphoranes was also noted later by other workers.[49,100]

Trivalent phosphorus reagents have also been used for this halogen removal reaction. These reactions involve fundamentally the displacement of an equilibrium involving a pair of trivalent phosphorus compounds and their corresponding halophosphoranes toward the side of the desired free trivalent phosphorus compound. The preparation of alkyldichlorophosphines from the corresponding alkyltetrachlorophosphoranes has been accomplished using methyl phosphorodichloridite,[101] triphenylphosphine,[75,102,103] and the anion of diethyl phosphite.[103] Phenyldiethylphosphine has been used for the generation of a free tertiary aromatic phosphine from its triaryldichlorophosphorane derivative.[105]

Other reagents used for the removal of halogen from halophosphoranes to generate phosphonous dichlorides and tertiary phosphines include ethyl nitrite[106] and thiols in the presence of tertiary amines.[107]

C. Other Abstraction Reactions

In addition to sulfur abstraction reactions of thiophosphoryl compounds, quasiphosphonium salts of the general type $[R_3PXR']^+[CF_3SO_3]^-$, where X is sulfur or selenium, undergo reaction with tris(dimethylamino)phosphine to form the phosphine, R_3P.[108] The reaction proceeds in good yield (76-80%) with a high stereoselectivity (79-82% retention of configuration) at phosphorus. The quasiphosphonium salts are available from the parent phosphine sulfides or phosphine selenides by reaction with methyl triflate. A similar reaction occurs with the quasiphosphonium salts of the type $[R_2P(OR')SR'']^+[CF_3SO_3]^-$ using alkyl sulfide salts to form alkyl phosphinites with retention of stereochemistry at phosphorus.[109]

A disproportionation reaction, which overall amounts to an oxygen abstraction process, has been observed to provide a conversion of secondary phosphine oxides to secondary phosphines.[110] Upon treatment of the secondary phosphine oxide with sodium hydroxide, both the secondary phosphine and a phosphinic acid are produced. A similar disproportionation has been reported in which the reaction is initiated by reaction of the secondary phosphine oxide with carbon tetrachloride.[111] The

reaction of di-1-octylphosphine oxide is shown in Eqn. 18.[110]

Eqn. 18

$$2\,(C_8H_{17})_2POH \xrightarrow{NaOH} (C_8H_{17})_2PH + (C_8H_{17})_2PO_2H$$

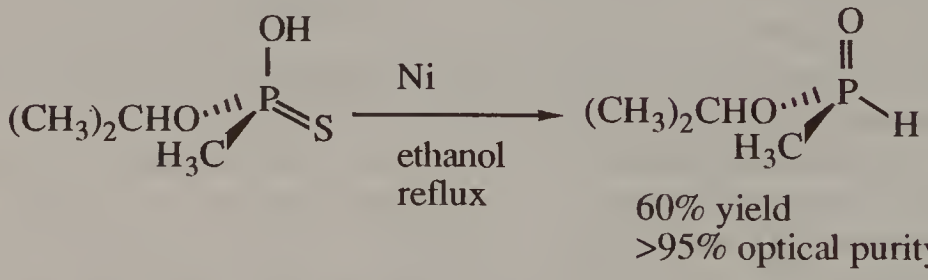
68%

V. The Use of Electropositive Metals

A. Nickel

Nickel, with its known ability to abstract sulfur from a variety of organic compounds,[112] is an obvious candidate for the conversion of phosphine sulfides and related quinquevalent phosphorus compounds to the trivalent state. The use of Raney nickel for the desulfurization of O-alkyl monoesters of thiophosphonic acids to generate phosphonite monoesters has been studied.[113,114] The reaction proceeds in a highly stereoselective manner, and in moderate yield with retention of configuration at stereogenic phosphorus. Care must be taken with the products, as racemization occurs readily in the presence of trace amounts of base. Raney nickel has also been used for the desulfurization of tertiary phosphine sulfides, species which are readily available from the corresponding phosphine oxides by treatment with P_2S_5.[115,116] An example is shown in Eqn. 19.[113]

Eqn. 19



Raney nickel has also been used for the removal of selenium from an O-alkyl monoester of a selenophosphonic acid, again with a high degree of retention of configuration at stereogenic

phosphorus in the formation of the phosphonite monoester.[117]

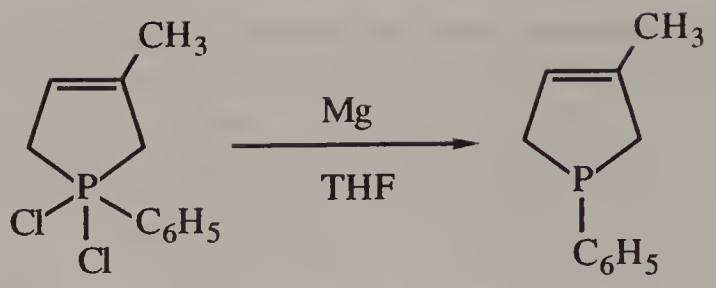
Several reports have also been made regarding the use of nickelocene for the desulfurization of tertiary phosphine sulfides.[118-120] Upon treatment of the phosphine sulfide with nickelocene and a primary alkyl iodide, an intermediate complex is formed which may be purified or decomposed directly to the tertiary phosphine by the addition of one of several reagents, including trimethyl phosphite and methanol. With this approach, a phosphinate ester has been reduced to the corresponding phosphinite ester without cleavage of the ester linkage, after exchange of sulfur for oxygen using P_2S_5.[121] The desulfurization proceeds with a high degree of stereoselectivity, the configuration at stereogenic phosphorus being retained.

B. Iron

In several instances it has been noted that metallic iron can be used efficiently for the removal of sulfur from tertiary phosphine sulfides. Heating (>250^o) triaryl- or trialkylphosphine sulfides with iron filings for several hours yields the tertiary phosphine in good yield.[122-124] When diphenylphosphine sulfide is treated in this manner, a disproportionation reaction of the resulting secondary phosphine occurs to form triphenylphosphine at the high temperature used. With diisobutylphosphine sulfide, however, the secondary phosphine product can be isolated by distillation from the reaction mixture as it is formed.[122]

C. Magnesium

Activated magnesium metal has proven to be of use for the preparation of P-substituted phospholenes from the corresponding dichlorophosphoranes,[125-129] as well as for the related preparation of aryldichlorophosphines from the corresponding aryltrichlorophosphonium tetrafluoroborate species.[130] Yields in these reaction were only moderate, ranging from as low as 10% to as high as 73% for the reported systems. An example is shown in Eqn. 20.[126]



Eqn. 20

39%

In one report, the use of magnesium metal for the reduction of a phosphine oxide and a phosphinate ester has been described.[131] The quinquevalent phosphorus compound is first treated with triethyloxonium tetrafluoroborate to generate an intermediate quasiphosphonium ion, which is subsequently treated with magnesium metal. The trivalent phosphorus products are isolated in moderate yield.

Magnesium in the form Mg-$(C_5H_5)_2TiCl_2$ has also been used for the reduction of tertiary phosphine oxides to the tertiary phosphine.[132] The simple reduction is successful only if at least one aryl carbon-phosphorus bond is present in the phosphine oxide. A 70% yield of triphenylphosphine is obtained with this reagent starting with triphenylphosphine oxide.

D. Alkali Metals

An early attempt at the reduction of a tertiary phosphine oxide to the tertiary phosphine involved initial treatment with phosphorus pentachloride to generate the dichlorophosphorane, followed by reaction with sodium amalgam.[133] Although the product triethylphosphine is described, no yield is given for the process. Much later efforts toward the accomplishment of the overall conversion of tertiary phosphine oxides to tertiary phosphines used sodium dispersed in toluene rather than the amalgam, yielding the free phosphine in good yield.[134] Attempts to use sodium metal dispersed in toluene directly with the parent tertiary phosphine oxide resulted in cleavage of a carbon-phosphorus bond and the formation of a phosphinic acid upon work-up.[135] However, the reduction of tertiary phosphine sulfides to tertiary phosphines has been accomplished using sodium naphthalenide.[123,124,133] An example of successful reduction is shown in Eqn. 21.[134]

$$(C_8H_{17})_3PCl_2 \xrightarrow[\text{toluene}]{\text{Na}} \underset{69\%}{(C_8H_{17})_3P} \qquad \text{Eqn. 21}$$

With phosphonium ions and quasiphosphonium ions, reduction and cleavage of a substituent from phosphorus occurs using either sodium dispersed in toluene,[135] or sodium in liquid ammonia.[136] With the latter reaction system, selective cleavage of differentially substitued nitrogen ligands at phosphorus is attained.

The use of potassium metal in THF in the presence of 18-crown-6 was also investigated for the reduction of tertiary phosphine sulfides.[137] The mechanism, involving radical anion formation, was compared to the reaction accomplished in an electrochemical approach.

E. Miscellaneous Metal-centered Systems

The reduction of dihalophosphoranes to tertiary phosphines using aluminum metal has been described.[138] The reaction proceeds in moderate yield (55-60%) in the presence of aluminum chloride and potassium chloride. An example is shown in Eqn. 22.

$$(CH_3)_2P(CH_2CH_3)Cl_2 \xrightarrow[\text{heat to fusion}]{\text{Al, AlCl}_3\text{, KCl}} \underset{57\%}{(CH_3)_2PCH_2CH_3} \qquad \text{Eqn. 22}$$

Carbanionic organometallic reagents have been found to react with dihalophosphoranes and with tertiary phosphine oxides to yield tertiary phosphines. Both organolithium and Grignard reagents react with dihalophosphoranes to yield as the major product tertiary phosphines.[139] In addition, there is formed as a minor product the quaternary phosphonium halide. An example is shown in Eqn. 23. A similar overall process has been observed starting with tertiary phosphine sulfides and organolithium reagents.[140]

$$(C_6H_5)_3PCl_2 \xrightarrow[\text{ether}]{C_6H_5MgBr} \underset{90\%}{(C_6H_5)_3P} + \underset{7\%}{(C_6H_5)_4\overset{+}{P}\ I^-} \qquad \text{Eqn. 23}$$

Further, triaryl thiophosphates have been reducted to the triaryl phosphites in good yield using trimethyltinhydride.[141] The reaction occurs thermally with trimethyltin radical intermediates serving as the sulfur abstraction species.

VI. Hydrogenolysis

The use of hydrogenolysis for the conversion of quinquevalent phosphorus to the trivalent state has been explored to only a limited extent. In an attempt to develop an industrially feasible process for the regeneration of tertiary phosphines from their oxides, a reaction system has been developed for the conversion of the tertiary phosphine oxide into the dichlorophosphorane using chlorine and carbon monoxide.[142] The dichlorophospohranes undergo hydrogenolysis in pyridine solution in the absence of a catalyst at 160° and 98 atmospheres pressure of hydrogen to give the tertiary phosphines in excellent yield (86-91%).[143] Without the basic solvent, yields of the phosphine are considerably lower. An example of the overall conversion is shown in Eqn. 24.[142]

Eqn. 24

$$(C_4H_9)_3P{=}O \xrightarrow[1\text{hr, } 60^\circ]{CO,\ Cl_2} (C_4H_9)_3PCl_2 \xrightarrow[2\text{ hrs}]{H_2,\ 180^\circ} (C_4H_9)_3P$$

94% 90%

VII. Electrochemical Reduction

A. Quaternary Phosphonium Salts

Early studies of the cathodic reduction of asymmetrically substituted quaternary phosphonium salts demonstrated that the reaction proceeds with selective cleavage of a benzyl group (compared to other alkyl or aryl groups) from phosphorus to generate the tertiary phosphine.[144] Reaction proceeds in reasonable yield (71-91%), and may be used for preparative purposes. With the phosphorus center being stereogenic, reaction occurs to generate the chiral tertiary phosphine with retention of configuration at phosphorus.

Later efforts also demonstrated that the cathodic reduction occurs with retention of configuration at phosphorus, and that *t*-butyl groups could be cleaved selectively as well relative to ordinary alkyl and phenyl groups.[145] Further investigations using a series of quasiphosphonium ions allowed a more complete description to be made of the relative tendencies of various groups to be cleaved from phosphorus.[146]

B. Phosphoryl Compounds

The electrochemical behavior of compounds of the general structure $R_3P{=}X$, where X = O, S, or Se, has been reported.[147,148] While the reports do not describe preparative techniques for the synthesis of tertiary phosphines from the starting quinquevalent phosphorus compounds, the formation of tertiary phosphines in two one-electron steps from the satrting materials is established. It is anticipated that this approach should be productive for the preparative synthesis of tertiary phosphines.

VIII. Thermolysis and Photolysis

In certain instances quinquevalent phosphorus compounds can undergo thermolysis or photolysis to generate trivalent species. A early investigation of the thermolysis of tertiary diarylalkylphosphine oxides in a sealed tube in the presence of water found a portion of the starting material to undergo deoxygenation, although other types of reactions also occurred.[149] Another early investigation of the direct thermolysis of acyclic aliphatic tertiary phosphine oxides demonstrated the formation of mixtures of alkenes and secondary phosphine oxides upon heating over 330°.[45] Presumably such thermolyses occur *via* a mechanism akin to the Cope elimination, as illustrated in Fig. 2. Neither of these approaches appear to be of general synthetic utility.

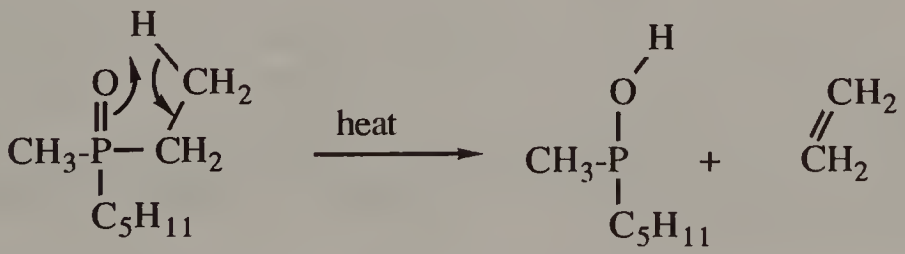


Fig. 2 - Mechanism of thermolysis of a tertiary phosphine

oxide - Additional products result from the corresponding degradation of the pentyl group which is also attached to phosphorus.

Tertiary phosphine oxides, in which the phosphorus is contained in a strained ring, are capable of undergoing thermolysis to yield trivalent phosphorus products when a suitable solvent is employed. For example, phosphirane oxides undergo thermolysis to form alkenes and a reactive phosphinidene oxide.[150,151] The alkene product is formed with retention of of the original geometry of the phosphirane oxide. In the presence of an alcohol solvent, the phosphinidene oxide is trapped to form a monoester of a phosphonous acid. This type of reaction is illustrated in Fig. 3.

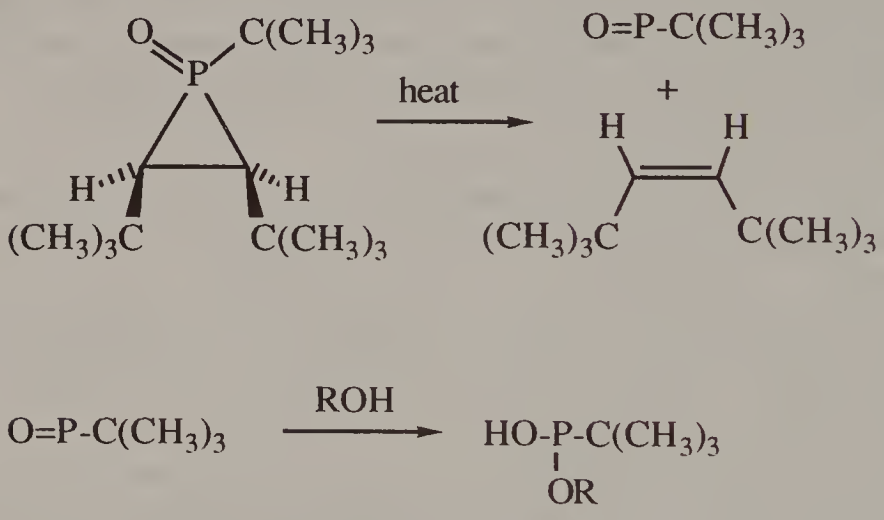


Fig. 3 - Thermal decomposition of a phosphirane oxide in the presence of an alcohol

The intermediacy of a phosphinidene oxide has also been implicated in the thermal decomposition of a 7-phospha-bicyclo[2.2.1]hept-5-ene oxide, as shown in Fig. 4.[152] The reactive intermediate phosphinidene oxide may be trapped by alcohol (among a variety of reagents) to produce a trivalent phosphorus product.

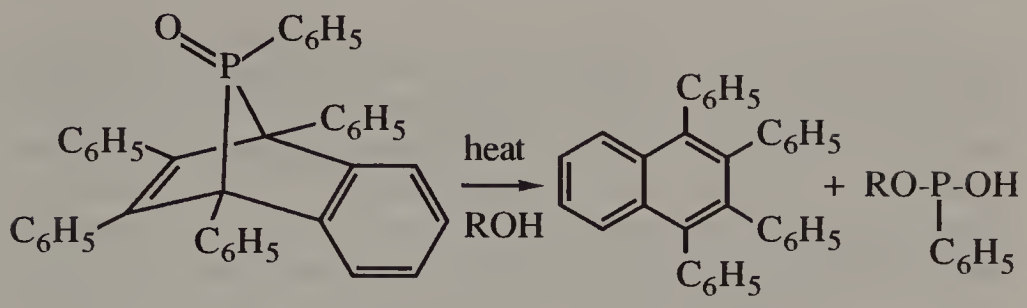
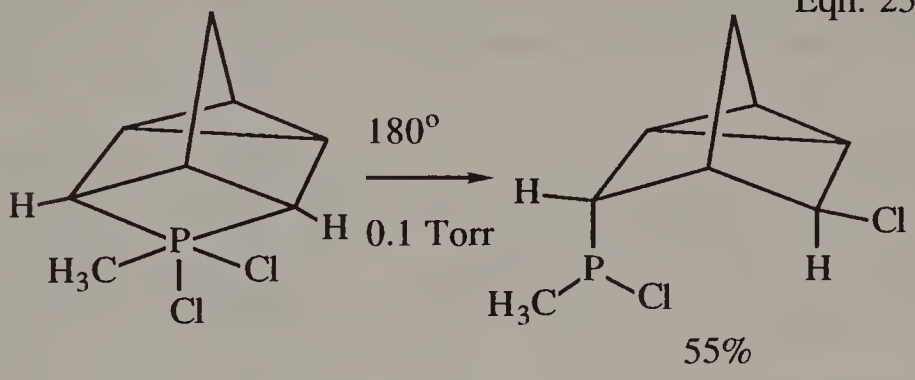


Fig. 4 - Thermal decomposition of a substituted 7-phosphabicyclo[2.2.1]hept-5-ene oxide with generation of a phosphinidine oxide intermediate

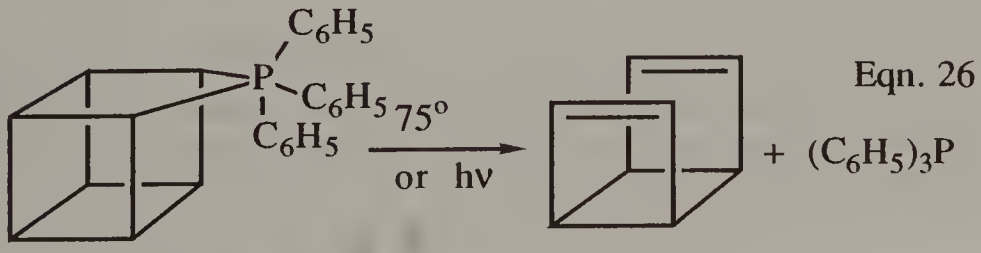
Examples are also available of phosphoranes which are part of a strained ring system undergoing thermolysis to form trivalent phosphorus products. For example, vacuum pyrolysis of a quadricyclic dichlorophosphorane bearing the phosphorus in a four-membered ring yields the chlorophosphine, as shown in Eqn. 25.[153]

Eqn. 25



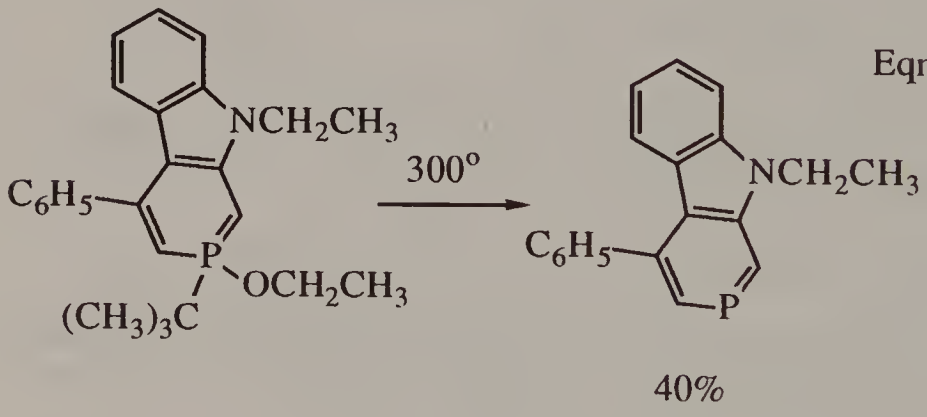
Similarly, homocubyltriphenylphosphorane undergoes a cheleotropic reaction of phosphorus exhibiting the elision of triphenylphosphine, as shown in Eqn. 26.[154]

Eqn. 26



Early studies of the pyrolysis of pentaphenylphosphorane found evidence that cleavage of carbon-phosphorus bonds occurred, although no triphenylphosphine could be isolated.[155] Later efforts provided evidence that triphenylphosphine was indeed formed in this reaction, along with biphenyl.[156] Subsequently, a variety of polyaromaticphosphoranes have been found to undergo carbon-phosphorus bond scission to form tertiary phosphine, along with new carbon-carbon bond formation.[157-159] Similar decompositions of phosphoranes to form phosphines and a by-product derived from the two elided groups are observed when the product phosphine is suitably stabilized, as with a phosphabenzene or other phosphaaromatic system.[160-163] An example of this type of thermolysis is shown in Eqn. 27.[162]

In addition to the thermolysis reactions previously noted, phosphinidene oxides are formed upon the photolysis of 1-substituted phospholene oxides.[163] Once generated, the phosphinidene oxide reacts with alcohol solvent to yield a monoester of a phosphonous acid. Similarly, phosphinidene sulfides are produced as intermediates in the photolysis of phospholene sulfides.[164,165] In these instances the phosphorus product is an *O*-ester of a thiophosphonous acid.



Eqn. 27

IX. Cleavage of α-Substituted Phosphonates

The cleavage of α-ketophosphonates, as illustrated in Fig. 5, provides an approach to the generation of trivalent from quinquevalent phosphorus species.

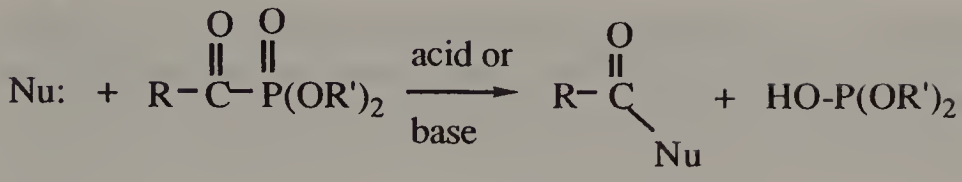


Fig. 5 - Cleavage of α-ketophosphonates in the presence of nucleophiles - The conversion could be envisioned as occurring under either acidic or basic conditions.

As the general synthetic approach for the preparation of α-ketophosphonates is by the Michaelis-Arbuzov reaction of phosphites with acyl halides,[166-190] their nucleophilic cleavage is simply a regeneration of another form of the original trivalent phosphorus reagent. Nonetheless, the reaction is of significant utility for the accomplishment of synthetic transformations at *carbon*, and holds promise as a general approach for the cleavage of carbon-phosphorus bonds.

While most attention has been given to the hydrolysis of the α-ketophosphonates to form carboxylate salts and dialkyl phosphites,[191-195] the cleavage is also accomplished using ammonia,[196] amines,[171,197] and alcohols.[198]

In a similar vein, α-hydroxyphosphonate diesters undergo cleavage readily in the presence of nucleophiles to generate dialkyl phosphites. Formed conveniently by the addition of dialkyl phosphites to carbonyl compounds,[199] the α-hydroxyphosphonate diesters provide convenient carbonyl *umpolung* reagents (see Chapter 8, this work).

X. Experimental Procedures

A. Reduction of a Phosphinate Ester to a Secondary Phosphine with LAH

Methylphenylphosphine[10] - Methyl methylphenylphosphinate (17 g, 0.1 mol) is added dropwise to a mixture of lithium aluminum hydride (6 g, 0.15 mol) and diethyl ether (100 mL). After heating at reflux for 4 hr, excess aqueous sodium hydroxide solution is added cautiously to decompose the salts and excess reagent. The aqueous phase, along with the insoluble

precipitate, is separated from the organic phase as far as possible with the exclusion of air. The organic phase is dried and distilled under vacuum to yield the methylphenylphosphine (6.6 g, 53%) of bp 62-63°/11 Torr.

B. Reduction of a Phosphonium Salt to a Tertiary Phosphine with LAH

Methyldiphenylphosphine[47] - To a mixture of dioxane (500 mL) and lithium aluminum hydride (16 g, 0.42 mol) is added methyltriphenylphosphonium bromide (100 g, 0.28 mol) and the reaction mixture is heated for 15 min. Along with the vigorous evolution of gas, the reaction mixture initially turns a deep red-brown color, ultimately becoming colorless. The reaction mixture is then cooled to room temperature and salts and excess reagent are decomposed by the dropwise addition of water until a precipitate forms in the form of compact lumps. The organic phase is decanted and the precipitate is washed with dioxane (2 x 150 mL). The combined organic phases are dried (calcium chloride), filtered, and the solvent is evaporated under reduced pressure. The residue is vacuum distilled to yield the methyldiphenylphosphine (39 g, 79%) of bp 107-110°/ 0.5 Torr.

C. Reduction of a Phosphorochloridate to a Dialkyl Phosphite with $NaBH_4$

Dibutyl phosphite[38] - In a three-necked flask (100 mL) equipped with reflux condenser, drying tube, compensating dropping funnel, and magnetic stirrer is placed dry dioxane (30 mL) and sodium borohydride (1.66 g, 0.044 mol). While stirring rapidly there is added in small portions dibutyl phosphorochloridate (5.0 g, 0.022 mol). Upon completion of addition, the reaction is heated at reflux for 5 hr, then cooled, and water (10 mL) is added cautiously followed by sufficient hydrochloric acid (6 *M*) to bring the pH<2. The mixture is filtered and the filtrate is evaporated under reduced pressure. The residue is washed with methylene chloride (2 x 50 mL) and the washings dried (magnesium sulfate), filtered, and evaporated under reduced pressure to yield the dibutyl phosphite (3.6 g, 85%).

D. Reduction of a Tertiary Phosphine Oxide to a Tertiary Phosphine with Methylpolysiloxane

(*o*-Aminophenyl)diphenylphosphine[51] - A mixture of

(*o*-aminophenyl)diphenylphosphine oxide (89 g, 0.30 mol), methylpolysiloxane (92 g, 1.53 mol), and diphenyl ether (600 mL) is stirred and heated to reflux for 4 hr. After cooling, sufficient methanol is added to triple the volume and the mixture is allowed to stand for 2 hr. The mixture separates into two layers, and the upper layer is carefully decanted. The lower layer is washed with methanol, and the methanol extracts are combined. There is then added a concentrated solution of nickel nitrate hexahydrate (50% excess) in methanol, and the mixture allowed to stand for 30 min. The precipitate is collected by filtration and boiled with a 1:1 benzene:water mixture until dissolution is complete. The benzene phase is passed through a Florisil column and the eluent evaporated to dryness. The residue is recrystallized from ethanol to yield the (*o*-aminophenyl)diphenylphosphine (60 g, 70%).

E. Reduction of a Tertiary Phosphine Oxide to a Tertiary Phosphine with Trichlorosilane

1,1,5,5,8-Pentamethylphosphalilolidine[57] - To a solution of phosphalilolidine oxide (1.3 g, 4.96 mmol) in benzene (10 mL) is added under nitrogen trichlorosilane (6 mL). The solution is refluxed for 5 hr, and then cooled with an ice bath, and decomposed by the dropwise addition of 25% aqueous sodium hydroxide solution (100 mL). The aqueous and organic layers are separated, and the aqueous layer is extracted with ether. The organic layers are combined, washed with brine until neutral, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to give a residual oil. Vacuum distillation of the oil yields the 1,1,5,5,8-pentamethylphosphalilolidine (1.0 g, 82%) of bp 133-134°/0.8 Torr.

F. Reduction of a Phosphinic Acid to a Secondary Phosphine with Diphenylsilane

3,4-Dimethyl-Δ^2-phospholine[55] - 1-Hydroxy-1-oxo-3,4-dimethyl-Δ^2-phospholine (21.8g, 150 mmol) and diphenylsilane (41.4 g, 225 mmol) are heated for 4 hr at 150-190° under a nitrogen atmosphere. The reaction mixture is then distilled to yield the 3,4-dimethyl-Δ^2-phospholine (13.8 g, 81%) of bp 146-148°/760 Torr.

G. Reduction of a Tertiary Phosphine Oxide to a

Tertiary Phosphine with Hexachlorodisilane

(*R*)-Benzylmethylphenylphosphine[72] - A solution of (*R*)-benzylmethylphenylphosphine oxide (optically pure, $[\alpha]_D$ = +51.4°, 210 mg, 0.91 mmol) in benzene (5 mL) is heated at reflux with hexachlorodisilane (0.21 mL) for 10 min. After cooling to 0°, the reaction mixture is treated by the cautious addition of 30% aqueous sodium hydroxide solution (3 mL). Benzene (10 mL) is then added and the organic layer is separated and washed with water (2 x 2 mL), dried (magnesium sulfate), filtered, and evaporated under reduced pressure. The residue is then vacuum distilled to yield the (*R*)-benzylmethylphenylphosphine (164 mg, 84%) of bp 90-95°/0.01 Torr and $[\alpha]_D$ = +81°.

II. Reduction of a Tertiary Phosphine Sulfide to a Tertiary Phosphine with Hexachlorodisilane

Allylmethylphenylphosphine[77] - A solution of allylmethylphenylphosphine sulfide (210 mg, 1.07 mmol) in benzene (5 mL) is refluxed with hexachlorodisilane (0.28 mL) for 6 hr. After this time the reaction mixture is cooled to 0° and a 30% aqueous solution of sodium hydroxide (3 mL) is added. Benzene (10 mL) is added, and the organic layer is separated, washed with water (2 x 2 mL), dried (magnesium sulfate) filtered, and concentrated under reduced pressure. The residue is vacuum distilled to yield the allylmethylphenylphosphine (114 mg, 65%) of bp 45°/0.1 Torr.

I. Reduction of a Dihalophosphorane to a Phosphine with Magnesium Metal

1-Methyl-3-phospholene[129] - In a nitrogen-flushed, flame-dried apparatus a slurry of 1-methyl-3-phospholene dichloride (34.2 g, 0.2 mol) in THF (400 mL) is treated with activated magnesium (5.4 g, 0.22 g-atom). After the initial exotherm subsides, the reaction mixture is refluxed for 10 hr. Upon cooling, concentrated hydrochloric acid (30 mL) is added cautiously. After all of the residual magnesium dissolves, the THF is evaporated under reduced pressure. The residue is taken up in water, made basic by the addition of 0.5 *M* aqueous sodium hydroxide, and steam distilled. The separating product is dried (calcium sulfate), filtered, and distilled to yield the

1-methyl-3-phospholene (14.6 g, 73%) of bp 114-115°.

J. Reduction of a Tertiary Phosphine Sulfide to a Tertiary Phosphine with Iron Metal

Triphenylphosphine[123] - To a 250 mL round-bottomed flask fitted with a reflux condenser and a thermometer, and maintained under a purging atmosphere of nitrogen is placed triphenylphosphine sulfide (29.4 g, 0.1 mol) and iron filings (0.1 g, 0.15 g-atom). The reaction mixture is heated to 370 ° for 2 hr. After cooling, the ethanol is added and the solution filtered. The filtrate is evaporated and the residue recrystallized from ethanol to yield the triphenylphosphine (18.0 g, 68%) of mp 79-81°.

K. Reduction of an Alkyltetrachlorophosphorane to an Alkylphosphonous Dichloride with Elemental Phosphorus

Isooctenylphosphonous dichloride[99] - Diisobutylene (428 g, 3.2 mol) is added dropwise over a period of 3 hr to a well-agitated slurry of phosphorus pentachloride (417 g, 2 mol) in benzene (750 mL) at 0°. An exothermic reaction ensues. Upon completion of the reaction, the flask is flushed with carbon dioxide and the reaction mixture is stirred during the addition of a solution of white phosphorus (41.3 g, 1.33 g-atom) in carbon disulfide (8 mL). This is followed by the addition of iodine (0.2 g). The reaction mixture is allowed to warm to 20° and reaction proceeds with maintenance of this temperature by cooling. Hydrogen chloride escapes from the reaction mixture through an exhaust tube protected with a drying agent. The reaction mixture is distilled to yield the isooctenylphosphonous dichloride (281 g, 66%) of bp 70-72°/3 Torr.

L. Reduction of an Alkylthiophosphonic Dichloride to an Alkylphosphonous Dichloride with a Tertiary Phosphine

Methylphosphonous dichloride[93] - Methylthiophosphonic dichloride (44.4 g, 0.28 mol) is added to tributylphosphine (65.3 g, 0.32 mol) to give a homogeneous, yellow mixture accompanied by a mild exotherm. The reaction mixture is then heated to 120°, at which point the product begins to distil, heating continuing until the temperature reaches 190°. There is obtained in the distillate the

methylphosphonous dichloride (20.4 g, 62%) of bp 79-80°/747 Torr.

XI. Bibliography

1. Horvat, R.J., and Furst, A. (1952). Phenylphosphine, *J. Am. Chem. Soc.*, *74*: 562.
2. Sander, M. (1960). Herstellung und Reaktionen von Phosphonig- und Phosphinigsaureestern, *Ber.*, *93*: 1220.
3. Becker,V.G., Mundt, O., Rossler, M., and Schneider, E. (1978) Synthese von Alkyl- und Arylbis- (trimethylsilyl)- sowie Alkyl- und Aryltrimethylsilylphosphanen, *Z. anorg. allg. Chem.*, *443*: 42.
4. Freedman, L.D., and Doak, G.O. (1952). The reduction of benzenephosphonyl dchloride, *J. Am. Chem. Soc.*, *74*: 3414.
5. Maier, L. (1965). Organische Phosphorverbindungen. XX. Zur Kenntnis der Reaktion von primaren aliphatischen Phosphinen mit Schwefel und von Phenylphosphin mit rotem Selen, *Helv. Chim. Acta*, *48*: 1190.
6. Bissey, J.E., Goldwhite, H., and Roswell, D.G. (1967). Reactions of 2,3-dichloro-tetrafluoropropene with nucleophiles containing phosphorus, *J. Org. Chem.*, *32*: 1542.
7. Weil, T., Prijs, B., and Erlenmeyer, H. (1953). Uber die Reduktion der phenylphosphinigen Saure mit Lithiumaluminiumhydride, *Helv. Chim. Acta*, *36*: 142.
8. Gallagher, M.J., Kirby, E.C., and Mann, F.G. (1963). Synthesis of the 1-substituted 1,2,3,4-tetrahydro-4-oxo-phosphinoline system, *J. Chem. Soc.*: 4846.
9. Hays, H.R., and Logan, T.J. (1966). *gem*-Diphosphino-alkanes. Preparation and characterization, *J. Org. Chem.*, *31*: 3391.
10. Horner, L., Hoffmann, H., and Beck, P. (1958). Phosphororganische Verbindungen, XVI. Wege zur Darstellung primarer, sekundarer und tertiarer Phosphine, *Ber.*, *91*: 1583.
11. Issleib, K., Brunner, H.U., and Oehme, H. (1970). Benzazaphospholine, *Organomet. Chem. Syn.*, *1*: 161.
12. Weichmann, H., Ochsler, B., Duchek, I., and Tzschach, A. (1979). Funktionell Substituierte Zinnorganische

Verbindungen. V. Phosphono- und Phosphonyl-methyl-triorgaonstannane, *J. Organomet. Chem.*, *182*: 465.

13. Cremer, S.E., Cowles, J.M., and Gamliel, A. (1987). Synthesis and stereochemical studies of 1-phospha-bicyclo[4.4.0]decane and 4-*t*-butylphosphorinane derivatives, *Phosphorus Sulfur*, *30*: 369.
14. Issleib, K., Krech, F., and Kuhne, U. (1984). Zur Synthese des Bisphosphino-methans, *Z. Chem.*, *24*: 261.
15. Sander, M. (1962). Herstellung von Bis-phosphonig-saureestern aus bifunktionellen Grignard-Verbindungen und Umsetzungen zu bifunktionellen phosphororganischen Verbindungen, *Ber.*, *95*: 473.
16. Issleib, K., and Weichmann, H. (1968). Synthese und Reaktionsverhalten der Athylen-bis-organophosphine, *Ber.*, *101*: 2197.
17. Hietkamp, S., Sommer, H., and Stelzer, O. (1984). Synthese und NMR-spektroskopische Charakterisierung PH-funktioneller methylenverbruckter Diphosphane R_2-P-CH_2-PRH und HRP-CH_2-PRH, *Ber.*, *117*: 3400.
18. Maier, L. (1966). Organische Phosphorverbindungen. XXII. Darstellung und Eigenschaften von diprimaren α,ω-Bis-phosphinoalkanen, *Helv. Chim. Acta*, *49*: 842.
19. Mann, F.G., Tong, B.P., and Wystrach, V.P. (1963). The abnormal hydrolysis of certain β-diarylphosphino-propionic esters. Part II. Correction and extension, *J. Chem. Soc.*: 1155.
20. Mallion, K.B., and Mann, F.G. (1964). The Mechanism of the reduction of diphenylphosphinic acid and its ethyl ester by lithium aluminum hydride, *J. Chem. Soc.*: 6121.
21. Kyba, E.P., and Liu, S.-T. (1985). Synthesis of unusual phosphine ligands. Use of the 1-naphthylmethyl moiety as a P-H protecting group in the synthesis of a phosphino macrocycle that contains a secondary-phosphino ligating site, *Inorg. Chem.*, *24*: 1613.
22. Campbell, I.G.M., and Way, J.K. (1960). Synthesis and stereochemistry of heterocyclic phosphorus compounds. Part I. Preparation of (+)- and (-)-10-*p*-dimethylamino-phenyl-9,10-dihydro-9-aza-10-phosphaphenanthrene, *J. Chem. Soc.*: 5034.

23. Campbell, I.G.M., and Way, J.K. (1961). Synthesis and stereochemistry of heterocyclic phosphorus compounds. Part II. Loss of optical activity in the reduction of (+)-2-carboxy-9-phenyl-9-phosphoafluorene 9-oxide, *J. Chem. Soc.*: 2133.
24. Henson, P.D., Naumann, K., and Mislow, K. (1969). Stereomutation of phosphine oxides by lithium aluminum hydride, *J. Am. Chem. Soc.*, *91*: 5645.
25. Cabioch, J.L., and Denis, J.M. (1989). Preparative synthesis of primary vinylphosphines by chemoselective reduction of the corresponding vinylphosphonates, *J. Organomet. Chem.*, *377*: 227.
26. Koster, R., Schusslre, W., and Synoradzki, L. (1987). Reaktionen von (Organo)Phosphor-Sauerstoff-Verbindungen mit Diorgano-hydro-boranen, *Ber.*, *120*: 1105.
27. Issleib, K., and Grams, G. (1959). Reduction of aromatic phosphine oxides with lithium aluminum hydride, *Z. anorg. allgem. Chem.*, *299*: 58.
28. Hein, F., Issleib, K., and Helm, R. (1956). The reduction of tertiary phosphine oxides or sulfides with lithium or calcium aluminum hydride to the corresponding phosphines, *Z. anorg. allgem. Chem.*, *287*: 208.
29. Christol, H., Cristau, H.-J., Fallouh, F., and Hullot, P. (1979). Synthese de Macrocycles Diphosphores Polyoxygenes, *Tetrahedron Lett.*: 2591.
30. Wife, R.L., van Oort, A.B., van Doorn, J.A., and van Leeuwen, P.W.N.M. (1983). phosphine oxide anions in the synthesis of phosphine ligands, *Synthesis*: 71.
31. Koster, R., and Morita, Y. (1965). Preparation of triphenylphosphine from triphenylphosphine oxide by reduction with boranes, *Angew. Chem.,, Int. Ed. Engl.*, *4*: 593.
32. Fritzsche, H., Hasserodt, U., and Korte, F. (1964). Reduktion tertiarer Phosphinoxyde zu tertiaren Phosphinen mit Silanen, *Ber.*, *97*: 1988.
33. Cernia, E., Giongo, G.M., Marcati, F., Marconi, W., and Palladino, N. (1974). Optically active phosphines by asymmetric reduction of racemic phosphine oxides, *Inorg. Chim. Acta*, *11*: 195.
34. MacPherson, A.J., and Smith, D.J.H. (1984). The

preparation of optically active phosphines by asymmetric reduction of racemic phosphine oxides, *J. Chem. Res. (S)*: 32.

35. Wetzel, R.B., and Kenyon, G.L. (1972). A convenient procedure for the synthesis of phosphorus-carbon bonds using sodium bis(2-methoxyethoxy)aluminum hydride, *J. Am. Chem. Soc.*, *94*: 1774.
36. Emmick, T.L., and Letsinger, R.L. (1968). Unsymmetrical secondary phosphine oxides. Synthetic, isotopic exchange, and stereochemical studies, *J. Am. Chem. Soc.*, *90*: 3459.
37. Musierowicz, S., Waszkuc, W.T., and Krawczyk, H.W. (1979). Annulation of secondary phosphine oxides containing δ-oxoalkyl group. 1-Phenyl-2-hydroxy-phospholane 1-oxides, *Phosphorus Sulfur*, *5*: 377.
38. Engel, R., and Chakraborty, S. (1988). Organophosphorus chemistry. 2. The reduction of quinquevalent phosphorus to the trivalent state, *Syn. Commun.*, *18*: 665.
39. Skrzypczynski, Z., and Michalski, J. (1988). Stereoselective synthesis and stereochemistry of optically active *tert*-butylphenylphosphine sulfide, *J. Org. Chem.*, *53*: 4549.
40. Issleib, K., and Tzschach, A. (1959). Darstellung sekundarer aliphatischer Phosphine, *Ber.*, *92*: 704.
41. Maier, L. (1961). Darstellung von unsymmetrischen Phosphinen und unsymmetrischen Phosphinsaurechloriden, *Ber.*, *94*: 3056.
42. Luckenbach, R. (1971). Stereospezifische Desulfurierung eines optisch aktiven Phosphinsulfids mit $LiAlH_4$, *Tetrahedron Lett.*: 2177.
43. Gough, S.T.D., and Trippett, S. (1961). The reduction of alkyltriphenylphosphonium halides with lithium aluminum hydride, *J. Chem. Soc.*: 4263.
44. Cristau, H.-J., Labaudiniere, L., and Christol, H. (1983). Synthese et Reduction Chimique de Sels de Vinylene-1,2 et Butadienylene-1,4 Bisphosphoniums, *Phosphorus Sulfur*, *15*: 359.
45. Bailey, W.J., Muir, W.M., and Marktscheffel, F. (1962). Phosphorus compounds. III. Pyrolysis of tertiary phosphine oxides, *J. Org. Chem.*, *27*: 4404.

46. Saunders, M., and Burchman, G. (1959). The reaction of triphenylphosphinemethylenes with lithium aluminum hydride, *Tetrahedron Lett.*: 8.
47. Makhaev, V.D., and Borisov, A.P. (1984). Reduction of phosphonium salts with lithium tetrahydroaluminate: convenient method for the preparation of alkyldiarylphosphines, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *54*: 2279.
48. Markl, G., and Olbrich, H. (1966). Derivatives of phospha-2,5-cyclohexadien-4-one and 4,4'-diphosphabi-(2,5-cyclohexadienylidene), *Angew. Chem., Int. Ed. Engl.*, *5*: 588.
49. Wunsch, von G., Wintersberger, K., and Geierhaus, H. (1969). Herstellung von Triphenylphosphin aus Triphenylphosphinoxid, *Z. anorg. allg. Chem.*, *369*: 33.
50. Markl, G., and Olbrich, H. (1966). 4-Methylenephospha-2,5- cyclohexadienes, *Angew. Chem., Int. Ed. Engl.*, *5*: 589.
51. Cooper, M.K., and Downes, J.M. (1978). Chelate complexes of phosphorus-nitrogen ligands. I. Deprotonation, *cis-trans* isomerism, and anion-catalyzed isomerization in platinum(II) complexes of (*o*-aminophenyl)diphenylphosphine, *Inorg. Chem.*, *17*: 880.
52. Quin, L.D., Symmes, C., Middlemas, E.D., and Lawson, H.F. (1980). Epoxides of bicyclic phospholane derivatives. Stereochemistry of epoxidation of 2- and 3-phospholene oxides, *J. Org. Chem.*, *45*: 4688.
53. Mazhur-ul-Haque, Horne, W., Cremer, S.E., Kremer, P.W., and Most, J.T. (1980). The synthesis, stereochemistry, and crystal structure of *exo*-3-*p*-nitrobenzyl-*endo*-3-phenyl-phosphoniabicyclo[3.2.1]octane bromide, *J. Chem. Soc., Perkin Trans. I*: 1467.
54. Hedden, D., and Roundhill, D.M. (1985). Synthesis of new hybrid phosphine amine and phosphine amide compounds. Preparation of a series of new phosphine amido chelate complexes of palladium(II) and platinum(II) and their reactions with bases and bronsted acids, *Inorg. Chem.*, *24*: 4152.
55. Fritzsche, H., Hasserodt, U., and Korte, F. (1965).

Darstellung primarer und sekundarer Phosphine mit Silanen, *Ber.*, *98*: 1681.
56. Fritzsche, H., Hasserodt, U., and Korte, F. (1965). Reduktion tertiarer Phosphinoxyde zu tertiaren Phosphinen mit Trichlorsilan, *Ber.*, *98*: 171.
57. Chen, C.H., Brighty, K.E., and Michaels, F.M. (1981). Synthesis of phosphalilolidine and phosphajulolidine, *J. Org. Chem.*, *46*: 361.
58. Petrov, K.A., Chauzov, V.A., and Agafonov, S.V. (1980). Alkoxymethylation of phenylphosphonous dichloride and diphenylphosphinous chloride with dialkoxymethanes, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *50*: 1220.
59. Butters, T., Haller-Pauls, I., and Winter, W. (1982). Addition von Wasser an *o*-phenylethinylsubstituierte Triphenylphosphane und Reduktion der entstehenden Phosphanoxid-en-ine, *Ber.*, *115*: 578.
60. Segall, Y., Granoth, I., and Kalir, A. (1974). Preparation of a dibenzo[*b,e*]phosphorin. Selective phosphine oxide reduction by trichlorosilane, *J. Chem. Soc., Chem. Commun.*: 501.
61. Cremer, S.E., and Chorvat, R.J. (1967). Syntheses of substituted phosphetanes and related derivatives, *J. Org. Chem.*, *32*: 4066.
62. Cremer, S.E. (1968). Alkaline hydrolysis of 2,2,3,4,4-pentamethyl-1-phenylphosphetanium bromide, *J. Chem. Soc., Chem. Commun.*: 1132.
63. Baccolini, G., and Todesco, P.E. (1975). Trichlorosilane reduction of some dioxaphospholene oxides, *J. Org. Chem.*, *40*: 2318.
64. Marsi, K.L. (1969). Stereochemistry of some reactions of phospholane derivatives, *J. Am. Chem. Soc.*, *91*: 4724.
65. Marsi, K.L. (1968). Stereochemistry of alkaline cleavage of *cis*- and *trans*-1-benzyl-1,3-dimethylphospholanium bromide, *J. Chem. Soc., Chem. Commun.*: 846.
66. Quin, L.D., Bryson, J.G., and Moreland, C.G. (1969). A study of 1-methylphosphole as a heteroaromatic substance, *J. Am. Chem. Soc.*, *91*: 3308.
67. Quin, L.D., and Bryson, J.G. (1967). 1-Methyl-phosphole, *J. Am. Chem. Soc.*, *89*: 4984.
68. Quin, L.D., Borleske, S.G., and Engel, J.F. (1973).

Synthesis and spectral characterization of some *C*-alkylphospholes and phospholecarboxylates, *J. Org. Chem.*, *38*: 1858.

69. Nief, F., Charrier, C., Mathey, F., and Simalty, M. (1981). A new application of the phosphole-phosphorin ring expansion reaction. Synthesis and complexing properties of 1-phenyl isophospholine, *Nouv. J. Chim.*, *5*: 187.
70. Markl, G., Hock, K., and Matthes, D. (1983). 3-Aryl-λ^3-phosphorines, 3-Aryl-λ^5-phosphorine, 3-Aryl-λ^4-phosphorinium-Salze, *Ber.*, *116*: 445.
71. Naumann, K., Zon, G., Mislow, K. (1969). Perchloropolysilanes: novel reducing agents for phosphine oxides and other organic oxides, *J. Am. Chem. Soc.*, *91*: 2788.
72. Naumann, K., Zon, G., and Mislow, K. (1969). The use of hexachlorodisilane as a reducing agent. stereospecific deoxygenation of acyclic phosphine oxides, *J. Am. Chem. Soc.*, *91*: 7012.
73. Deleris, G., Dunogues, J., and Calas, R. (1974). Reeuction de l'oxyde de triphenylphosphine par des disilanes chlores issus de la synthese industrielle des methylchlorosilanes, *Bull. Soc. Chim. Fr.*: 672.
74. DeBruin, K.E., Zon, G., Naumann, K., and Mislow, K. (1969). Stereochemistry of nucleophilic displacement at phosphorus in some phosphetanium salts, *J. Am. Chem. Soc.*, *91*: 7027.
75. Myers, D.K., and Quin, L.D. (1971). Synthesis and properties of some 1-halophospholenes, *J. Org. Chem.*, *36*: 1285.
76. Cristau, H.J., Chiche, L., Fallouh, F., Hullot, P., Renard, G., and Christol, H. (1984). Mise au point d'une methode de synthese controlee de ligands macrocycliques polyphosphores. Application a la preparation de macrocycles diphosphores polyoxygenes, *Nouv. J. Chim.*, *8*: 191.
77. Zon, G., DeBruin, K.E., Naumann, K., and Mislow, K. (1969). The stereospecific desulfurization of acyclic phosphine sulfides with hexachlorodisilane and the alkaline hydrolysis of monoalkoxy- and monoalkylmercapto-

phosphonium salts. Stereochemistry and mechanism, *J. Am. Chem. Soc.*, *91*: 7023.

78. Grim, S.O., and Mitchell, J.D. (1977). Unsymmetrical bis-phosphorus ligands. 10. Synthesis and group 6 metal carbonyl derivatives of (diphenylphosphino)-(diorganophosphino)methane, $Ph_2PCH_2PR^1R^2$, *Inorg. Chem.*, *16*: 1770.
79. Horner, L., and Balzer, W.D. (1965). Phosphororganische Verbindungen. XL. Zum sterischen Verlauf der Desoxygenierungen von tertiaren Phosphinoxyden zu tertiaren Phosphinen mit Trichlorsilan, *Tetrahedron Lett.*: 1157.
80. Quin, L.D., Caster, K.C., Kisalus, J.C., and Mesch, K.A. (1984). Bridged ring systems containing phosphorus: structural influences on the stereochemistry of silane reductions of *P*-oxides and on ^{13}C and ^{31}P NMR properties of phosphines, *J. Am. Chem. Soc.*, *106*: 7021.
81. Quin, L.D., Hughes, A.N., Kisalus, J.C., and Pete, B. (1988). Synthesis and NMR spectral properties of phosphines in the 2-phosphabicyclo[2.2.2]oct-5-ene and 2-phosphabicyclo[2.2.2]octa-5,7-diene, *J. Org. Chem.*, *53*: 1722.
82. Cremer, S.E., Farr, F.R., Kremer, P.W., Hwang, H.-o., Gray, G.A., and Newton, M.G. (1975). Stereochemistry and reactions of 4-methyl-4-phosphatetracyclo-[3,3,0,$0^{2,8}0^{3,6}$]octane 4-oxide, *J. Chem. Soc., Chem. Commun.*: 374.
83. Burg, A.B. (1954). Triethylamine adducts of the chlorosilanes, *J. Amer. Chem. Soc.*, *76*: 2674.
84. Quin, L.D., Kisalus, J.C., and Mesch, K.A. (1983). Insertion of oxygen into C-P bonds of some strained phosphorus heterocycles, *J. Org. Chem.*, *48*: 4466.
85. Mathey, F., and Mercier, F. (1979). Sur une voie d'acces potentiellement aux phosphines functionnelles a phosphore optiquement actif, *Tetrahedron Lett.*: 3081.
86. Valentine, D., Blount, J.F., and Toth, K. (1980). Synthesis of phosphines having chiral organic groups ligated to chiral phosphorus, *J. Org. Chem.*, *45*: 3691.
87. Fujii, M., Ozaki, K., Kume, A., Sekine, M., and Hata, T. (1986). Acylphosphonates. 6. Reaction mechanism of

Zn/Me_3SiCl mediated conversion of 2,2,2-trichloro-ethoxy-carbonylphosphonates to silyl phosphites, *Tetrahedron Lett.*, *27*: 3365.

88. Marsi, K.L. (1974). Phenylsilane reduction of phosphine oxides with complete stereospecificity, *J. Org. Chem.*, *39*: 265.
89. Pietrusiewicz, K.M., and Zablocka, M. (1988). Optically active phosphine oxides. 5. P-Chiral 2-aminoethyl phosphine oxides, *Tetrahedron Lett.*, *29*: 1991.
90. Oram, R.K., and Trippett, S. (1973). Reactions of 1-substituted 2,2,3,4,4-pentamethylphosphetans with hexafluoroacetone and the ^{19}F nuclear magnetic resonance spectra of the resulting 1,3,2-dioxa- phospholans, *J. Chem. Soc., Perkin Trans. I*: 1300.
91. Calas, R., Dunogues, J., Deleris, G., and Duffaut, N. (1982). Some practical uses of the disilane residue from the direct synthesis of methylchlorosilanes, *J. Organomet. Chem.*, *225*: 117.
92. Parshall, G.W. (1960). A new synthesis of tetramethyl-ethylenediphosphine, *J. Inorg. Nucl. Chem.*, *14*: 291.
93. Ulmer, H.E., Groenweghe, L.C.D., and Maier, L. (1961). A preparative method for alkylhalophosphines, *J. Inorg. Nucl. Chem.*, *20*: 82.
94. Uhing, E., Rattenbury, K., and Toy, A.D.F. (1961). Chemistry of chloromethylphosphinic acid. I. Preparation and alkaline hydrolysis, *J. Am. Chem. Soc.*, *83*: 2299.
95. Genkina, G.K., and Gilyarov, V.A. (1969). Synthesis of bis(chloromethyl)chloro-phosphine, *Izv. Akad. Nauk S.S.S.R., Ser. Khim., Engl. Transl.*: 185.
96. Horner, L., and Jordan, M. (1980). Phosphororganische Verbindungen. 91. Entschwefelungsstudien an optisch aktiven Thiophosphinsaurederivaten mit dem Ziele der Darstellung optisch aktiver Phosphinigsaurederivate, *Phosphorus Sulfur*, *8*: 221.
97. Wada, M., Kanzaki, M., Ohta, H., Tenma, K., Hashizume, N., Hirata, K., and Erabi, T. (1989). Facile desulfurization of tris(2,6-dimethoxyphenyl)phosphine sulfide by acids, *Chem. Express*, *4*: 257.
98. Woodstock, W.H., and Walsh, E.N. (1954). Alkenylphosphonous dichlorides, *U.S. Patent 2,685,602*.
99. Walsh, E.N., Beck, T.M., and Woodstock, W.H. (1955).

A new method of preparation for alkenylphosphonous dichlorides and alkenylthionophosphonic dichlorides, *J. Am. Chem. Soc.*, *77*: 929.
100. Federova, G.K., and Kirsanov, A.V. (1960). Reaction of phosphorus pentachloride with unsaturated hydrocarbons, *Zhur. Obshch. Khim.*, *30*: 4044.
101. Quin, L.D., and Rolston, C.H. (1958). Preparation of trichloromethylphosphonous dichloride. Reduction of tetrachlorophosphoranes with methyl phosphorodichloridite, *J. Org. Chem.*, *23*: 1693.
102. Timokhin, B.V., Vengel'nikova, V.N., Kalabina, A.V., and Donskikh, V.I. (1981). Reduction of chlorophosphonium compounds by compounds of P(III) as a halophilic reaction, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *51*: 1307.
103. Timokhin, B.V., Dmitriev, V.K., and Dmitriev, V.I. (1982). Electrophilic properties of chlorine in the trigonal bipyramid of phosphorus chlorides, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *52*: 476.
104. Timokhin, B.V., Dmitriev, V.I., Vengel'nikova, V.N., Donskikh, V.I., and Kalabina, A.V. (1983). Diethylphosphorous acid - new reducing agent for pentavalent phosphorus derivatives, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *53*: 252.
105. Hoffmann, H., and Schellenbeck, P. (1968). Uber die Umsetzung von Tritylhalogeniden mit Phosphorverbindungen, *Ber.*, *101*: 2203.
106. Yakubovich, A.Y., and Ginsburg, V.A. (1952). Derivatives of trichloromethane-phosphonic acid, *Doklady Akad. Nauk S.S.S.R.*, *82*: 273.
107. Masaki, M., and Fukui, K. (1977). Reaction of tertiary phosphine dichlorides with thiols in the presence of triethylamine. A convenient method for the reduction of phosphine oxides to phosphines, *Chem. Lett.*: 151.
108. Omelanczuk, J., and Mikolajczyk, M. (1984). A general synthesis of optically active phosphines, phosphonites, and thiophosphinites from alkylthio(alkylseleno)phosphonium salts and tris(dimethylamino)phosphine as a thiophilic agent, *Tetrahedron Lett.*, *25*: 2493.
109. Omelanczuk, J., Perlikowska, W., and Mikolajczyk, M.

(1980). Stereospecific synthesis of diastereoisomerically pure (-)-(R_P)-*O*-menthyl methylphenylphosphinite and ethylphenylphosphinite: key intermediates in synthesis of chiral tertiary phosphines, *J. Chem. Soc., Chem. Commun.*: 24.

110. Miller, R.C. (1959). Phosphine oxides. VI. formation of disubstituted phosphine oxides by hydrolysis of disubstituted phosphinous halides, *J. Org. Chem.*, *24*: 2013.
111. Majewski, P. (1987). A convenient and facile synthesis of dialkylphosphines, *Synthesis*: 554.
112. Truce, W.E., and Perry, F.M. (1965). A new selective desulfurization method, *J. Org. Chem.*, *30*: 1316.
113. Reiff, L.P., and Aaron, H.S. (1970). Stereospecific synthesis and reactions of optically active isopropyl methylphosphinate, *J. Am. Chem. Soc.*, *92*: 5275.
114. Szafraniec, L.J., Szafraniec, L.L., and Aaron, H.S. (1987). Synthesis, reactions, and stereochemical correlations of an optically active tervalent phosphorus thio ester, *Phosphorus Sulfur*, *31*: 177.
115. Mathey, F. (1979). Synthese de la Phenyl-2-dimethyl-4,5-phosphorine a Partir du Benzyl-1-dimethyl-3,4-phosphole, *Tetrahedron Lett.*: 1753.
116. Nief, F., Charrier, C., Mathey, F., and Simalty, M. (1980). Phenyl-6 phospha-5 phenanthrene, *Tetrahedron Lett.*, *21*: 1441.
117. Buina, N.A., Giniyatullina, M.A., Nuretdinov, I.A., and Sibgatullina, F.G. (1977). Optically active phosphonic acid monoesters, *Izv. Akad. Nauk S.S.S.R., Ser. Khim., Engl. Transl.*: 1324.
118. Mathey, F., and Sennyey, G. (1976). Reduction-Complexation des Sulfures de Phospholenes Functionnels par le Nickelocene; Illustration d'une Nouvelle Synthese des Phosphines Functionnelles, *J. Organomet. Chem.*, *105*: 73.
119. Mathey, F., and Mercier, F. (1979). An evaluation of the P(IV)=S reduction-complexation by nickelocene as a synthetic tool in organophosphorus chemistry; towards the synthesis of functional phosphines with an optically active phosphorus center, *J. Organomet. Chem.*, *177*: 255.
120. Mathey, F., Mercier, F., and Santini, C. (1980).

1,3-Butadienylphosphines and some of their complexes, *Inorg. Chem.*, *19*: 1813.
121. Mathey, F., and Mercier, F. (1980). Conversion of phosphinic into phosphinous esters through nickelocene reduction-complexation of phosphinothioic *O*-esters. A new synthesis of carbon-phosphorus heterocycles, *J. Chem. Soc., Chem. Commun.*: 191.
122. Maier, L. (1964). Organische Phosphorverbindungen. XVI. Reduktion von Phosphinsulfiden zu den entsprechenden dreiwertigen Phosphorverbindungen, *Helv. Chim. Acta*, *47*: 2137.
123. Olah, G.A., and Hehemann, D. (1977). Friedel-Crafts type preparation of triphenylphosphine, *J. Org. Chem.*, *42*: 2190.
124. Olah, G.A., Berrier, A., and Ohannesian, L. (1985). Organophosphorus chemistry. 14. Friedel-Crafts preparation of triarylphosphine sulfides from arenes with phosphorus pentasulfide, *Nouv. J. Chem.*, *10*: 253.
125. Quin, L.D., and Humphrey, J.S. (1960). A new synthesis of arylphosphonous dichlorides, *J. Am. Chem. Soc.*, *82*: 3795.
126. Quin, L.D., and Mathews, D.A. (1964). Synthesis of 3-phospholenes by reduction of diene-phosphonous dichloride adducts, *J. Org. Chem.*, *29*: 836.
127. Quin, L.D., Peters, J.A., Griffin, C.E., and Gordon, M. (1964). Preservation of the 3-phospholene nucleus in reactions of diene-methylphosphonous dichloride adducts, *Tetrahedron Lett.*: 3689.
128. Quin. L.D., Gratz, J.P., and Montgomery, R.E. (1965). Geometrical isomers from the Diels-Alder synthesis of 3-phospholene derivatives, *Tetrahedron Lett.*: 2187.
129. Quin, L.D., Gratz, J.P., and Barket, T.P. (1968). Structure of diene-phosphonous dihalide addition products and of derived phospholenes and phospholene oxides, *J. Org. Chem.*, *33*: 1034.
130. Quin, L.D., and Humphrey, J.S. (1961). Synthesis of arylphosphonous dichlorides by reduction of diazonium fluoroborate-phosphorus trichloride reaction products, *J. Am. Chem. Soc.*, *83*: 4124.
131. Rohmberg, A., and Tavs, P. (1967). Reduktion der *O*-Alkylsalze von Phosphinoxiden, Phosphonaten und

Phosphoniten, *Monats. Chem.*, *98*: 105.
132. Mathey, F., and Maillet, R. (1980). Reduction des Oxydes de Phosphines par le Systeme Cp_2TiCl_2-Mg, *Tetrahedron Lett.*, *21*: 2525.
133. Collie, J.N., and Reynolds, F. (1915). The removal of oxygen from triphenylphosphine oxide, *J. Chem. Soc.*, *107*: 367.
134. Horner, L., Beck, P., and Hoffmann, H. (1959). Reduktion von Phosphorverbindungen mit Alkalimetalles, *Ber.*, *92*: 2088.
135. Horner, L., and Beck, P. (1960). Uber den Verlauf der Spaltung von Triphenylphosphinoxyd mit Natrium, *Ber.*, *93*: 1371.
136. Marchenko, A.P., Koidan, G.N., Povolotskii, M.I., Pinchuk, A.M. (1983). Reduction of tetrakis(dialkylamino)phosphonium halides with sodium in liquid ammonia, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *53*: 1364.
137. Kaim, W., Hanel, P., Lechner-Knoblauch, U., and Bock, H. (1982). Radikalanionen als Zwischenstufen bei der reduktiven Entschwefwlung tertiarer Phosphansulfide, *Ber.*, *115*: 1265.
138. Ivin, S.Z., Karavanov, K.V., and Lysenko, V.V. (1964). Study of complex compounds of alkyl- and polyalkylchlorophosphines with aluminum chloride. III. preparation of complex compounds of trialkyldichlorophosphines with aluminum chloride and their reduction, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *34*: 846.
139. Denney, D.B., and Gross, F.J. (1967). Reaction of triphenylphosphine dihlaides with Grignard and organolithium reagents, *J. Org. Chem.*, *32*: 3710.
140. Wittig, G., and Cristau, H.-J. (1969). Reaction du phenyllithium avec l'oxyde de triphenylphosphine, *Bull. Soc. Chim. Fr.*: 1293.
141. Avar, G., and Neumann, W.P. (1977). Abfangreaktionen Kurzlebiger Radikale. XVII. Reaktionen von Radikalen $Me_3Sn^{\cdot}$ mit P=S- oder P-S-Gruppen in Organophosphorverbindungen, *J. Organomet. Chem.*, *131*: 215.
142. Masaki, M., and Kakeya, N. (1977). Hydrogenolysis of trisubstituted dichloro- phosphoranes - a new method for

deoxygenation of oxophosphoranes, *Angew. Chem., Int. Ed. Engl., 16*: 552.
143. Masaki, M., and Kakeya, N. (1979). Tertiary phosphines, *Jpn. Kokai Tokkyo Koho 79 84,528.*
144. Horner, L., Winkler, H., Rapp, A., Mentrup, A., Hoffmann, H., and Beck, P. (1961). Phosphororganische Verbindungen. XXX. Optisch akitve tertiare Phosphine aus optisch aktiven quartaren Phosphoniumsalzen, *Tetrahedron Lett.*; 161.
145. Samaan, S. (1979). Synthese, Konfiguration und Konformation Isomerer 1,4-Heterophos-phorinane, *Phosphorus Sulfur*, *7*: 89.
146. Horner, L., and Jordan, M. (1980). Phosphororganische Verbindungen. 89. Quartare Phosphoniumsalze mit Heteroatomen am Phosphor Herstellung. Eigenschaften und Elektroduktive Spaltung, *Phosphorus Sulfur*, *8*: 209.
147. Matschiner, Von H., Tzschach, A., and Steinert, A. (1970). Kathodische Reduktion von Phosphor- und Arsenoorganoverbindungen, *Z. anorg. allg. Chem., 373*: 237.
148. Kaim, W. (1981). On the reduction of aromatic phosphane derivatives with electrons. I., *Z. Naturfor., 86b*: 150.
149. Morgan, P.W., and Herr, B.C. (1952). Some dicarboxylic acids and esters containing the phosphine oxide group, *J. Am. Chem. Soc., 74*: 4526.
150. Quast, H., and Heuschmann, M. (1978). 1,2,3-Tri-*tert*-butylphosphirane oxide and its thermal decomposition into (Z)-2,2,5,5-tetramethyl-3-hexene and *tert*-butylphosphinidene oxide, *Angew. Chem., Int. Ed. Engl., 17*: 867.
151. Quast, H., and Heuschmann, M. (1982). *tert*-Butylphosphinidenoxid und (Z)-2,2,5,5-Tetramethyl-3-hexen durch stereospezifische thermische [2+1]-Cycloeliminierung aus *r*-1,*t*-2,*t*-3-Tri-*tert*-butylphosphiran-1-oxid, *Ber., 115*: 901.
152. Stille, J.K., Eichelberger, J.L., Higgins, J., and Freeburger, M.E. (1960). Phenylphosphinidene oxide. Thermal decomposition of 2,3-benzo-1,4,5,6,7-pentaphenyl-7-phosphabicyclo[2.2.1]hept-5-ene oxide, *J. Am. Chem. Soc., 94*: 4761.
153. Green, M. (1965). The reaction of bicyclo[2.2.1]-heptadiene with methylphosphonous dichloride, *J. Chem.*

Soc.: 541.
154. Katz, T.J., and Turnblom, E.W. (1970). Stable cycloalkyl pentavalent phosphoranes, *J. Am. Chem. Soc.*, *92*: 6701.
155. Wittig, G., and Rieber, M. (1949). Preparation and properties of pentaphenylphosphorus, *Ann.*, *562*: 187.
156. Wittig, G., and Geissler, G. (1953). Zur Reaktionsweise des Pentaphenyl-phosphors und einiger Derivate, *Ann.*, *580*: 44.
157. Wittig, G., and Maercker, A. (1964). Zur Reaktionweise aromatischer Spirophosphorane, *Ber.*, *97*: 747.
158. Hellwinkel, D. (1965). at-Komplexe mit sechsbindungem Phosphor, *Ber.*, *98*: 576.
159. Hellwinkel, D., and Lindner, W. (1976). Die Phosphoran-Phosphin-Umlagerung; Mechanismus und Stereochemie, *Ber.*, *109*: 1497.
160. Markl, G., and Merz, A. (1971). Umlagerung von 1.2-Dialkyldihydrophosphabenzolen zu 1.1-Dialkyl-phosphabenzolen, Thermolyse zu 1-unsubstituierten Phosphabenzolen, *Tetrahedron Lett.*: 1215.
161. Kanter, H., Mach, W., and Dimroth, K. (1977). 1,1-Dihalogen-λ^5- phosphorine, *Ber.*, *110*: 395.
162. Markl, G., Habel, G., and Baier, H. (1979). 2- und 3-Phospha-9-azafluorene Indolo-λ^5-phosphrine, *Phosphorus Sulfur*, *5*: 257.
163. Tomioka, H., and Izawa, Y. (1977). Stereochemistry and kinetics of photochemical fragmentation of 1-phenyl-3-phospholene oxides, *J. Org. Chem.*, *42*: 582.
164. Tomioka, H., Takata, S., Kato, Y., and Izawa, Y. (1980). Photochemistry of phospholenes. Part 7. Element effects on the photofragmentation of 3,4-dimethyl-1-phenyl-3-phospholene. Phosphinothioylidene, *J. Chem. Soc., Perkin Trans. II*: 1017.
165. Holand, S., and Mathey, F. (1981). New method for building carbon-phosphorus heterocycles, *J. Org. Chem.*, *46*: 4386.
166. Berlin, K.D., and Taylor, H.A. (1964). The reactions of aroyl halides with phosphites. Esters of aroylphosphonic acids, *J. Am. Chem. Soc.*, *86*: 3862.
167. Kabachnik, M.I., and Rossiiskaya, P.A. (1945). Esters of α-ketophosphonic acids, *Izv. Akad. Nauk S.S.S.R., Otd.*

Khim. Nauk: 365.
168. Scherer, H., Hartmann, A., Regitz, M., Tungyai, B.D., and Gunther, H. (1972). Carbene. V. 7-Phosphono-7-aryl-norcaradiene, *Ber.*, *105*: 3357.
169. Kugler, R., Pike, D.C., and Chin, J. (1978). Kinetics and mechanism of the reaction of dimethyl acetylphosphonate with water. Expulsion of a phosphonate from a carbonyl hydrate, *Can. J. Chem.*, *56*: 1792.
170. Kojima, M., Yamashita, M., Yoshida, H., Ogata, T., and Inokawa, S. (1979). Useful methods for the preparation of unsaturated phosphonates (1-methylenealkane-phosphonates), *Synthesis*: 147.
171. Sekine, M., Satoh, M., Yamagata, H., and Hata, T. (1980). Acylphosphonates: P-C bond cleavage of dialkyl acylphosphonates by means of amines. Substituent effects for acylation of amines, *J. Org. Chem.*, *45*: 4162.
172. Zon, J. (1981). A simple preparation of diethyl 1-acylamino-1-ethenephosphonates, *Synthesis*: 324.
173. Zon, J. (1984). Synthesis of diisopropyl 1-nitroalkenephosphonates from diisopropyl 1-oxoalkanephosphonates, *Synthesis*: 661.
174. Ohler, E., El-Badawi, M., and Zbiral, E. (1985). Ein einfacher Weg zu α-substitutieren (*E*)-3-Oxo-1-alkenyl-phosphonsaureestern, *Monatsh. Chem.*, *116*: 77.
175. Vishnyakova, G.M., Smirnova, T.V., and Tarakanova, L.A. (1985). Synthesis of coumarin-containing α-ketophosphonates, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *55*: 1076.
176. Sekine, M., and Hata, T. (1978). Convenient synthesis of unesterified acylphosphonic acids, *J. Chem. Soc., Chem. Commun.*: 285.
177. Sekine, M., Kume, A., Nakajima, M., and Hata, T. A new method for acylation of enolates by means of dialkyl acylphosphonates as acylating agents, *Chem. Lett.*: 1087.
178. Sekine, M., Yamagata, H., and Hata, T. Silyl phosphite equivalents: 2,2,2-trichloroethoxycarbonylphosphonates, *J. Chem. Soc., Chem. Commun.*: 970.
179. Alfonsov, V.A., Zamaletdinova, G.U., Batyeva, E.S., and Pudovik, A.N. (1984). New path in reaction of silyl phosphites with acetyl chloride, *J. Gen. Chem. U.S.S.R.*,

Engl. Transl., *54*: 414.
180. Welter, W., Hartmann, A., and Regitz, H. (1978). Isomerization reactions of phosphoryl-vinyl-carbenes to phosphorylated cyclopropenes, allenes, acetylenes, indenes, and 1,3-butadienes, *Ber.*, *111*: 3068.
181. Horner, L., and Roder, H. (1970). Notiz uber die reduktive Umwandlung von Carbonsaure in ihre Aldehyde, *Ber.*, *103*: 2984.
182. Terauchi, K., and Sakurai, H. (1970). Photochemical studies of the esters of aroylphosphonic Acids, *Bull. Chem. Soc. Jpn.*, *43*: 883.
183. Dyakov, V.M., Orlov, N.F., Gusakova, G.S., and Zakharova, N.M. (1971). Triorganosilyl derivatives of *o*- and *p*-substitutedbenzoylphosphonic acids, *Kremniiorg. Mater.*: 139.
184. Dyakov, V.M., and Voronkov, M.G. (1973). Trialkylsilyl esters of polyfluoroacylphosphonic acids, *Bull. Acad. Sci. U.S.S.R., Engl. Transl.*: 379.
185. Winkler, T., and Bencze, W.L. (1980). Perkow reaction induced C,C-bond formation, *Helv. Chim. Acta*, *63*: 402.
186. Tam, C.C., Mattocks, K.L., and Tischler, M. (1981). Enol-keto tautomerism of α-ketophosphonates, *Proc. Nat. Acad. Sci. U.S.A.*, *78*: 3301.
187. Szpala, A., Tebby, J.C., and Griffiths, D.V. (1981). Reaction of phosphites with unsaturated acid chlorides: synthesis and reactions of dimethyl but-2-enoylphosphonate, *J. Chem. Soc., Perkin Trans. I*: 1363.
188. Griffiths, D.V., Jamali, H.A.R., and Tebby, J.C. (1981). Reactions of phosphites with acid chlorides. Phosphonic attack at the carbonyl oxygen of α-ketophosphonates, *Phosphorus Sulfur*, *11*: 95.
189. Ohler, E., and Zbiral, E. (1984). Cyclisierungsreaktionen von Diazoalkenylphosphonsaureestern Synthese von Pyrazolyl- und 2,3-Benzodiazepinylphosphonsaure-estern, *Monatsh. Chem.*, *115*: 629.
190. Cann, P.F., Warren, S., and Williams, M.R. (1972). Electrophilic substitution at phosphorus: reactions of diphenylphosphinyl systems with carbonyl compounds, *J. Chem. Soc., Perkin Trans. I*: 2377.
191. Jugelt, W., Andreae, S., and Schubert, G. (1971). Zur

Kinetik der Spaltung der Phosphor-Kohlenstoff-Bindung in Aroyl-Phosphonsaurediathylestern, *J. prakt. Chem.*, *313*: 83.

192. Andreae, S., and Jugelt, W. (1973). Allgemeine Basekatalyse der hydrolytischen Spaltung der Phosphor-Kohlenstoff-Bindung des Benzoyl-Phosphonsaurediathylestern, *Z. Chem.*, *13*: 136.
193. Kluger, R., and Chin, J. (1978). Rates of formation and decomposition of tetrahedral intermediates in the hydrolysis of dimethyl aroylphosphonates. Substituent effects on a model for carboxylate ester hydrolysis, *J. Am. Chem. Soc.*, *100*: 7382.
194. Narayanan, K.S., and Berlin, K.D. (1979). Hydrolysis of diethyl benzoylphosphonate in aqueous and hydrochloric acid solutions. Postulation of a stable pentavalent phosphorus-containing intermediate, *J. Am. Chem. Soc.*, *101*: 109.
195. Lindner, E., and Frey, G. (1980). Untersuchungen uber sterische und elektronische Einflusse auf die Reaktivitat von Acetyl(diorganyl)phosphanen und deren Oxide, *Ber.*, *113*: 3268.
196. Soroka, M., and Mastalerz, P. (1973). Cleavage of the phosphorus-carbon bond in α-oxo phosphonic esters, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *44*: 446.
197. Pudovik, A.N., Gazizov, T.K., and Pashinkin, A.P. (1968). Cleavage of phosphorus-carbon bond in (chlorine-substituted acetyl)phosphonic esters, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *38*: 2712.
198. Pashinkin, A.P., Gazizov, T.K., and Pudovik, A.N. (1970). Cleavage of phosphorus-carbon bond in α-oxo phosphonic esters, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *40*: 24.
199. Engel, R. (1988). Phosphorus addition at sp^2 carbon, *Org. React.*, *36*: 175.

CHAPTER 6

PHOSPHORUS CONTAINING *UMPOLUNG* REAGENTS

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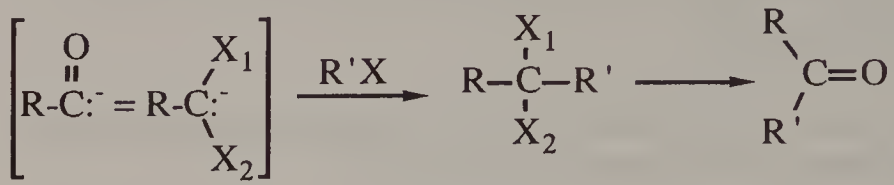
I. Introduction

One of the most important synthetic concepts to emerge within the past two decades is the principle of charge affinity inversion or *umpolung*. It was Seebach who in a review article first drew attention to the important potential of this concept to synthetic organic chemistry.[1] Reversible polarity inversions offer the greatest flexibility as they permit subsequent restoration of the normal reactivity mode. Of particular interest has been the design and development of a wide variety of acyl anion equivlents (nucleophilic acyl anions). The carbon atom of the C=O group as found in aldehydes, ketones, esters, acid halides, anhydrides, *etc.* is electrophilic, *i.e.* the polarization of the CO bond puts a partial plus charge on the carbonyl carbon atom ($C{=}O \leftrightarrow {}^{+}C\text{-}O^{-}$). Many different types of carbon nucleophiles will attack at this electrophilic carbon atom to form a new C-C bond. To complement this type of carbonyl group reactivity, a process of reversed polarity, *i.e.* one in which the C=O function is the nucleophilic and not the electrophilic reactant, has been sought for a long time. The desired synthetic transformations to which nucleophilic acylation might be applied are quite ordinary: protonation, alkylation, heteroatom-heteroatom bond heterolysis, C=O, C=N and C≡N addition, acylation of organic substrates, heterocycle ring cleavage, acylation of metalloid and metal halides, to list just the most obvious ones. An example of one of these processes is shown in Scheme I. Thus, treatment of such an anion equivalent with electrophiles such as aldehydes, ketones, or oxiranes give the desired adducts. Subsequent unmasking of the latent carbonyl function then produces the hydroxycarbonyl or dicarbonyl compounds.

Among the most popular acyl anion equivalents are the dithioacetals,[2] α-(dialkylamino)acetonitriles,[3] and the O-protected cyanohydrins[4,5] as well as phosphorus containing reagents.[2,6]

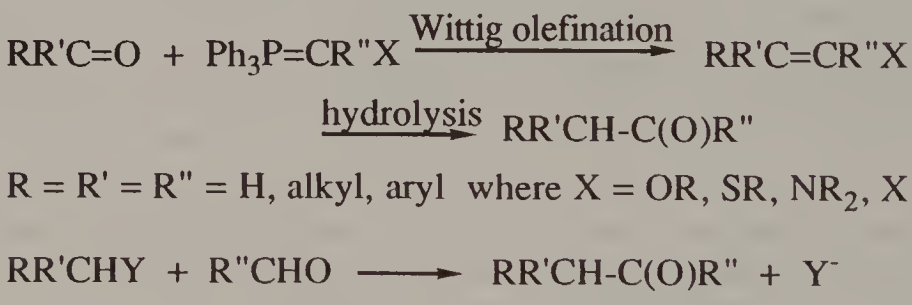
Major developments after Seebach's review through 1984 including acyllithium reagents have been outlined.[7,8]



Scheme I

The prospective provided in this Chapter is intended to review research in the area of polarity inversion and latent functionality in phosphorus containing *umpolung* reagents which function as synthetic equivalents of normally inaccessible intermediates. This review, however, should not be taken as a comprehensive one, though a serious effort has been made to include the most important developments.

The net operations obtained using acyl anion equivalents may be classified into two main categories: (a) direct addition of masked acyl anions, and (b) reductive nucleophilic acylation (as illustrated in Scheme II). For these transformations involving phosphorus compounds, three classes of reagents were used, namely, phosphoranes, α-heterosubstituted phosphonate carbanions, and α-heterosubstituted phosphine oxides.



Scheme II

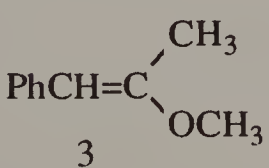
II. Phosphoranes

Phosphoranes bearing OR, SR, SeR, halogens, or NR_2 groups at the ylide carbon atom act as acyl anion equivalents. The heteroatom substituted olefins resulting from a Wittig reaction -

vinyl ethers, thioethers, or selenoethers in the case of OR, SR, and SeR respectively, and vinyl halides in the case of halogen yield carbonyl compounds after hydrolysis. They were obtained *via* a reaction involving an acyl anion (Scheme II).

As early as 1958, Levine,[9] and a little later Wittig[10] used a phosphorane, namely methoxymethylenetriphenylphosphorane (1) as an acyl anion equivalent for a novel aldehyde synthesis. The American author used this synthon for the preparation of 5α,22β,25-D-spirostane-3-carboxaldehyde whereas Wittig obtained diphenylacetaldehyde by the reaction of (1) with benzophenone and subsequent hydrolysis. Triphenyl(methoxymethyl)phosphonium chloride was prepared by the reaction of triphenylphosphane and chloromethyl methyl ether. Upon treatment with base it is converted *in situ* to (1). Since then there have been numerous reports on utilizing (1) for a one carbon homologation of carbonyl compounds.[11-27] The phosphorane (1) is also the intermediate in a key step of multisequence syntheses to a variety of interesting, naturally occurring molecules and their analogues, *e.g.* L-vancosamine,[18] (-)-upial,[24] a prostaglandin, PGH_2, and dehydroogoniol.[27] It has been reported that occasionally the hydrolysis step (unmasking) of the enol ether is troublesome and consequently several methods for the unmasking were developed.[28,29]

Coulson[30] in 1964 reported the synthesis of methyl ketones in good to excellent yields by reaction of α-methoxyethylidenetriphenylphosphorane (2) with a variety of aldehydes including benzaldehyde. However, an independent study by Schubert and Fischer[31] revealed that the reaction of benzaldehyde with (2) did not give the reported olefin (3). Instead, α-methoxypropiophenone (4) was obtained from this reaction. Its formation occurs by elimination of triphenylphosphane *via* the intermediacy of a zwitterionic species which rearranges by a hydride shift to (4).



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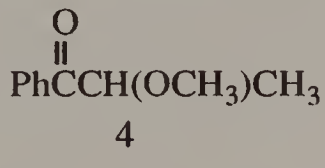
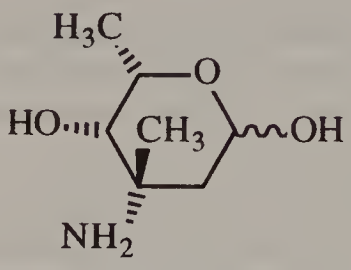


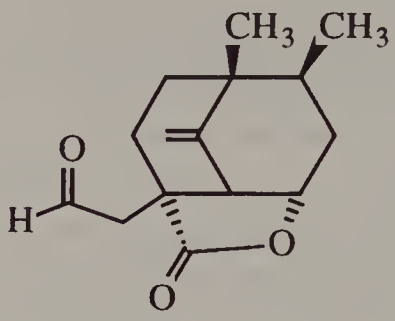
4

Based on the fact that tetrahydropyranyloxy compounds could be hydrolyzed under milder conditions than their methoxy

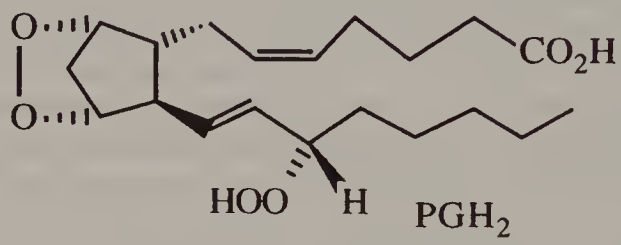
analogues, H. Schlude[32] had unsuccessfully attempted to employ triphenyl[(tetrahydropyranyloxy-2)methyl]phosphonium chloride toward the synthesis of the nitroxy aldehyde (5).



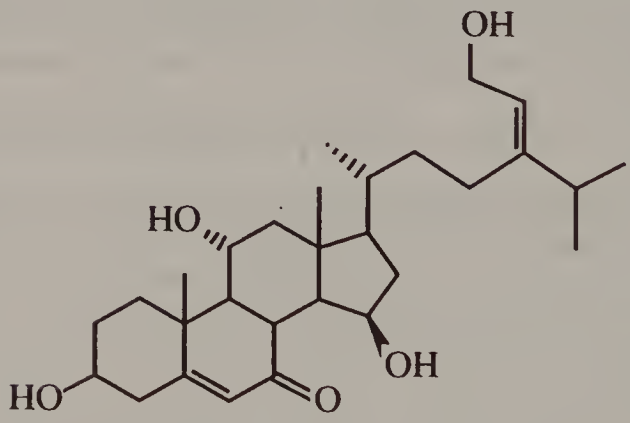
L-vancosamine



(-)-upial



PGH_2

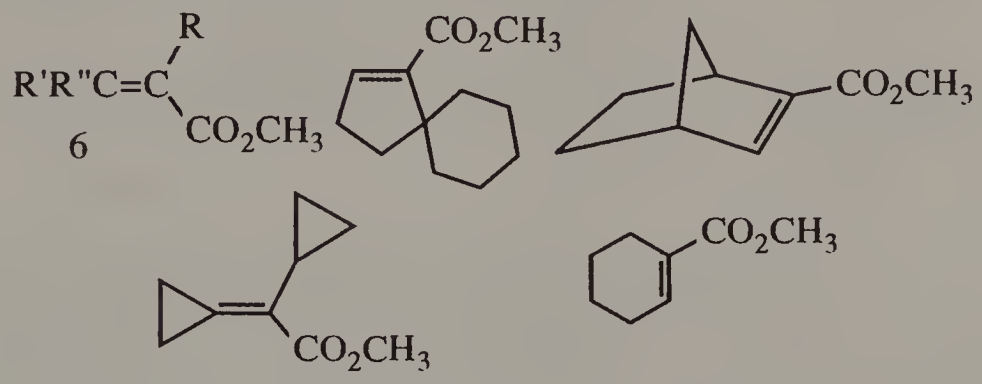


dehydrooogoniol

5

An attractive procedure for the preparation of α,β-unsaturated esters (6) involving the acyl anion equivalent (3) from carbonyl

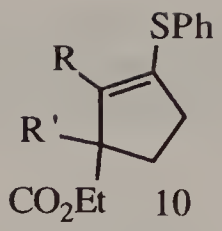
compounds by one-carbon chain elongation involves the fragmentation of allylic hydroperoxides that may be obtained by a singlet oxygen oxidation of methyl vinyl ethers. Examples of the resulting α,β- unsaturated esters are shown.



The unsymmetrical ketones and aldehydes (7) were synthesized in good yield via vinyl sulfide derivatives (8) obtained from α-thioalkylidenetriphenylphosphorane (9) and carbonyl compounds.[34] The phosphorane (9) was obtained from 2 mol of the appropriate alkylidenetriphenylphosphorane and 1 mol of sulfenyl chloride (RSCl).

R = Ph, *n*-C_4H_9; R' = H, CH_3; R" = $PhCH_2$, *n*-C_4H_9; R"' = H

In 1975, Marino and Landick[35] reported an elegant synthesis of cyclopentenones (14) *via* the nucleophilic acylation methodology. The masked acyl anion is ylide (11), formed by treatment of β-ketoesters (12) with the phosphonium salt (13). The annelation sequence involves an intramolecular Wittig cycloolefination of (11) to form the vinyl sulfides (10) which could be hydrolyzed to the γ-ketoacid (14). The phosphonium salt (13) represents the equivalent of the acyl zwitterion $^{+}CH_2CH_2C(O)^{-}$.



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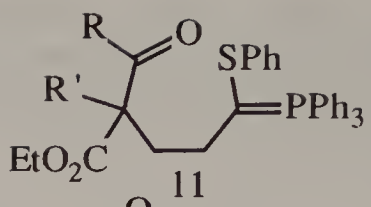

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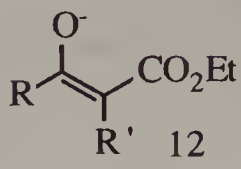

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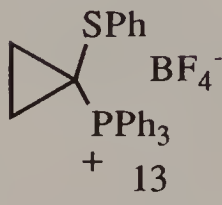

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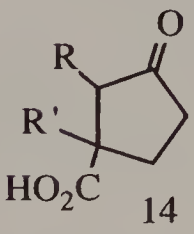
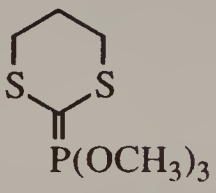


14

R = CH_3, H;
R' = H, $PhCH_2$

The 1,3-dithiacyclohexylidenetrimethoxyphosphorane (15) was recognized as a useful reagent (namely, a carboxylic acid anion equivalent) for the selective transformation of aldehydes to the homologous acids. In this transformation ketene thioacetals are intermediates (16). The ylide (15) was easily obtained by the reaction of 1,3-dithiacyclohexan-2-thione with excess trimethyl phosphite.



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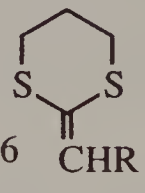
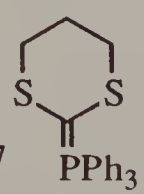


16

Ten years later Kruse, *et al.* reported on the application of Wittig reactions using 1,3-dithiacyclohexylidenetriphenylphosphorane for the same purpose.[37] This synthon was prepared from the readily available 1,3-dithiane. Upon chlorination with sulfuryl chloride, 1,3-dithiane afforded 2-chloro-1,3-dithiane which reacted with triphenylphosphane to give the corresponding phosphonium chloride. This salt was easily converted to ylide (17) on treatment with base. Though the ylide showed a good reactivity toward aldehydes, it did not react with ketones.



17

In analogy to vinyl sulfides, phenylselenovinyl ethers (19)

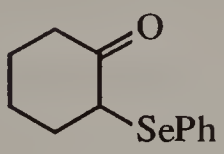
could be obtained in good yield by the reaction of the selenophosphoranes (18) with aldehydes.[38] These were converted into the corresponding carbonyl compounds by treatment with mercuric chloride in aqueous acetonitrile.[39]

$Ph_3P{=}CHRSePh$ (18) $\qquad$ $R'CH{=}CRSePh$ (19)

R = H, CH_3; R' = Ph, Et, *n*-C_6H_{13}, *p*-$CH_3C_6H_4$, *p*-$NO_2C_6H_4$

However, the reaction of ylide (18) with ketones (*e.g.* cyclohexanone) produced α-phenylselenoketones such as (20) as the only products.[40] The α-phenylselenophosphoranes (18) were prepared by a transylidation reaction of PhSeBr with two equivalents of an alkylidenetriphenylphosphorane. The type (18) compounds also could be obtained by treating the corresponding selenophosphonium salts with *n*-BuLi. These salts were prepared by quaternization of triphenylphosphane with PhSeCHRBr.

By using phosphoranes of type (21), both aldehydes and ketones may be converted in fair yields to di- or trisubstituted vinyl halides.[41-48]



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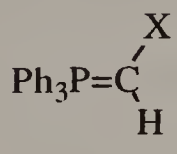


21

R = H, CH_3, C_2H_5, C_3H_7
X = Cl, Br

Although most synthetic procedures for the hydrolysis of vinyl halides to the corresponding carbonyl compounds generally involve strong acidic conditions,[49] several milder methods have recently been reported which employ transition metal catalysts such as salts of Cu(I),[50] Ti(IV),[51], Hg(II),[52,53] or Pd(II).[54] The chloroylide (21) was synthesized either by the reaction of methylene chloride with *n*-BuLi and triphenylphosphane[41] or from the reaction of chloroiodomethane with triphenylphosphane to yield chloromethyltriphenylphosphonium iodide which was treated with potassium *t*-butoxide.[44] The bromoylide (21) (R = H) was obtained from triphenylhydroxymethylphosphonium bromide and

phosphorus pentabromide followed by treatment of the resultant bromomethyltriphenylphosphonium bromide with lithium piperidide.[55] The bromoylides (21) (R = methyl, ethyl) were prepared by first alkylating triphenylphosphonium dibromomethylide with methyl or ethyl bromide to yield the corresponding salts, which then react smoothly with butyllithium at low temperature.[45]

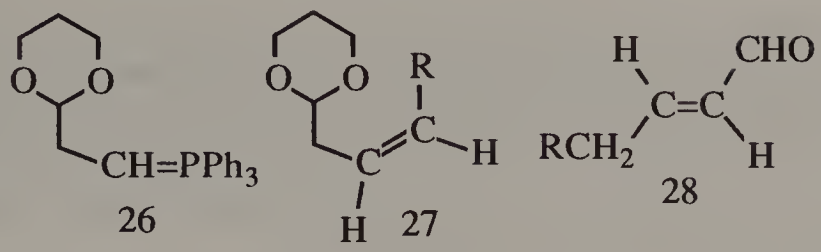
The reaction of silylated ylides, *e.g.* (trimethylsilylmethylene)triphenylphosphorane (22)[56] with carbonyl compounds[57] did not proceed according to the usual scheme, but led to unexpected products by rather involved mechanisms which were invoked to explain the generally complicated product distribution.

An efficient procedure for the vinylogous, reductive nucleophilic acylation of carbonyl groups has recently been developed.[59,60] Thus, 3-methoxyallylidenetriphenylphosphorane has been found to be a highly useful reagent for the facile transformation of aldehydes or ketones into 1-methoxy-1,3-butadienes (23) which may be either isolated or converted directly to the corresponding α,β-unsaturated aldehydes by acid hydrolysis.[59] The ylide (24) could be obtained by treating 3-methoxy-2-propenyltriphenylphosphonium bromide with *n*-BuLi. The phosphonium salt (25) was synthesized in good yield by the reaction of methoxyallene with triphenylphosphonium bromide.[59]

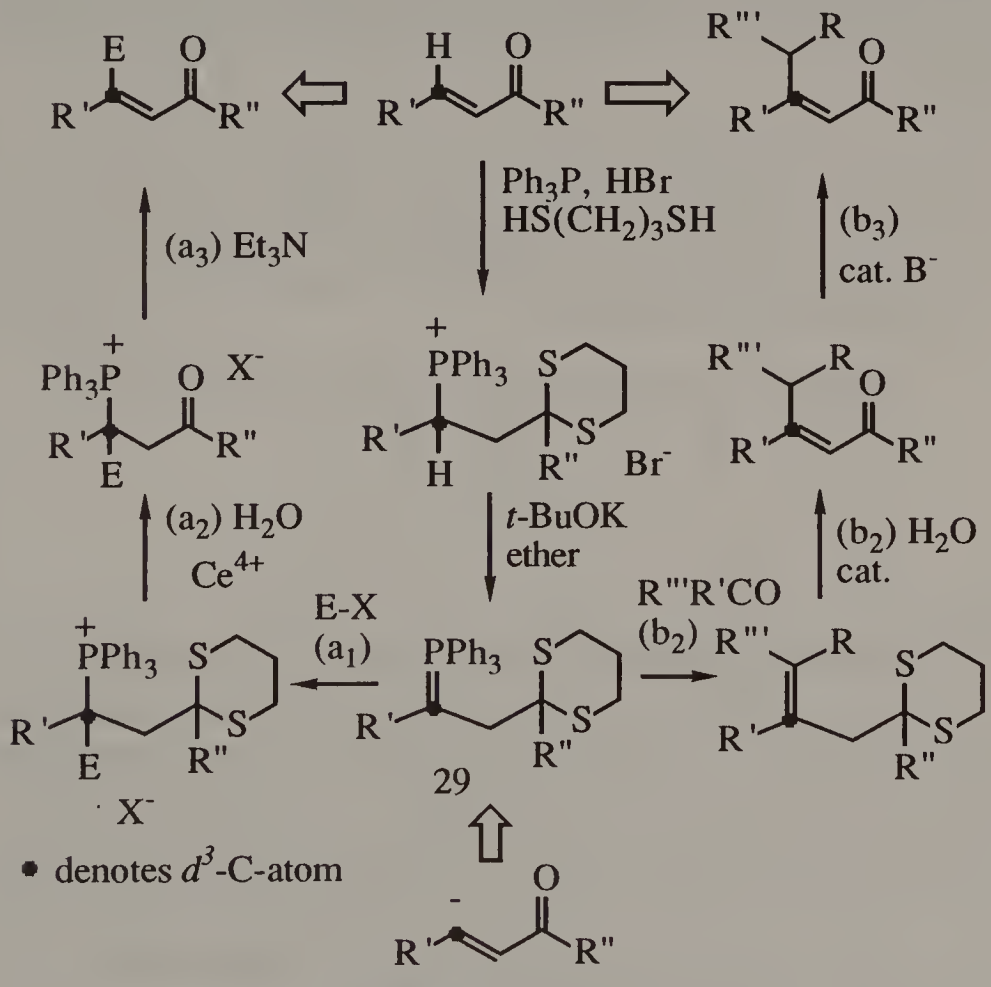
$Ph_3P{=}CH\text{-}SiMe_3$ (22) $\qquad$ $RR'C{=}CH\text{-}CH{=}CH\text{-}OMe$ (23)

$Ph_3P{=}CH\text{-}CH{=}CH\text{-}OMe$ (24) $\qquad$ $Ph_3\overset{+}{P}\text{-}CH_2\text{-}CH{=}CH\text{-}OMe\ Br^-$ (25)

2-(1,3-Dioxan-2-yl)ethylidenetriphenylphosphorane (26) was introduced by Stowell and Keith[60] as a convenient new reagent for providing α,β-unsaturated aldehydes. Thus, reaction of (26) with various aliphatic aldehydes in Wittig fashion furnished the cyclic acetals of *cis*-3-alkenals (27). Hydrolysis of (27) occurred with concomitant isomerization of the double bond using an acidic chromium(III) chloride solution to give the α,β-unsaturated aldehydes (28) (R' = H).[60] The phosphorane (26) was generated from 2-(1,3-dioxan-2-yl)ethyltriphenylphosphonium bromide upon treatment with potassium *t*-butoxide.[60]



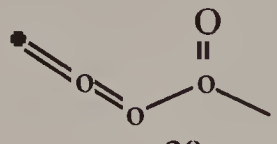
The reversible d^3 (the donor site is three carbon atoms removed from the O-heteroatom) *umpolung* of α,β-ethylenic ketones and aldehydes was reported to occur *via* ylides of the type (29) which were synthetic equivalents of β-acylvinylanions along two different pathways, (a) and (b), as illustrated in Scheme III.[61-64]



Scheme III

The preparation of the ylides (29) was easily accomplished from the corresponding phosphonium salts upon reaction with one equivalent of potassium *t*-butoxide in ether at room temperature.[61] The phosphonium salts were synthesized by the reaction of triphenylphosphonium bromide with α,β-unsaturated carbonyl compounds and subsequent thioacetalation.

In 1982 Cristau, *et al.* reported on an a^4 (an acceptor site four carbon atoms removed from the O-heteroatom) *umpolung* of α-allenic ketones (30) using the triphenylphosphino group.[65] It resulted in inducing an electrophilic character at the carbon in the γ-position relative to the carbonyl function. It also changed the regioselectivity of the additions of active hydrogen compounds on the carbon- carbon double bond to give finally the adducts (31). The adoption of this concept was used to furnish a novel synthetic approach to the functionalized morpholine molecules (32) and (33).[66]



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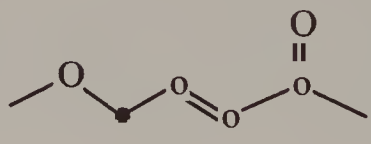
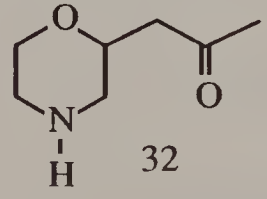


31

• denotes an a^4-C-atom

o denotes C-atom between an a^4-C-atom and heteroatom



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33

III. α-Heterosubstituted Phosphonate Carbanions

α-Heterosubstituted phosphonate carbanions in a modified Horner-Emmons reaction can also serve as acyl anion equivalents, and thus serve as *umpolung* reagents. The Horner-Emmons reaction, which is quite different from the Wittig reaction since it proceeds *via* a carbanion instead of a neutral ylide, also was used in *umpolung* reactions. Thus, with aldehydes and ketones the α-heterosubstituted phosphonate stabilized carbanions would effect conversions as shown in Scheme IV.

$$(RO)_2\overset{\overset{O}{\|}}{P}\text{-}CXR' + R''R'''C{=}O \longrightarrow R''R'''C{=}CRX$$

R = Me, Et, Ph; R' = R'' = R''' = H, alkyl, aryl
X = Cl, I, NR', OR'''', SR'
R'''' = alkyl, 2-THPyl, $SiMe_3$

Scheme IV

Such reactions have led to numerous studies. The work by Zimmer's group starting in 1965 with N and Cl as heteroatoms led *via* enamine, vinylogous enamine, and enynamines hydrolyses to the corresponding deoxybenzoins, vinylogous deoxybenzoins, and yne analogs of deoxybenzoins. Strategic substitution opened the way for the synthesis of numerous heterocycles, including indoles, quinolines, benzoquinolines, naphthyridines, phenanthrolines and benzofurans.[6,66a,67,97,100,109]

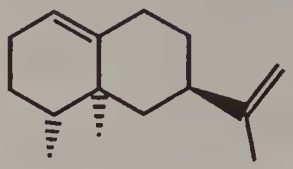
In 1963 Green reported on the synthesis of methylsubstituted vinyl sulfides (8) (R' = Me; R = H) upon treatment of a variety of aldehydes and ketones with diethyl methylthiomethanephosphonate (34) in ethylene glycol dimethyl ether and the presence of sodium hydride at 50-60°.[68] Compound (34) was synthesized by an Arbuzov reaction between methylthiomethyl chloride and triethyl phosphite.

$$(EtO)_2\overset{\overset{O}{\|}}{P}CH_2SCH_3$$

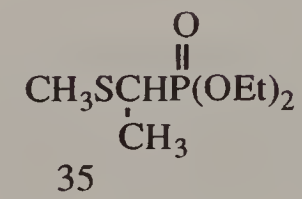
34

Later, Corey and Shulman utilized the olefin synthesis *via* phosphonate carbanions for the preparation of vinyl sulfides.[39] Subsequent hydrolysis of these compounds furnished unsymmetrical ketones. These authors had found that (34) was metalated readily by *n*-BuLi in tetrahydrofuran at -70° and could be alkylated to yield diethyl (1-methylthio)ethanephosphonate (35) or diethyl (1-methylthio)nonanephosphonate (36). Sequential treatment of phosphonates (35) and (36) with *n*-BuLi and an aldehyde or ketone gave vinyl sulfides (8).[39] Similarly, phosphonates (37) and (38) were used as readily accessible reagents to synthesize vinyl sulfides.[69,70] This synthetic methodology has been used as an

approach for the synthesis of (±)-valencene.[71]



valencene



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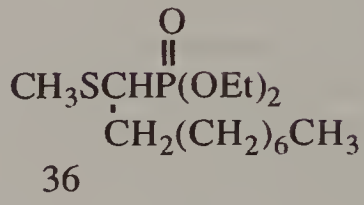

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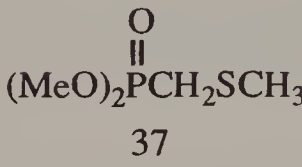

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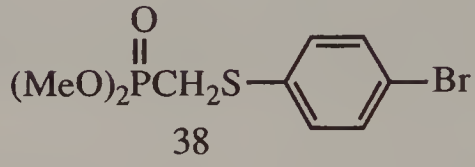
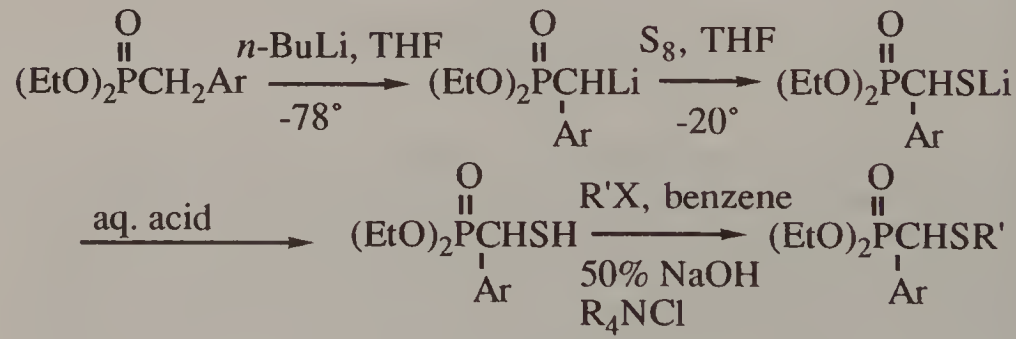


38

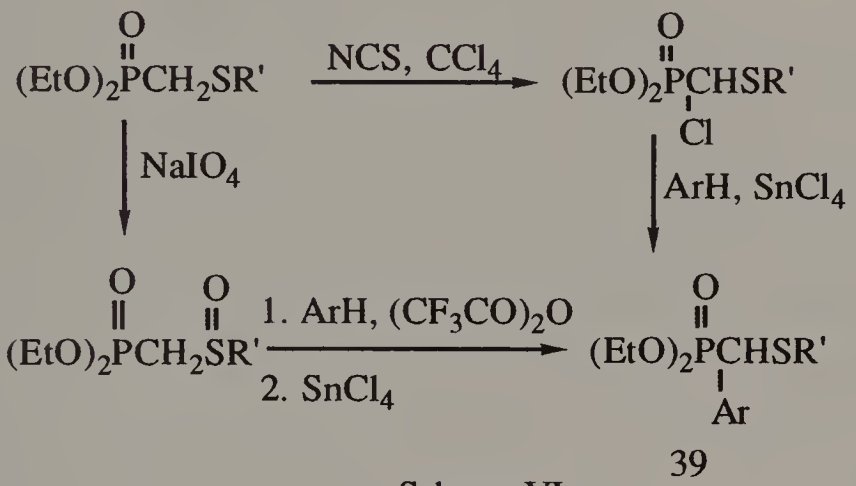
Whereas the synthesis of α-unsubstituted alkylthiomethanephosphonates was well established,[68,72-74] the preparation of the aryl analogues was only introduced much later. Their synthesis was accomplished by reaction of the anion derived from diethyl benzylphosphonate with either elemental sulfur[75] (Scheme V), or by reaction of the same anion with dialkyl disulfides.[76]



Scheme V

Recently a number of novel approaches toward this class of compounds has appeared. Thus, Oh, *et al.* reported that the Lewis acid catalyzed Friedel-Crafts reaction of aromatic compounds with diethyl chloro(methylthio)methanephosphonate afforded diethyl

1-aryl-1-methylthiomethanephosphonates (39) as shown in Scheme VI.[77] These authors also found that a Pummerer intermediate generated from diethyl methylsulfinylmethanephosphonate by a reaction with trifluoroacetic anhydride interacted with aromatic compounds in the presence of tin(IV) to provide a new synthetic route to (39).[78]



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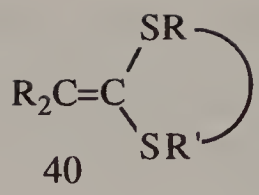
Scheme VI

A general synthesis of ketene S,S-acetals (40) and ketene O,S-acetals (41) by the Horner-Emmons reaction of carbonyl compounds with the metallated S,S- and O,S-acetals of formylphosphonates (42) and (43) respectively was reported.[37,79] Compounds of the type (42) could be prepared by three routes: (a) Arbuzov reaction of trialkyl phosphites with chlorodithioacetals,[37,79,80] (b) reaction of diethyl trimethylsilyl phosphite with orthothioformates,[81] or (c) the recently described reaction of sulfur with the lithio derivative of diethyl methylthiomethanephosphonate to give the corresponding hemiacetal which upon alkylation afforded (42).[75]

Compounds of type (43) were easily prepared by one of the following methods: (a) a Pummerer-type reaction of diethyl methylsulfinylmethanephosphonates with alcohols in the presence of iodine,[37,79] (b) reaction of the anion of diethyl methoxymethanephosphonate with sulfur followed by treatment with an alkyl halide,[75] (c) reaction of diethyl 1-chloromethanephosphonates with alcohols,[82] and (d) electrolysis of diethyl methylthiomethanephosphonate in carbon dioxide saturated 0.1 molar sodium methoxide/methanol solution.[83]



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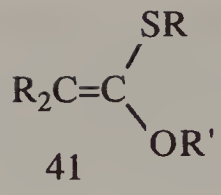

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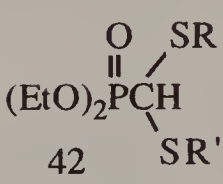

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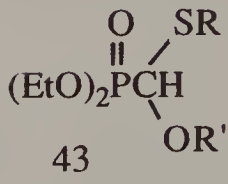
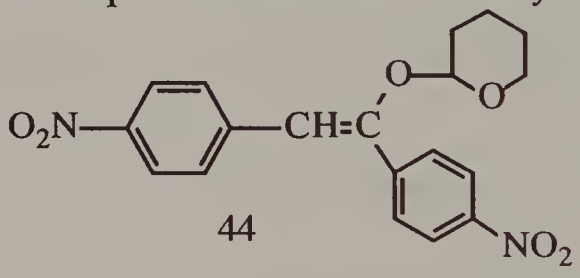


43

As early as 1969 diphenyl 1-(4-nitrophenyl)-1-tetrahydropyranylphosphonate was used by Zimmer and Hickey to synthesize the first enol ether *via* an α-heterosubstituted phosphonate carbanion when they synthesized 1,2-bis-(4-nitrophenyl)-1-tetrahydropyroxyethene (44).[83a] The phosphonate was obtained as an oily substance from diphenyl 1-hydroxy-(4-nitrophenyl)methanephosphonate and tetrahydropyran in the presence of catalytic amounts of HCl. It was converted by NaH in THF to its carbanion which reacted as anticipated with 4-nitrobenzaldehyde to yield (44).



44

Kluge (1978) used the two phosphonate reagents (45a-b) for the synthesis of enol ethers.[84] Earlier it was reported that diethyl methoxymethylphosphonate was recovered unchanged after attempted reaction with benzaldehyde and sodium hydride.[67] However, (45a-b) could be metalated with lithium diisopropylamide. Addition of aldehydes or ketones gave high yields of 1,2-adducts. Two methods were then used to prepare the desired enol ethers: (a) by treatment of the adduct with 2 equivalents of potassium *t*-butoxide (50°, 5 min), or (b) by refluxing the reaction mixture. Reagent (45a) was prepared by the reaction of methoxyethoxymethyl chloride with triethyl phosphite, and (45b) was obtained analogously from tetrahydropyranylation of dibutyl hydroxymethylphosphonate.[84]

$$(RO)_2P(=O)CH_2OR'$$

45

a R = Et, R' = $CH_2CH_2OCH_3$
b R = Bu, R' = THP

Though the synthesis and use of 1-alkoxymethanephosphonates is well documented,[85-89] the preparation of 1-alkoxy-1-arylmethanephosphonates (46), first reported by Schaumann and Grabley,[86] proved to be rather difficult and cumbersome. Their procedure called for the treatment of the cancerogenic α-chlorobenzyl alkyl ethers with triethyl phosphite in an Arbuzov reaction. Zimmer and Burkhouse found that arylaldehyde diethyl acetals reacted with triethyl phosphite in the presence of boron trifluoride diethyl etherate to yield (46). Adopting the method by Zimmer, *et al.*, the synthesis of (46) was also achieved by the reaction of arylaldehyde acetals with diethyl trimethylsilyl phosphite in the presence of stannic chloride.[91]

$$(EtO)_2P(=O)CHAr(OR)$$

46

Using O,O-acetals of diethyl formylphosphonates (47) for the synthesis of ketene O,O-acetals (48) *via* a Horner-Emmons reaction is of rather limited utility since the alkoxy group affects the stability of the α-carbanionic center.[79] Compounds of the type (48) were obtained in only low yield using (47b).[79]

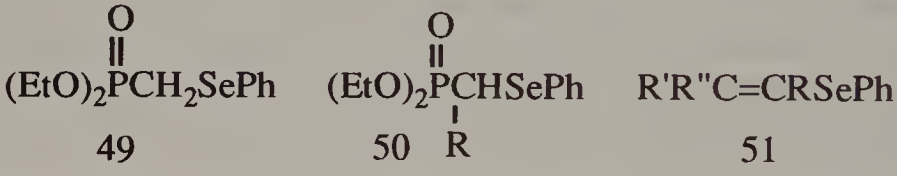
$(RO)_2P(=O)CH(OR')_2$ (47) $\qquad$ $R_2C{=}C(OR')_2$ (48)

a R = Et, R' = Et
b R = Et, 2R' = 4,5-dichloro-1,2-phenylyl

Synthesis of vinyl halides using α-chlorosubstitutedphosphonates has received little attention with respect to their service as

precursors for carbonyl functionality and to complete the reductive carbonylation sequence.[92-97]

Diethyl α-selenophosphonate (49) can be prepared by the reaction of diethyl iodomethylphosphonate and PhSeNa. The material (49) was easily alkylated by deprotonation with *n*-butyl lithium and subsequent reaction with the appropriate alkyl halide to furnish (50).[98] Unlike the selenophosphoranes, the selenophosphonate carbanions reacted with both aldehydes and ketones and thus have an advantage over the seleno substituted ylides. This methodology permits the synthesis of trisubstituted vinylic selenides of the type (51) (R" = H). They could easily be hydrolyzed at room temperature using trifluoroacetic acid to the corresponding ketones, thus completing the carbonylation sequence.



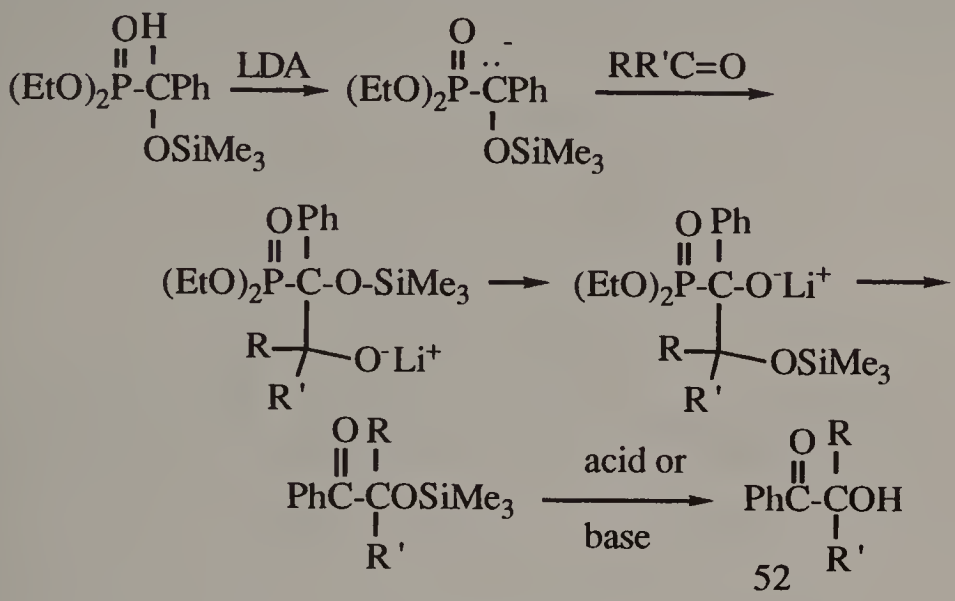
49 50 51

Independent studies by Zimmer's and Hata's groups introduced diethyl 1-(trimethylsiloxy)-1-phenylmethanephosphonate as an acyl anion equivalent.[99-100a] This compound could be prepared in excellent yield *via* an Arbuzov-type reaction by refluxing a mixture of triethyl phosphite, chlorotrimethylsilane, and benzaldehyde.[99] Zimmer observed when the anion derived from this compound reacted with aldehydes or ketones that a 1,4-oxygen-oxygen silicon migration takes place with subsequent loss of diethyl lithium phosphite and simultaneous formation of α-hydroxyketones of type (52). The ketones (52) were obtained in good yields as shown in Scheme VII.

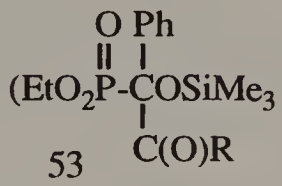
Hata, *et al.*[101,102] reported that lithiated diethyl 1-trimethylsiloxyalkylphosphonates could be alkylated and converted to the corresponding ketones by treatment with 1 *N* NaOH-EtOH (1:1, v/v) or by a two-step procedure involving pretreatment with a catalytic amount of *p*-toluenesulfonic acid in methanol.

Diethyl 1-(trimethylsiloxy)-1-phenylmethanephosphonate was used as an α-hydroxybenzyl anion equivalent.[103,104] The lithiated form of this compound underwent facile acylation with various acylating agents to afford the corresponding α-acylated

products (53) which upon treatment with NaOH-EtOH underwent P-C bond cleavage with simultaneous elimination of diethyl phosphate to give α-hydroxyketones as major products along with small amounts of the corresponding 1,2-diketones.



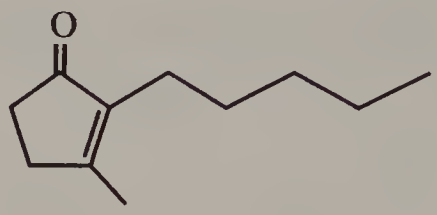
Scheme VII



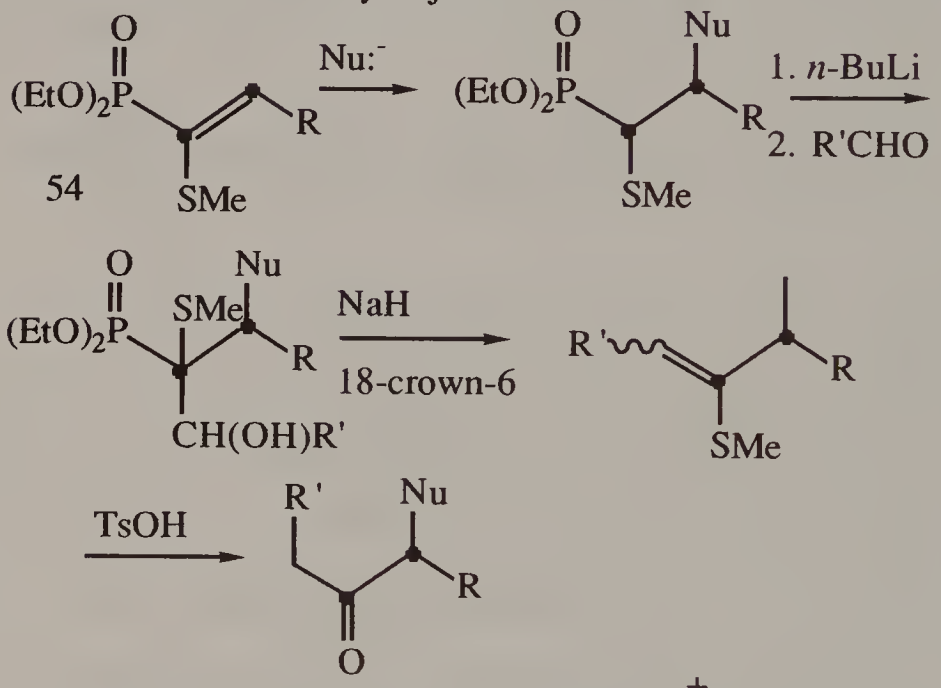
R = Ph, *p*-Cl-C_6H_4, Me

Diethyl 1-methylthioethenephosphonate (54) was first introduced in 1981[105] as a novel masked reagent of the dipolar synthon $^{+}CH_2$-^{-}C=O type as shown in Scheme VIII. It was used successfully in the total synthesis of dihydrojasmone.[105] The preparation of vinylphosphonates of the type of (54), the key reagents for this synthesis, was accomplished in three ways: (a) consecutive addition of sulfur and selenium to the phosphonate α-carbanion of a β-substituted dialkyl ethylphosphonate followed by the known selenoxide elimination reaction,[105] (b) addition of

methylsulfenyl chloride to diethyl β-substitutedethenylphosphonate followed by dehydrochlorination,[106] and (c) reaction of the lithiated salt of diethyl (methylthio)(trimethylsilyl)methanephosphonate with saturated, α,β-unsaturated, and aromatic aldehydes.[107]



dihydrojasmone



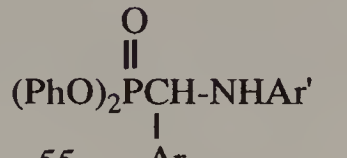
• denote C-atoms of the dipolar system $\overset{+}{C}H_2\text{-}\overset{-}{C}\text{=}O$

Scheme VIII

In 1965 Zimmer reported on the utilization of 1-(substituted-anilino)-1-arylmethanephosphonates (55) as acyl anion equivalents for a novel synthetic approach to deoxybenzoins (56).[6,108-110] Compounds of type (55) could be prepared in high yield by the reaction of the corresponding Schiff bases with diphenyl phosphite.[6,111] This methodology furnished new synthetic

sequences to indoles[108] and benzo[*b*]furans.[109]

Diethyl 1-dialkylamino-1-arylmethanephosphonates were also shown to be easily accessible reagents for the synthesis of deoxybenzoins.[112] These reagents could be prepared by the treatment of trialkyl phosphites with carbimonium salts which were substituted in the α-position by aromatic or heterocyclic groups.[112]



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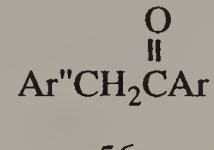
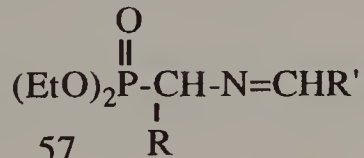


56

The reaction of the anion of imino derivatives (57) of diethyl 1-aminoalkanephosphonates with carbonyl compounds was reported to give 2-azadienes (58).[113-115] The 2-azadienes were hydrolyzed under very mild conditions to give the corresponding carbonyl compounds.[113] They were also treated with *n*-BuLi to generate the metallo enamines which, following the addition of electrophiles such as methyl iodide, allyl bromide, or methyl disulfide, and subsequent hydrolysis[115] furnished the corresponding aldehydes or ketones. The diethyl substituted methyleneaminomethanephosphonates were obtained in quantitative yield by condensation of the corresponding diethyl 1-aminoalkanephosphonates with aldehydes followed by azeotropic removal of the generated water.[116]



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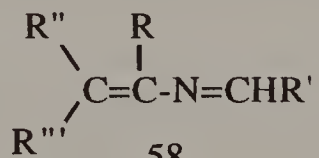
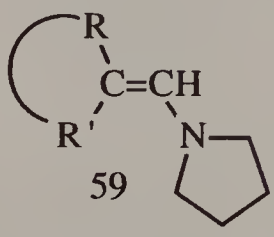


58

The condensation of 2,4-*O*-ethylidene-D-erythrose with the sodium salt of ethyl (diethylphosphono)piperidino acetate yielded an enamino-lactone which was converted under mild conditions into an α-ketoester, 3-deoxy-D-erythrohexulosonic acid.[117]

In attempts to develop a novel method for the creation of a quaternary carbon center to achieve a versatile synthesis of spirosesquiterpene natural products, Martin described the conversion of ketonic carbonyl groups into the pyrrolidine enamines (59) using

the lithiated diethyl pyrrolidinomethanephosphonate. Subsequent reaction of (59) with an excess of allyl bromide and hydrolysis of the intermediate immonium ion salt afforded the α-allylaldehyde (60) in good yield. Also, reaction of (59) with an excess of 2,3-dibromopropene yielded a latent γ-ketoaldehyde (61) which could be unmasked by acid catalyzed hydrolysis. The material (61) underwent direct cyclization to five-membered ring compounds (62).[118,119]



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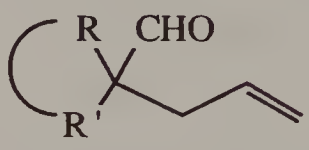

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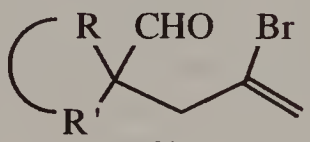

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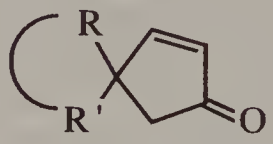
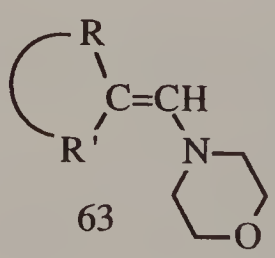
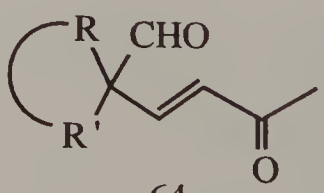


62

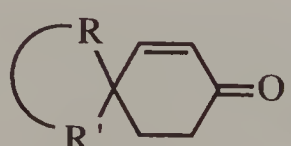
Using diethyl morpholinomethanephosphonate instead of diethyl pyrrolidinomethanephosphonate as the reagent for this type of reaction the spiroannelation could be extended to yield six-membered rings.[120] Thus, the reaction of ketones with diethyl lithiomorpholinomethanephosphonate afforded the corresponding morpholine enamines of the homologous aldehydes (63). Treatment of (63) with methyl vinyl ketone followed by acid-catlayzed hydrolysis of the intermediate adduct afforded the δ-ketoaldehydes (64). These spontaneously underwent a cycloaldol condensation and subsequent dehydration to give the 4,4-disubstituted-2-cyclohexen-1-ones (65).



63



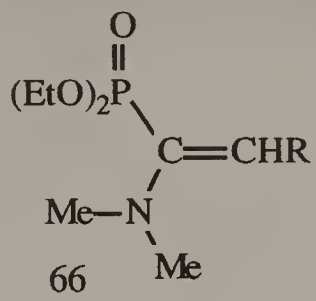
64



65

Gross and Costisella have introduced several phosphonate

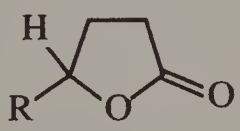
reagents as carboxylic anion equivalents. As early as 1968 they reported on the reaction of the metallated tetraethyl dimethylaminomethane-bis-phosphonate with aldehydes, which afforded (66). These compounds hydrolyzed smoothly in strongly acid media to give carboxylic acids.[121] Tetraethyl dimethylaminomethane-bis-phosphonate was easily synthesized by warming a mixture of dimethyl formamide acetal with a two molar amount of diethyl phosphite. Later, a variety of N-substituted aminomethane-bis-phosphonates were prepared by the same authors. The resulting stereochemistry of phosphonoenamines (66) from a Horner-Emmons-olefination was investigated.[122,123]



66

Diethyl 1-*t*-butoxy-1-cyanomethanephosphonate[124] as well as diethyl 1-dimethylamino-1-cyanomethanephosphonate[125] were used as carboxylic anion equivalents in the same manner.

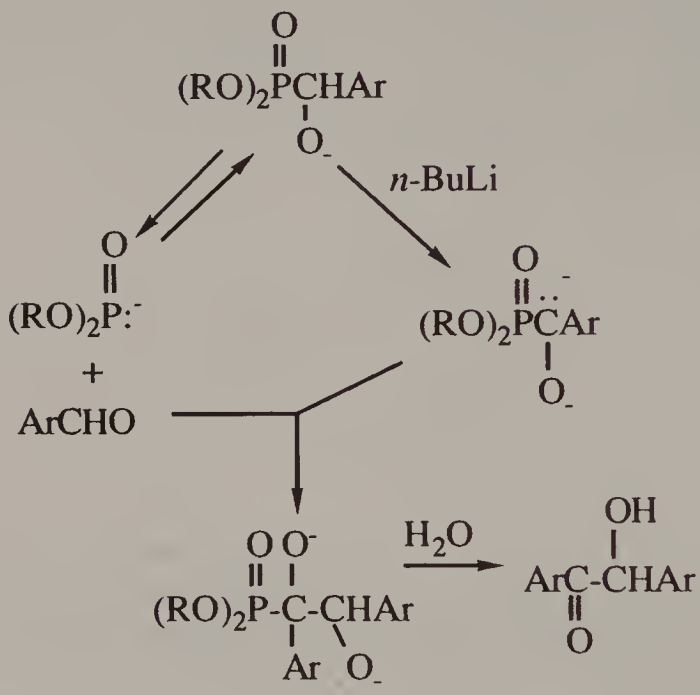
Enamines of the type (66) with an anion stabilizing substituent like the $P(O)(OEt)_2$ group were found to undergo deprotonation using LDA to give aminoallyl anions that reacted with carbonyl compounds to furnish γ-substituted butyrolactones (67).[125]



67

The phosphate-phosphonate rearrengement has also played an interesting role in the process of charge affinity inversion *umpolung* research. Sturtz and Corbel (1973) reported on utilizing dialkyl substitutedbenzyl phosphates as α-acyl anion equivalents. Butyllithium catalyzed the rearrangements of these phosphates to

α-hydroxyphosphonate anions, which underwent a fragmentation and recombination sequence to furnish finally the benzoins according to the mechanism shown in Scheme IX.[126] The dialkyl substitutedbenzyl phosphates could be prepared by nucleophilic substitution reactions involving the substituted benzylate anions and dialkyl phosphorochloridate.



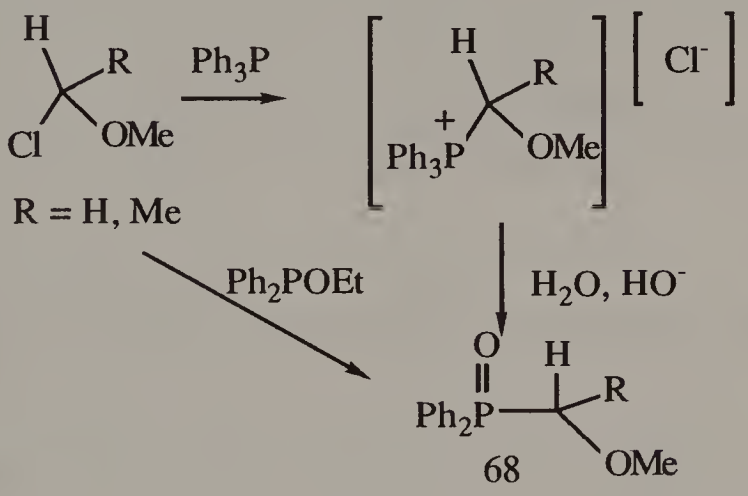
Scheme IX

Of mechanistic interest is the generation of acetophenone by using benzyl bis(dimethylamido) phosphate as an acyl anion equivalent. Treatment of benzyl bis(dimethylamido) phosphate with two equivalents of *n*-BuLi led *via* phosphate-phosphonate rearrangement to a dianion which could undergo C-alkylation followed by hydrolysis to give acetophenone.[126]

The use of diethyl *N*-methyl-*N*-(1,2-propadienyl) phosphoramide as a masked reagent of $O{=}C^{-}\text{-}CH{=}CH_2$ and $O{=}C^{-}\text{-}CH{=}CH^{-}$ was described.[128] Thus, treatment of this reagent with *n*-BuLi and alkyl halides followed by hydrolysis gave alkyl vinyl ketones. This starting reagent was prepared by the action of NaH/THF on diethyl *N*-methyl-*N*-propargyl phosphoramide which in turn was synthesized from diethyl *N*-methyl phosphoramide using NaH and propargyl bromide.

IV. Phosphine Oxides

The often superior properties of diphenylphosphine oxides compared to phosphonates and phosphonium salts in Horner-Emmons reactions (*e.g.* they usually give crystalline species, their reactivity is greater, and their yields are higher, and further the separation of the Wittig reaction by-product, diphenylphosphinic acid is very convenient) has led Warren to develop α-heterosubstituted phosphine oxides as acyl anion equivalents. Thus, in 1977 he reported on the synthesis of α-methoxyalkyl diphenylphosphine oxides (68) and investigated the reactions of their anions with aldehydes and ketones.[129] Two different routes for the synthesis of (68) were introduced as shown in Scheme X.



Scheme X

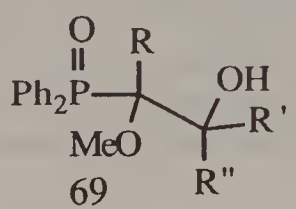
The anions of (68) give good yield of adducts (69) when added to aldehydes and ketones. Completion of the Horner-Emmons reaction afforded vinyl ethers.[129,130]

The sulfenylated phosphine oxides $Ph_2P(O)CH(SR')R$ (R' = Me, Ph; R = H, Et, CH_2Ph, *i*-Pr) (70) were prepared from triphenylphosphane, diphenyl or dimethyl disulfide, and an alkyl halide in good yields. The scope and the limitation of their reactivity with aldehydes and ketones were described.[131] The bis(phenylthio)-compound (71) was synthesized by sulfenylation of (72).[131]

The synthesis of 2-azadienes (73) from the diphenyl-

phosphine oxide reagent (74) has been reported.[114]

The enamines of type (63) were easily synthesized in high yield utilizing *N*-morpholinomethyl(diphenyl)phosphine oxide (75)[132] and can be regarded as a new formyl anion equivalent. This reagent can be prepared conveniently by an Arbuzov reaction between chlorodiphenylphosphine with *N*-ethoxymethylmorpholine or by reaction of ethyl diphenylphosphinite with *N*-chloromethylmorpholine.



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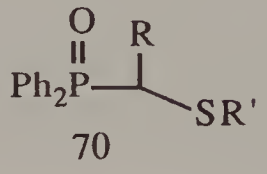

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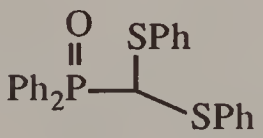

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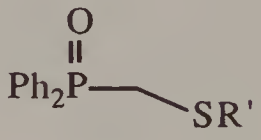
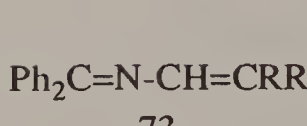
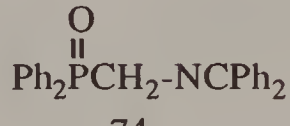


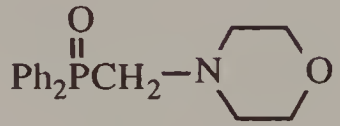
72



73



74



75

The cyclic as well as acyclic ketones, both saturated and α,β-unsaturated, could be converted into their homologous enamines utilizing *N*-methyl-*N*-anilinomethyl(diphenyl)phosphine oxide.[133] The *N*-methyl-*N*-phenylaminomethyl(diphenyl)phosphine oxide was prepared by the reaction of *N*-methoxymethyl-*N*-methylaniline with chlorodiphenylphosphine.

V. Bibliography

1. Seebach, D. (1969). Methods and possibilities of nucleophilic acylation, *Angew. Chem., Int. Ed. Engl.*, *8*: 639.
2. Martin, S.F. (1979).Synthesis of aldehydes, ketones and carboxylic acids from lower carbonyl compounds by C-C coupling reactions, *Synthesis*: 633.
3. McEvoy, F.J., and Albright, J.D. (1979). Alkylations and

acylations of α-aryl-4-morpholinoacetonitriles (masked acyl anion equivalents) and their use in 1,4-addition, *J. Org. Chem.*, *44*: 4597.

4. Jacobson, R.M., Lahm, G.P., and Clader, J.W. (1980). Three-carbon annelations. Regiocontrolled reactivity of trimethylsilyl- and ethoxyethyl-protected cyanohydrins. Versatile homoenolate and acyl anion equivalents, *J. Org. Chem.*, *45*: 395.
5. Stork, G., and Maldonado, L. (1971). Anions of protected cyanohydrins as acyl anion carbanion equivalents and their use in a new synthesis of ketones, *J. Am. Chem. Soc.*, *93*: 5286.
6. Zimmer, H., and Bercz, J.P. (1965). Syntheses with α-aminoalkylphosphonic acid ester, *Ann.*, *686*: 107.
7. Lever, O.W. (1976). New horizons in carbonyl chemistry: Reagents for nucleophylic acylation, *Tetrahedron*, *32*: 1943.
8. Seyferth, D., Weinstein, R.M., Wang, W.-L., Hui, R.C., and Archer, C.M. (1984). Direct nucleophilic acylation with acyllithium reagents: Acyl anion synthons unmasked, *Isr. J. Chem.*, *24*: 167.
9. Levine, S.G. (1958). A new aldehyde synthesis, *J. Am. Chem. Soc.*, *80*: 6150.
10. Wittig, G., Boell, W., and Krueck, K. (1962). Synthesis of ethers, *Ber.*, *95*: 2514.
11. Takeda, K., and Yamamoto, S. (1972). Synthesis and spectral properties of 2,6-disubstituted *trans*-decalins, *Chem. Pharm. Bull.*, *20*: 314.
12. Hagiwara, H., Miyashita, M., Uda, H., and Yoshikoshi, A. (1975). An alternative synthesis of (+)-1,7-dimethyl-4-*endo*-isopropyl-8-*syn*-(2-hydroxyethyl)bicyclo[3.2.1]ocy-6-ene, the key intermediate for the synthesis of (+)-sativene and (+)-cyclosativene, *Bull. Chem. Soc. Jpn.*, *48*: 3723.
13. Scott, J.W., Bizzarro, F.T., Parrish, D.R., and Saucy, G. (1976). Synthesis of (2*R*,4'*R*,8*R*)-α-tocopherol and (2*R*,3'*E*,7'*E*)-α-tocotrienol, *Helv. Chim. Acta*, *59*: 290.
14. Narasimhan, N.S., and Mali, R.S. (1975). Synthetic application of lithiation reaction. IX. A simplified synthesis of isocoumarin, *Synthesis*: 797.
15. Jenneskens, L.W., Krul, A.H.P., Kraakman, P.A., Moene, W., DeWolf, W.H., and Bickelhaupt, F.W. (1986). Flash

vacuum thermolysis of 5,6,8,9-tetrahydro-4'-methylenespiro[7H, benzocycloheptene-7,1'-cyclohexa-2',5'-diene]. The intermediate formation of [3,2]ortho-paracyclophane, *J. Org. Chem.*, *51*: 2162.

16. Misumi, A. Furuta, K., and Yamamoto, H. (1984). A new and unusually flexible route to cyclopentanoids. Synthesis of sarkomycin and prostaglandins, *Tetrahedron Lett.*, *25*: 671.
17. Hamada, Y., Kawai, A., and Shiori, T. (1984). A highly efficient stereoselective synthesis of L-daunosamine through direct C-acylation using diphenyl phosphorazidate (DPPA), *Tetrahedron Lett.*, *25*: 5409.
18. Hamada, Y., Kawai, A., and Shioiri, T. (1984). A stereo-selective synthesis of a derivative of L-vancosamine, a carbo-hydrate component of the antibiotics vacomycin and sporaviridin, *Tetrahedron Lett.*, *25*: 5413.
19. Hamada, Y., Kawai, A., and Shioiri, T. (1985). A stereoselective synthesis of a derivative of D-ristosamine, *Chem. Pharm. Bull.*, *33*: 5601.
20. Hatakeyama, S., Saijo, K., and Takano, S. (1985). Enantioselective synthesis of (-)-elenolic acid and (-)-ajamalicine, *Tetrahedron Lett.*, *26*: 865.
21. Bennett, S.M., and Clive, D.J. (1986). Synthesis of spiro-compounds related to Fredericamycin, *J. Chem. Soc., Chem. Commun.*: 878.
22. Burke, S.D., Saunders, J.O., Oplinger, J.A., and Murtiashaw, C.W. (1985). Vinylsilane-mediated polyene cyclization. Synthesis of the octahydronaphthalenol portion of dihydrocompactin, *Tetrahedron Lett.*, *26*: 1131.
23. Mehta, G., and Rao, H.S.P. (1986). The trioxa[5]peristyl-ene system, *J. Chem. Soc., Chem. Commun.*: 472.
24. Taschner, M.J., and Shahripour, A. (1985). Total synthesis of (-)-upial, *J. Am. Chem. Soc.*, *107*: 5570.
25. Corey, E.J., Shibasaki, M., Nicolaou, K.C., Malmsten, C.L., and Samuelson, B. (1976). Simple, stereocontrolled total synthesis of a biologically active analog of the prostaglandin endoperoxides (PGH_2, PGG_2), *Tetrahedron Lett*: 737.
26. Magerlein, B.J. (1981). δ-Lactol prostaglandin intermed-iates, *Aust. Pat. AU 519,229.*
27. McMorris, T., Phu Huu Le, Preus, M., Schow, S., and Weihe, G. (1983). Synthesis of dehydroooagoniol, a female-activating hormone of *Achlya*, *J. Org. Chem.*, *48*:

3370.
28. Kosarych, Z., and Cohen, T. (1980). Rapid, high-yield cleavage of enol and dienol methyl ethers under mild condition using chlorotrimethylsilane/sodium iodide, *Tetrahedron Lett.*, *21*: 3959.
29. Richardson, K.A., Saunders, J., and Taylor, R.J.K. (1985). Keto-alkyne cyclization reactions: Heterocyclic prostacyclin analogues, *Tetrahedron Lett.*, *26*: 1171.
30. Coulson, D.R. (1964). A new synthesis of methyl ketones, *Tetrahedron Lett.*: 3323.
31. Schubert, U., and Fischer, E.O. (1973). α-(Methoxybenzyl-iden)triphenyl phosphorane and (1-methoxyethylene)triphenyl phosphorane, *Ber.*, *106*: 1062.
32. Schlude, H. (1975). New phosphonium salts for the Wittig synthesis of aldehydes from ketones, *Tetrahedron*, *31*: 89.
33. Rousseau, G., LePerchec, P., and Conia, J.M. (1978). A novel synthesis of α,β-unsaturated aldehydes and esters by dye-photooxygenation of methyl enol ethers, *Synthesis*: 67.
34. Mukaiyama, T., Fukuyama, S., and Kumamoto, T. (1968). New methods for the preparation of thiovinyl ethers and unsym-ketones, *Tetrahedron Lett.*: 3787.
35. Marino, J.P., and Landick, R.C. (1975). 1-Phenylthiocyclo-propyl triphenyl phosphonium fluoborate: A new synthon for cyclopentanone synthesis, *Tetrahedron Lett.*: 4531.
36. Corey, E.J., and Markl, G. (1967). Generation of phosphite ylides from trithiocarbonates and trimethyl phosphite and their application to the extension of carbon chains, *Tetrahedron Lett.*: 3201.
37. Kruse, C.G., Broekhof, N.L.J.M., Wijsman, A., and van der Gen, A. (1977). Synthetic application of 2-chloro-1,3-dithiane. Preparation of ketene dithioacetals, *Tetrahedron Lett.*: 885.
38. Petragnani, N., Rodrigues, R., and Comasseto, J.V. (1976). The reaction of selenyl halides with Wittig reagents, *J. Organomet. Chem.*, *114*: 281.
39. Corey, E.J., and Shulman, J.I. (1970). The application of lithium reagents from (1-methylthio)alkylphosphonate esters to the synthesis of ketones, *J. Org. Chem.*, *35*: 777.
40. Petragnani, N., Comasseto, J.V. Rodrigues, R., and Brocksom, T.J. (1977). The attempted Wittig reaction of

selenophosphoranes with ketones: The formation of 2-selenosubstituted ketones, *J. Organomet. Chem.*, *124*: 1.
41. Wittig, G., and Schlosser, M. (1960). Triphenylphosphine-methylene chloride, *Angew. Chem.*, *72*: 324.
42. Wittig, G., and Schlosser, M. (1961). Phosphinealkylenes as olefin-forming reagents. Preparation of vinyl ethers, vinyl thioethers and vinyl halides from ylids, *Ber.*, *94*: 1373.
43. Seyferth, D., Grim, S.O., and Read, T.O. (1961). Studies in phosphinemethylene chemistry. III. Triphenylphosphino-chloromethylene, *J. Am. Chem. Soc.*, *83*: 1617.
44. Miyano, S., Izumi. Y., and Hashimoto, H. (1978). Conversion of aldehydes and ketones into chloro olefins and acetylenes using chloroiodomethane as a chloromethylene source, *J. Chem. Soc., Chem. Commun.*: 446.
45. Smithers, R.W. (1978). A new stereoselective route to trisubstituted bromo olefins utilizing α-bromoalkylides produced by halogen-metal exchange, *J. Org. Chem.*, *43*: 2833.
46. Mitchell, W.L., Ravenscroft, P., Hill, M.L., Knutsen, L.J.S., Judkins, B.D., Newton, R.F., and Scopes, D.I.C. (1985). Synthesis and antiviral activity of 5-halovinyl-6-aza-2'-deoxyuridines, *Nucleosid. Nucleotid.*, *4*: 173.
47. Kondo, K., Cottens, S., aand Schlosser, M. (1984). The ylide route to fluorodienes, *Chem. Lett.*: 2149.
48. Muenstedt, R., Wannagat, U., and Wrobel, D. (1984). Trimethylsilyl- and halogen-substituted 2-methyl-1-pentenes, *J. Organomet. Chem.*, *264*: 135.
49. Stetter, H. (1973). *Methoden der Organischen Chemie, 4th Ed., Vol 7/2a*, (Muller, E., ed.), Georg Thieme Verlag, Stuttgart, p. 813 ff.
50. Klumpp, G.W., Bos, H., Schakel, M., Schmitz, R.F., and Vrielink, J.J. (1975). Vinyl acetates from vinyl bromides, *Tetrahedron Lett.*: 3429.
51. Mukaiyama, T., Imamoto, T., and Kobayashi, S. (1973). A convenient method for the hydrolysuis of vinyl chlorides to ketones, *Chem. Lett.*: 261.
52. Arzoumanian, H., and Metzger, J. (1973). The reaction of vinyl halides with mercury(II) salts, *J. Organomet. Chem.*, *57*: C1.
53. Martin, S.F., and Chou, T.-S. (1978). A facile procedure for the hydrolysis of vinyl halides to ketones, *Tetrahedron Lett.*: 1943.

54. Julia, M., and Blasioli, C. (1976). Synthesis of vinyl halides, aldehydes and ketones, *Bull. Soc. Chim. Fr.*: 1941.
55. Kobrich, G. (1962). Introduction of bromomethylene group using the Wittig reaction, *Angew. Chem., Int. Ed. Engl., 1*: 51.
56. Schmidbaur, H., and Tronich, W. (1967). Isosteric organometallic compounds (VII). Organometal-substituted phosphine alkylenes, *Ber., 100*: 1032.
57. Schmidbaur, H., and Stuhler, H. (1973). Silylated ylides as components for Wittig reactions, *Angew. Chem., Int. Ed. Engl., 12*: 321.
58. Gilman, H., and Tomasi, A. (1962). α-Silyl-substituted ylides. Tetraphenylallene *via* the Wittig reaction, *J. Org. Chem., 27*: 3647.
59. Martin, S.F., and Garrison, P.J. (1977). A facile procedure for the synthesis of α,β-unsaturated aldehydes by three carbon homologation, *Tetrahedron Lett.*: 3875.
60. Stowell, J.C., and Keith, D.R. (1979). 2-(1,3-Dioxan-2-yl)-ethylidenetriphenylphosphorane, a new three-carbon homologating agent, *Synthesis*: 132.
61. Cristau, H.-J., Vors, J.-P., and Christol, H. (1979). Synthesis (thio)acetalisation of 3-oxoalkyltriphenyl-phosphonium salts, *Synthesis*: 538.
62. Cristau, H.-J., Vors, J.-P., and Christol, H. (1979). Thioacetalized γ-ketophosphonium ylides as synthetic equivalents of β-acylethyl and β-acylvinyl anions, *Tetrahedron Lett.*: 2377.
63. Cristau, H.-J., Vors, J.-P., Niangoran, C., and Christol, H. (1981). *Umpolung* of α,β-ethylenic ketones and aldehydes by phosphorus groups, *ACS Symp. Ser. (Phosphorus Chemistry), 171*: 59.
64. Cristau, H.-J., Chabaud, B., and Niagoran, C. (1983). Inversion of reactivity (*Umpolung*) of α,β-ethylenic ketones and aldehydes. Electrochemical deprotection of γ-thioacetylated phosphonium salts, *J. Org. Chem., 48*: 1527.
65. Cristau, H.-J., Viala, J., and Christol, H. (1982). Inversion of a^4 polarity of α-allenic ketones by the triphenylphosphino

group, *Tetrahedron Lett.*, *23*: 1569.
66. Cristau, H.-J., Fonte, M., and Torreilles, E. (1989). "*Umpolung*" using a phosphorus group. A novel method for the chemoselective synthesis of 2-acetonyl or 3-acetonyl morpholines, *Synthesis*: 301.
66a. Zimmer, H., Bercz, P.J., and Heuer, G. (1968). Synthesen von Amidinen mittels Phosphonat Carbanion, *Tetrahedron Lett.*: 171.
67. Zimmer, H. (1981). Synthetic and spectroscopic investigation involving α-heterosubstituted phosphonate carbanion, *ACS Symp.Ser. (Phosphorus Chemistry)*, *171*: 37.
68. Green, M. (1963). The preparation and properties of diethyl methylthiomethylphosphonate, *J. Chem. Soc.*: 1324.
69. Shahak, I., and Almog, J. (1969). Horner-Wittig synthesis of α,β-unsaturated sulfides and sulfones, *Synthesis*: 170.
70. Shahak, I., and Almog, J. (1970). Horner-Wittig synthesis of α,β-unsaturated sulfides and sulfones, Part II, *Synthesis*: 145.
71. McGuire, H.M., Odom, H.C., and Pinder, A.R. (1974). Further synthetic studies in the nootkatane sesquiterpine group. A new total synthesis of (±)-valencene and (±)-nootkatone, *J. Chem. Soc., Perkin Trans. I*: 1879.
72. Smith, J.G., Finck, M.S., Kontoleon, B.D., Trecoske, M.A., Giordano, L.A., and Renzulli, L.I. (1983). A convenient synthesis of dimethyl [(alkylthio)methyl]-phosphonates and dimethyl [(arylthio)methyl]phosphonates, *J. Org. Chem.*, *48*: 1110.
73. Arbuzov, B.A., and Bogonostseva, N.P. (1957). Synthesis of some phosphonosulfides and phosphonosulfones, *Zh. Obshch. Khim.*, *27*: 2360.
74. Comins, D.L., Jacobine, A.F., Marshall, J.L., and Turnbull, M.M. (1978). Phosphonate ester preparation from active methylene compounds and phosphorochloridate esters, *Synthesis*: 309.
75. Mikolajczyk, M., Grzejszczak, S., Chefczynska, A., and Zatorski, A. (1979). Addition of elemental sulfur to phosphonate carbanions and its application for synthesis of α-phosphoryl organosulfur compounds. Synthesis of aromatic ketones, *J. Org. Chem.*, *44*: 2967.

76. Mikolajczyk, M., Balczewski, P., and Grzejszczak, S. (1980). Sulphenylation of phosphonates. A facile synthesis of α-phosphoryl sulfides and S,S-acetals of oxomethanephosphonates, *Synthesis*: 127.
77. Kim, T.H., and Oh, D.Y. (1986). Synthesis of 1-(substituted-aryl)methylthiomethylanephosphonate by Friedel-Crafts reaction of aromatic compounds with chloro(methylthio)methanephosphonate, *Tetrahedron Lett.*, *27*: 1165.
78. Kim. T.H., Kim, D.Y., and Oh, D.Y. (1987). Reaction of Pummerer rearrangement intermediate with aromatic compounds: A novel synthesis of 1-(substituted-aryl)-methylthiomethanephosphonates, *Synth. Commun.*, *17*: 755.
79. Mikolajczyk, M., Grzejszczak, S., Zatorski, A., Mlotkowska, B., Gross, H., and Costisella, B. (1978). A new and general synthesis of ketene S,S- and O,S-thioacetals based on the Horner-Wittig reaction, *Tetrahedron*, *34*: 3081.
80. Gross, H., Keitel, I., Costisella, B., Mikolajczyk, M., and Midura, W. (1983). α-Substituted phosphonates 44. Organosulfur compounds XXXIII. Synthesis of dialkyl bis(alkylmercapto- methane)phosphonates, *Phosphorus Sulfur*, *16*: 257.
81. Kim, D.Y., and Oh, D.Y. (1986). A facile synthesis of bis-alkylmercaptomethanephosphonates, *Bull. Korean Chem. Soc.*, *7*: 486.
82. Kim, T., and Oh, D. (1985). New synthetic method of O,S-thioacetals of formylphosphonates, *Tetrahedron Lett.*, *26*: 3479.
83. Costisella, B., and Keitel, I. (1987). α-Substituted phosphonates. O,S-Acetals of phosphonoformaldehyde and ortho esters of phosphonoformic acid by anodic methoxylation, *Synthesis*: 44.
83a. Hickey, K.R. (1969). Ph.D. Thesis, University of Cincinnati.
84. Kluge, A.F. (1978). Phosphonate reagents for the synthesis of enol ethers and aldehyde homologation, *Tetrahedron Lett.*: 3629.
85. Grell, W., and Machleidt, H. (1966). PO-Activated alkoxyolefins, *Ann.*, *699*: 53.
86. Schaumann, E., and Grabley, F.-F. (1977). Preparation and

properties of α-alkoxyalkylphosphonates, *Ann.*: 88.
87. Ireland, R.E., Mueller, R.H., and Willard, A.K. (1976). The ester enolate Claisen rearrangement. Construction of the prostanoid skeleton, *J. Org. Chem.*, *41*: 986.
88. Dinizo, S.E., Freerksen, R.W., Pabst, W.E., and Watt, D.S. (1976). Synthesis of α-alkoxyacrylonitriles using substituted diethyl cyanomethylphosphonates, *J. Org. Chem.*, *41*: 2846.
89. Kluge, A.F., and Cloudsdale, I.S. (1979). Phosphonate reagents for the synthesis of enol ethers and one-carbon homologation to aldehydes, *J. Org. Chem.*, *44*: 4847.
90. Burkhouse, D., and Zimmer, H. (1984). Novel synthesis of 1-alkoxy-1-arylmethanephosphonic acid esters, *Synthesis*: 330.
91. Kim, D.Y., and Oh, D.Y. (1986). A facile synthesis of diethyl 1-alkoxy-1-arylmethanephosphonates, *Synth. Commun.*, *16*: 859.
92. Petrova, J., Coutrot, P., Dreux, M., and Savignac, P. (1975). α-Chlorination and carbonyl olefination; arylchloromethanephosphonic acid esters; preparation, alkylation and Wittig-Horner reactions, *Synthesis*: 658.
93. Savignac, P., Snoussi, M., and Coutrot, P. (1978). Carboxychloro olefination: A convenient synthesis of α-chloro-α,β-ethylenic carboxylic acids, *Synth. Commun.*, *8*: 19.
94. Villieras, J., Perriot, P., and Normant, J. (1978). α-Chloroenolates, VI. Diethyl 1-chloro-1-lithio-2-oxoalkane-phosphonates; synthesis of α-chloro-α,β-unsaturated ketones, *Synthesis*: 29.
95. Xu, L., Tao, F., and Wu, J. (1984). Preparation of the derivatives of α-chlorostyrene by reaction of diethyl chlorobenzylphosphonate with aldehydes and ketones, *Gaodeng Xuexiao Huaxue Xuebao*, *5*: 129.
96. Gajda, T. (1990). A convenient synthesis of diethyl 1-chloroalkylphosphonates, *Synthesis*: 717.
97. Zimmer, H., and Crenshaw, M.D. (1983). Synthesis with α-heterosubstituted phosphonate carbanions. XIII. Synthesis of trisubstituted vinyl chlorides, *J. Org. Chem.*, *48*: 2782.

98. Comasseto, J.V., and Petragnani, N. (1978). The reaction of selenophosphonates with carbonyl compounds. Vinylic selenides, *J. Organomet. Chem.*, *152*: 295.
99. Zimmer, H., and Koenigkramer, R.E. (1980). α-Heterosubstituted phosphonate carbanions. IX. Diethyl 1-phenyltrimethylsiloxymethane phosphonate as an acyl anion equivalent; A novel method for the preparation of α-hydroxyketones, *Tetrahedron Lett.*, *21*: 1017.
100. Zimmer, H., and Koenigkramer, R.E. (1980). α-Heterosubstituted phosphonate carbanions. XI. Benzoines *via* an acyl anion equivalent; Novel one pot preparation of benzo[*b*]furans *via* benzoins using hydroiodic acid, *J. Org. Chem.*, *45*: 3994.
100a. Engel, R.R. (1988). Phosphorus addition at sp^2 carbon, *Org, React.*, *36*: 175.
101. Hata, T., Hashizume, A., Nakajima, M., and Sekine, M. (1978). A convenient method of ketone synthesis utilizing the reaction of diethyl trimethylsilyl phosphite with carbonyl compounds, *Tetrahedron Lett.*: 363.
102. Sekine, M., Nakajima, M., Kume, A., and Hata, T. (1979). Studies on alkylation of acyl anion equivalents. Unsymmetrical ketone synthesis by use of diethyl 1-trimethylsiloxy-alkylphosphonates, *Tetrahedron Lett.*: 4475.
103. Hata, T., Hashizume, A., Nakajima, M., and Sekine, M. (1979). α-Hydroxybenzyl anion equivalent: A convenient method for the synthesis of α-hydroxy ketones utilizing α-trimethylsiloxybenzylphosphonate, *Chem. Lett.*: 519.
104. Sekine, M., Nakajima, M., and Hata, T. (1982). A new type of P-C and C-C bond cleavage reactions in α-trimethylsiloxy-β-oxophosphonates and α-ethoxy-β-oxophosphonates. The synthesis of unsymmetrical α-hydroxyketones utilizing 1:1 carbonyl adducts of diethyl trimethylsilyl phosphite with benzaldehyde, *Bull. Chem. Soc. Jpn.*, *54*: 218.
105. Mikolajczyk, M., Grzejszczak, S., and Korbacz, K. (1981). Addition of elemental selenium to phosphonate carbanions - a key step in the synthesis of vinyl phosphonates. A new

synthetic approach to 1,4-dicarbonyl systems, *Tetrahedron Lett.*, *22*: 3097.

106. Mikolajczyk, M., Kielbasinski, P., and Grzejsczczak, S. (1983). A new synthesis of α-alkylthio-ketones (α-sulphenylated ketones), *Synthesis*: 332.
107. Mikolajczyk, M., and Balczewski, P. (1989). Synthesis and reactivity of diethyl (methylthio)(trimethylsilyl)-methylphosphonate, *Synthesis*: 101.
108. Zimmer, H., and Nene, D.M. (1977). Synthesis with α-heterosubstituted phosphonate carbanions. VII. Synthesis of deoxybenzoins and indoles, *Chimia*, *31*: 330.
109. Seemuth, P.D., and Zimmer, H. (1978). α-Heterosubstituted phosphonate carbanions. VII. Synthesis of deoxybenzoins and benzo[*b*]furans, *J. Org. Chem.*, *43*: 3063.
110. Zimmer, H., and Servay, T.K. (1991). Synthesis with α-heterosubstituted phosphonate carbanion. LXVII. Preparation of diacylated aromatics, *Phosphorus Sulfur*, 61: 201.
111. Pudovik, A.N., and Krupnov, G.P. (1961). New method of synthesis of esters of phosphonic acid and thiophosphonic acids. XXXVI. Synthesis of derivatives of phosphonic acids with cyclic radicals in the ester groups, *Zh. Obshch. Khim.*, *31*: 4053.
112. Bohme, H., Haake, M., and Auterhoff, G. (1972). Enamines with aromatic or heterocyclic substituent in α- and β-position, *Arch. Pharm.*, *305*: 88.
113. Dehnel, A., Finet, J.P., and Lavielle, G. (1977). α-Aminophosphonates: I. Synthesis of 2-azadienes and their hydrolysis to carbonyl compounds, *Synthesis*: 474.
114. Kauffmann, T., Koch, U., Steinseifer, F., and Vahrenhorst, A. (1977). New reagents. 7. 2-Azadiene synthesis with 1,1-diphenyl-3-triphenylsilyl- and 1,1-diphenyl-3-diphenyl phosphoryl-2-azaallyllithium, *Tetrahedron Lett.*: 3341.
115. Martin, S.F., and Phillips, G.W. (1978). Homologation alkylation of carbonyl compounds *via* regiospecifically generated metallo enamines, *J. Org. Chem.*, *43*: 3792.
116. Ratcliffe, R.W., and Christensen, B.G. (1973). Total synthesis of β-lactam antibiotics. I. α-Thioformamidodiethylphosphono acetates, *Tetrahedron Lett.*: 4645.

117. Baschang, G., and Fritz, H. (1969). Synthesis of 3-deoxyaldulosonic acids, *Helv. Chim. Acta*, *52*: 300.
118. Martin, S.F., and Gompper, R. (1974). A facile method for the transformation of ketones into α-substituted aldehydes, *J. Org. Chem.*, *39*: 2814.
119. Martin, S.F., Chou, T.-S., and Payne, C.W. (1977). Carbonyl homologation with α-substitution. A new synthesis of 4,4-disubstituted 2-cyclopentenones, *J. Org. Chem.*, *42*: 2520.
120. Martin, S.F. (1976). Carbonyl homologation with α-substitution. A new approach to spiroannelation, *J. Org. Chem.*, *41*: 3337.
121. Gross, H., and Costisella, B. (1968). Synthesis of carboxylic acids *via* PO-activated olefination of tetraethyl dimethyl- aminomethylenediphosphonate, *Angew. Chem., Int. Ed. Engl.*, *7*: 391.
122. Costisella, B. Keitel, I., and Gross, H. (1981). α-Substituted phosphonate. 36. α-Phosphonoenamines and acyl- phosphonates by Horner-olefination, *Tetrahedron*, *37*: 1227.
123. Costisella, B., and Gross, H. (1982). α-Substituted phosphonate. 38. 1-Dimethylamino-1-cyanomethane-phosphonic acid diethyl ester, a new approach to the preparation of carboxylic acids, 1-cyanoenamines, and homoenolates, *Tetrahedron*, *38*: 139.
124. Dinizo, S.E., Freeksen, R.W., Pabst, W.E., and Watt, D.S. (1977). A one-carbon homologation of carbonyl compounds to carboxylic acids, esters and amides, *J. Am. Chem. Soc.*, *99*: 182.
125. Costisella, B., Gross, H., and Schick, H. (1984). γ-Butyro-lactones from metallated enamines, *Tetrahedron*, *40*: 733.
126. Sturtz, G., and Corbel, B. (1973). Action of butyllithium on some substituted benzyl dialkyl and bis(dimethylamido) phosphates. Phosphate-phosphonate rearrangement, *Compt. Rend. Acad. Sci., Ser. C*, *276*: 1807.
127. Cheymol, J., Chabrier, P., Selim, M., and Leduc, P. (1958). New method of preparation of mixed diesters of orthophosphoric acid, *Compt. Rend. Acad. Sci., Ser. C.*, *247*: 1014.

128. Corbel, B., Paugam, J.-P., Dreux, M., and Savignac, P. (1976). *N*-Propargylphosphoramides. New synthetic reaction, *Tetrahedron Lett.*: 835.
129. Earnshaw, C., Wallis, C., and Warren, S. (1977). Stereo- and regio-specific vinyl ether synthesis by Horner-Emmons reaction, *J. Chem. Soc., Chem. Commun.*: 314.
130. Earnshaw, C., Wallis, C.J., and Warren, S. (1979). Synthesis of E- and Z-vinyl ethers by the Horner-Wittig reaction, *J. Chem. Soc., Perkin Trans. I*: 3099.
131. Grayson, J.I., and Warren, S. (1977). Acyl anion equivalents: Synthesis of ketones and enones from α-phenylthioalkylphosphine oxides, *J. Chem. Soc., Perkin Trans. I*: 2263.
132. Broekhof, N.L.J.M., Jonkers, F.L., and van der Gen, A. (1979). Enamine synthesis by the Horner-Wittig reaction, *Tetrahedron Lett.*: 2433.
133. Broekhof, N.L.J.M., Jonkers, F.L., and van der Gen, A. (1980). *N*-Methyl-*N*-anilinomethyl diphenylphosphine oxide: A versatile reagent for the synthesis of enamines, *Tetrahedron Lett, 21*: 2671.

CHAPTER 7

α-SUBSTITUTED PHOSPHONATES

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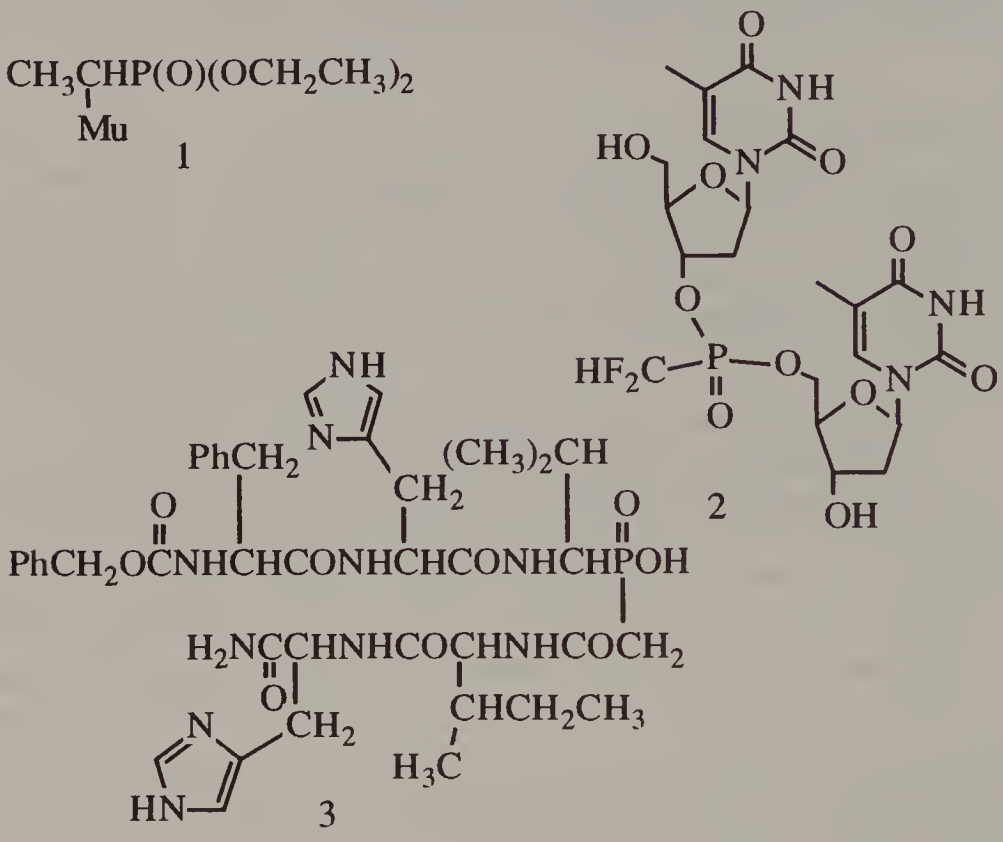
I. Introduction

The phosphonates which are dealt with in this Chapter are derived from alkylphosphonic acids. According to the general usage, the term "phosphonate" covers summarily the phosphonic acids as well as their derivatives with a modified phosphonic acid function. Because of the similarity of properties and methods of preparation it is purposeful to include here also the dialkylphosphinic acids with substituents at the α-position.

Introduction of heteroatom substituents opens enormous possibilities of structural variation. Any functional group may appear in a substituted phosphonate in combination with any phosphorus-containing groups that are compatible with the general definition of phosphonates. The derivatives with substituents at the α-position deserve special treatment because of new chemical properties resulting from the close proximity of the functional groups; and because numerous α-substituted phosphonates have rather interesting biochemical and biological properties. This is particularly true for 1-aminoalkylphosphonates and for phosphonates substituted with fluorine atoms or alkoxy groups. In fact, the search for new biologically active compounds has stimulated a substantial part of recent studies on the synthesis of α-substituted phosphonates.

It is perhaps useful to visualize the structural diversity of the recently synthesized phosphonates with three specific examples. At one extreme there is the deceptively simple compound (1) in which one of the hydrogen atoms is replaced with muonium, the light isotope of hydrogen containing the unstable muon particle instead of a proton.[1] The chemical simplicity of (1) is contrasted with (2) and (3) which represent the extreme structural complexity of substituted phosphonates prepared during the last decade.[2,3] However, the coverage presented in this Chapter is limited to the

methods of preparation of simpler α-substituted phosphonates. The syntheses of more complex structures usually begin with simple phosphonates and are carried out using reactions which take place without direct participation of the phosphonate moiety and are thus not relevant to organophosphorus chemistry.



II. α-Halogenated Phosphonates

A. Syntheses Involving the Formation of P-C Bonds

1. The Arbuzov Reaction

Interest in α-halogenated phosphonates has been stimulated recently with the recognition that isopolar α-substituted phosphonates are superior mimics of biologal phosphates than the simple isosteric methylene compounds.[4] The Arbuzov reaction is not generally useful for the synthesis of α-halogenated phosphonates. In fact, most of the syntheses performed using this reaction are limited to derivatives of methylphosphonic acid, with

only few exceptions.[5,6] Triethyl fluorophosphonoacetate was obtained by Arbuzov reaction of ethyl bromofluoroacetate.[7]

$$\begin{matrix}(CH_3CH_2O)_3P \\ + \\ FBrCHCO_2CH_2CH_3\end{matrix} \xrightarrow{3\text{ hr, }145^\circ} \underset{83\%}{(CH_3CH_2O)_2\overset{\overset{O}{\|}}{P}CHFCO_2CH_2CH_3}$$

Polyhalogenomethanes display varied reactivities toward trialkyl phosphites. While carbon tetrachloride reacts easily upon heating with triethyl phosphite to give a high yield of diethyl trichloromethylphosphonate, the trifluorohalogenomethanes are totally unreactive under thermal conditions. However, a photochemical Arbuzov reaction of trifluoroiodomethane takes place at room temperature.[8]

$$CF_3I + (CH_3CH_2O)_3P \xrightarrow[\text{r.t., 10 hr}]{h\nu,\ 250\text{ nm}} \underset{51\%}{CF_3\overset{\overset{O}{\|}}{P}(OCH_2CH_3)_2}$$

Prolongation of the reaction time to 48 hr gave a quantitative yield of diethyl trifluoromethylphosphonate.[9]

Photochemical activation is not necessary for fluorinated tetrahalomethanes containing fewer than three fluorine atoms. On the contrary, unusually high reactivities were observed in some cases. For example, dibromodifluoromethane and tributyl phosphite gave a quantitative yield of dibutyl bromodifluoromethylphosphonate after 36 hr at room temperature.[9] Tribromofluoromethane appears to be still more reactive; a 78% yield of diethyl dibromofluoromethylphosphonate was obtained in a reaction with triethyl phosphite after 4 hr at 0°.[10]

The non-photochemical reactions of polyhalogenomethanes with trialkyl phosphites appear to take place *via* a free radical instead of the usual ionic mechanism of typical Arbuzov reactions.[5] A carbene-trapping mechanism has been proposed for the reaction of dibromodifluoromethane with trialkyl phosphites.[11]

Unusual behaviour (displacement of fluorine rather than of iodine) was observed in the Arbuzov reaction of trifluorovinyl iodide.[12]

$$F_2C{=}CFI + (i\text{-}PrO)_3P \xrightarrow{80^\circ,\ 60\ hr} (i\text{-}PrO)_2\overset{\overset{O}{\|}}{P}CF{=}CFI \quad 68\%$$

The same product, together with trimethylfluorosilane, was obtained when diethyl trimethylsilyl phosphite was used instead of triisopropyl phosphite.[13]

2. The Michaelis-Becker Reaction

The usefulness of this reaction appears to be limited to halogenated derivatives of methylphosphonic and methylenebisphosphonic acid. Several fluorine-containing dialkylhalogenomethylphosphonates have been obtained recently from polyhalomethanes CH_2ClF, CH_2BrF, $CHCl_2F$, $CHClF_2$, and CCl_3F with sodium dialkyl phosphonates but the yields were moderate at best.[14-17] For example, $CHCl_2F$ and sodium diisopropyl phosphonate gave 38% of diisopropyl chlorofluoromethylphosphonate.[16]

$$CHCl_2F + (i\text{-}PrO)_2PONa \xrightarrow[0^\circ,\ 1\ hr]{toluene} (i\text{-}PrO)_2P(O)CHClF \quad 38\%$$

The yields are not high owing to side reactions of which the most important is the formation of tetraalkyl halogenomethylenebisphosphonates. Thus, a mixture of diethyl chlorodifluoromethylphosphonate and tetraethyl difluoromethylenebisphosphonate was obtained from dichlorodifluoromethane and sodium diethyl phosphonate.[14]

The first synthesis of tetraalkyl difluoromethylenebisphosphonates was accomplished by the Michaelis-Becker reaction of dialkyl bromodifluoromethylphosphonates with sodium dialkyl phosphonates.[18]

The Michaelis-Becker reactions of halogenomethanes and halogenomethylphosphonates are not as straightforward as they appear superficially.[11,14,15,19] Illustrative of the mechanistic complexities encountered here is the formation of unexpected products such as the tetraisopropyl monofluoromethylenebisphosphonate and tetraisopropyl pyrophosphate obtained in the following reaction.[19]

$$(i\text{-PrO})_2\text{PONa} + (i\text{-PrO})_2\text{PCFBr}_2 \xrightarrow[-78^\circ,\ 2\ \text{hr}]{\text{hexane}} \underset{65\%}{(i\text{-PrO})_2\text{P(O)CHFP(O)(OPr-}i)_2} + \underset{35\%}{(i\text{-PrO})_2\text{P(O)OP(O)(OPr-}i)_2}$$

Similarly, the formation of symmetrical tetraalkyl methylenebisphosphonates from sodium dibutyl phosphonate and diethyl bromodifluoromethylphosphonate is not compatible with a mechanism of simple nucleophilic displacement.[11]

The formation of pyrophosphates and the observed dehalogenations are explained by mechanisms involving nucleophilic attack of dialkyl phosphonate anions upon positive halogen atoms.[19] Mechanisms with carbene participation were also discussed.[11,15]

3. Phosphorylation of Carbanions with Phosphorochloridates

Moderate yields of fluorinated tetraalkyl methylenebisphosphonates were obtained by phosphorylation of carbanions derived from fluorinated methylphosphonates.[17]

$$(i\text{-PrO})_2\text{P(O)CHFLi} + (\text{EtO})_2\text{P(O)Cl} \xrightarrow[1\ \text{hr}]{\text{THF, } -70^\circ} \underset{37\%}{(i\text{-PrO})_2\text{P(O)CHFP(O)(OEt)}_2}$$

In the same fashion Obayashi prepared tetraethyl difluoromethylenebisphosphonate from diethyl lithiodifluoromethylphosphonate.[20]

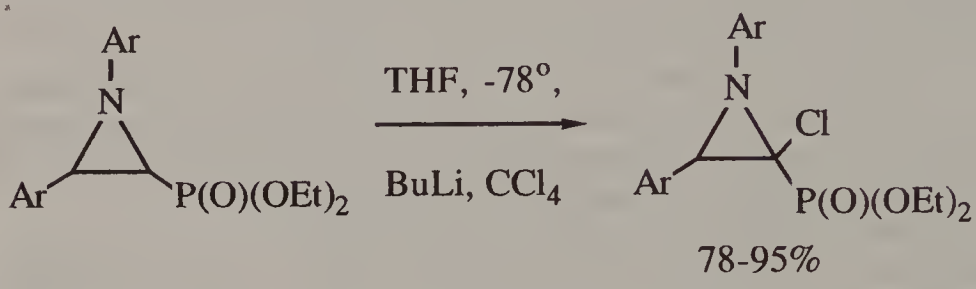
The versatility of carbanion phosphorylation has been demonstrated with the syntheses of the biologically interesting isosteric and isopolar analogue of farnesyl pyrophosphate.[21]

B. Syntheses Involving the Formation or Breaking of Carbon-Halogen Bonds

1. Syntheses by Substitution of Hydrogen Atoms

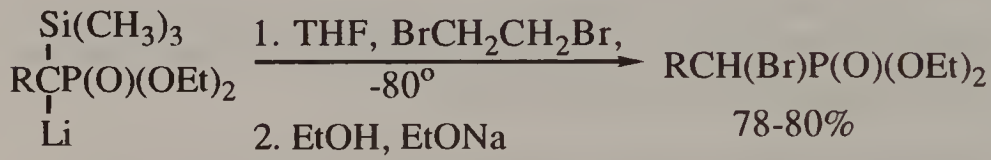
Phosphonates without additional C-H activating groups at the α-carbon atom are halogenated only in the presence of very strong bases needed to generate carbanions which may then react with a

variety of halogen sources. Chlorination appears to be accomplished most conveniently with carbon tetrachloride.[22-24] An example is provided by α-chlorination of aziridynyl phosphonates.[24]

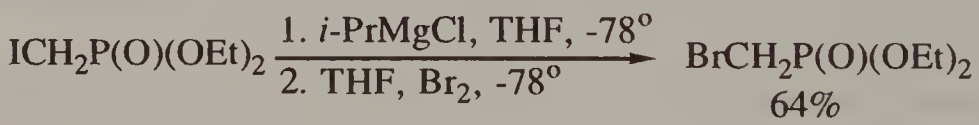


78-95%

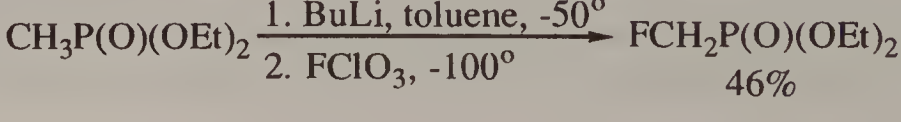
Bromination and iodination of diethyl 1-lithio-1-trimethylsilylalkylphosphonates were performed with 1,2-dibromo- and 1,2-diiodoethane. Subsequent removal of the trimethylsilyl group by treatment with sodium ethoxide provided diethyl 1-bromoalkylphosphonates in very good overall yields.[25]



Diethyl 1-bromomethylphosphonate was prepared from the readily available iodomethylphosphonate by iodine replacement with bromine *via* a Grignard intermediate.[26] Dialkyl bromomethylphosphonates are difficult to obtain by other routes.



The carbanion route is useful also for fluorination of phosphonates with perchloryl fluoride. Exclusive monofluorination was achieved in the case of diethyl methylphosphonate[17] while tetraethyl methylenebisphosphonate gave mixtures of mono- and difluorinated products.[27]



Phosphonates with additional activating groups, *e.g.* phosphonoacetates[28] or methylenebisphosphonates[29] are halogenated very easily. Bromination and chlorination with sodium hypohalites in neutral aqueous solutions afford halogenated products in yields of over 90%.[28]

α-Phosphorylated aldehydes and ketones are also readily halogenated.[30,31] Another example of facile halogenation is provided by diethylphosphorylacetamide which was found to undergo bromination instead of Hofmann degradation when treated with bromine in aqueous alkaline solution.[32]

Strong activation by the combined effects of a sulfur atom and phosphoryl group is illustrated by mild chlorination of diethyl phenylthio- and methylthiomethylphosphonates with *N*-chlorosuccinimide.[33,34]

$$CH_3SCH_2P(O)(OEt)_2 \xrightarrow{NCS,\ CCl_4,\ r.t.} \underset{90\%}{CH_3SCHClP(O)(OEt)_2}$$

2. Syntheses Involving the Cleavage of Carbon-Halogen Bonds

Selective removal of halogen from polyhalogenated phosphonates offers some advantages when the more halogenated species are easier to obtain than the less halogenated ones. Dehalogenation can be accomplished by nucleophilic displacement of positive halogens or by reductive processes. Catalytic hydrogenation and reduction by electrolysis were used to prepare dialkyl mono- and dichlorophosphonates from the readily available trichloromethylphosphonates.[23,35]

By a combination of halogenation with selective removal of halogens McKenna has recently prepared the entire families of triethyl phosphonoacetates[28] and tetraethyl methylenebisphosphonates[29] with all possible combinations of bromine, chlorine, and fluorine in the methylene group. The readily available triethyl dichlorophosphonoacetate (Section II.B.1) was dechlorinated to the monochloroderivative in 95% yield by reduction with sodium sulfite. Similarly, triethyl monobromophosphonoacetate was obtained from the dibromo ester by reduction with stannous chloride. The same reducing agents were used for selective dehalogenations in the methylenebisphosphonate series.[29]

Nucleophilic dehalogenation by the anions of dialkyl phosphonates was already discussed (Section II.A.2). Another nucleophile shown to be an effective dehalogenating agent is the naked fluoride anion employed by Hutchinson and Semple to prepare tetraisopropyl monochloro- and monobromomethylenebisphosphonates.[36] The treatment of the readily available esters of dichloro- and dibromomethylenebisphosphonic acid with KF in acetonitrile in the presence of a crown ether afforded monohalogenated esters in yields of about 50%.

A rare example of dehydrohalogenation producing an α-halogenated phosphonate was observed during an attempted preparation of 1,1-difluoro-3-oxo-4-hydroxy-1-butylphosphonic acid, an analogue of dihydroxyacetone phosphate.[37]

Diethyl 1-bromovinylphosphonate, useful as the starting material for the synthesis of 2-aziridinephosphonates, was obtained by HBr elimination from the dibromo ester.[38]

3. Syntheses by Halogen Addition to 1,2-Unsaturated Phosphonates

Only a few examples of these rather trivial syntheses were described.[38-40] The easy addition of chlorine to dialkyl perfluoro-2-propenylphosphonates is somewhat unusual in view of the accumulation of electron-withdrawing substituents.[39]

$$F_2C{=}C(CF_3)P(O)(OMe)_2 \xrightarrow[\text{r.t., 10 min}]{Cl_2,\ CCl_4,} CF_2ClCClP(O)(OMe)_2 \quad (CF_3)\ 78\%$$

More interesting is the reaction of hydroxyhalogenation.[41] Diethyl vinylphosphonate reacts with hypochlorous and hypobromous acids to give separable mixtures of 1-halo-2-hydroxyethylphosphonates with 1,2-dihalogenated products.

$$H_2C{=}CHP(O)(OEt)_2 \xrightarrow[HX]{NaOX,\ H_2O} CH_2XCHXP(O)(OEt)_2 + HOCH_2CHXP(O)(OEt)_2$$

X = Cl, 86%; X = Br, 70%

4. Syntheses from Hydroxyphosphonates

The well known conversion of alcohols to alkyl chlorides

was employed also in organophosphorus chemistry.[5] According to recent procedures good yields of dialkyl 1-chloroalkylphosphonates are obtained from dialkyl 1-hydroxyalkylphosphonates by treatment with thionyl chloride[42] or with CCl_4 in the presence of triphenylphosphine.[43]

Diethyl 1-fluoro-1-arylmethylphosphonates are accessible by fluorination of hydroxyphosphonates with dimethylaminosulfur trifluoride. Unfortunately, the reaction is limited to hydroxyphosphonates in which the OH group is located at a benzylic carbon.[44]

C. Syntheses by Formation of C-C Bonds

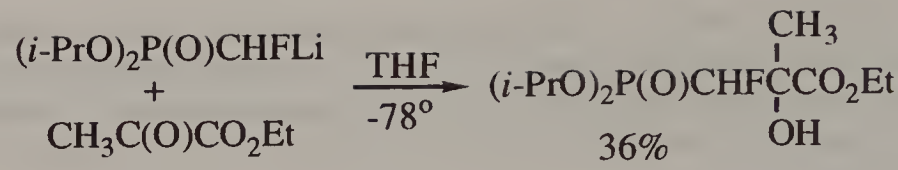
1. Alkylation of Carbanions Derived from Halogenomethylphosphonates

A general route to 1,1-dichloroalkylphosphonates takes advantage of the easy formation and alkylation of diethyl lithiodichloromethylphosphonate at low temperatures.[45] A wide range of alkyl iodides and bromides were used for efficient alkylation. The yields were in excess of 70% and depended on the nature of alkyl halide and the mode of preparation of the lithium derivative. An extension of the lithiation and alkylation process to diethyl 1,1-dichloroalkylphosphonates afforded good yields of branched 1-chloroalkylphosphonates.[46]

Straight-chain diethyl 1-chloroalkylphosphonates were obtained from diethyl trichloromethylphosphonate by lithiation and silylation followed with alkylation and desilylation. The silylated anions are sufficiently stable to be alkylated at 0^{o} in good yield.[25]

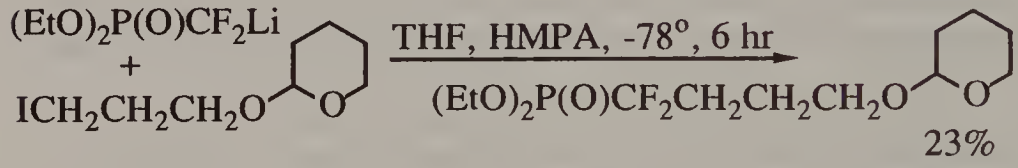
Diethyl 1-chloro-1-alkenylphosphonates are accessible *via* a Peterson-type alkenylation of diethyl lithiochlorotrimethylsilylmethylphosphonate with aliphatic and aromatic aldehydes. The reaction is fast at -78^{o} and the trimethylsilyl is eliminated.[25]

A general, although not very efficient (15-60%), synthesis of functionalized 1-fluoroalkylphosphonates is based on the reaction of dialkyl fluoromethylphosphonate carbanion with aldehydes, ketones, alkyl halides, and acyl halides. The reaction with aldehydes and ketones gives dialkyl 1-fluoro-2-hydroxyalkylphosphonates with the exception of formaldehyde which gives exclusively dialkyl 1-fluorovinylphosphonates. Possible Wadsworth-Emmons reactions are avoided by suitable control of time and temperature. The reaction with ethyl pyruvate is illustrative.[16]



Several 1,1-difluoro-2-hydroxyalkylphosphonates were prepared by a similar hydroxyalkylation of diethyl lithiofluoromethylphosphonate.[20] In one of the described syntheses the carbanion of diethyl difluoromethylphosphonate was generated from diethyl trimethylsilyldifluoromethylphosphonate and cesium fluoride and was treated with carbonyl compounds to give good yields of diethyl 1,1-difluoro-2-hydroxyalkylphosphonates.[47]

Alkylation of dialkylphosphoryldifluoromethyl carbanion with alkyl halides presents difficulties resulting from the low nucleophilicity and poor stability of this carbanion species. Thus, the reaction with 3-(tetrahydropyranyloxy)propyl iodide provided the desired product in only 23% yield. No alkylation was observed without added hexamethylphosphoramide.[48]



Problems resulting from poor stability of the dialkyl difluoromethylphosphonate carbanions may be avoided by using the more stable organocadmium and organozinc derivatives. [(Diethylphosphoryl)difluoromethyl]zinc bromide is stable at room temperature and is quite unreactive. It will react only with the most active electrophiles such as acyl chlorides or halogens. It was found recently that the reactivity of this reagent is sufficiently enhanced by addition of catalytic amounts of cuprous halides to make possible the alkylation with allylic bromides and chlorides. The products, diethyl 1,1-difluoro-3-alkenylphosphonates, were obtained in ~50% yield.[49]

[(Diethylphosphoryl)difluoromethyl]cadmium bromide[50] is sufficiently reactive without catalyst. The cadmium reagent was prepared *in situ* and was treated with allylic and benzylic halides at room temperature to give fair yields of the expected products.[51]

$$(EtO)_2P(O)CF_2Br \xrightarrow[\text{2. allyl bromide, NaI, THF, 25°, 20 hr.}]{\text{1. Cd, THF, 65°, 3 hr.}} H_2C{=}CHCH_2CF_2P(O)(OEt)_2 \quad 62\%$$

Conventional chemistry of the double bond in diethyl 1,1-difluoro-3-butenyl-1-phosphonate followed by deprotection of the phosphonate function was used to prepare 1,1-difluoro-3,4-dihydroxybutylphosphonic acid, the difluoromethylenephosphonate analogue of glycerol phosphate.[37]

2. Acylation of Carbanions Derived from Halogenomethylphosphonates

Dialkyl 1-chloro-2-oxoalkylphosphonates were prepared by acylation of lithiochloromethylphosphonate carbanions with esters of carboxylic acids. Derivatives of phosphonoacetaldehyde were obtained with ethyl formate while diethyl carbonate gave chlorinated esters of phosphonoacetic acid.[52]

$$(EtO)_2P(O)CHClLi \xrightarrow{HCOOEt,\ THF,\ -78^\circ} (EtO)_2P(O)CHClCHO \quad 70\text{-}85\%$$

$$(EtO)_2P(O)CHClLi \xrightarrow[-78^\circ]{C(O)(OEt)_2,\ THF} (EtO)_2P(O)CHClCO_2Et \quad 82\%$$

1-Chloro-2-oxophosphonates are obtained also by acylation of lithiodichloromethylphosphonates. Efficient preparation of products with two chlorine atoms is not possible owing to rapid Cl/Li exchange between the primary acylation product and the starting carbanion. The yields of products with one chlorine atom are increased to 60-85% when excess butyl lithium is added. Butyl lithium enters a Cl/Li exchange with the acylation products and prevents the counterproductive reaction with dichloromethylphosphonate carbanion.[53]

Dialkyl lithiofluoromethylphosphonates and lithiodifluoromethylphosphonates were acylated with benzoyl chloride[16,20] and carboxylated with carbon dioxide[54] to the expected products.

It appears that the difluoromethylphosphonate carbanion is less useful in acylation reactions than the monofluoro species. In

fact, the benzoylation, carboxylation, and the reaction with ethyl isocyanate are the only described processes in which the diethyl lithiodifluoromethylphosphonate gave adequate yields of acylation products. Unexpected products were obtained in an attempted ethoxycarbonylation with ethyl chlorocarbonate.[17]

$$(EtO)_2P(O)CF_2Li \xrightarrow[THF,\ -78^\circ]{ClCO_2Et} \begin{array}{l} (EtO)_2P(O)CF_2COOEt \quad 3\% \\ + \\ (EtO)_2P(O)CF_2P(O)(OEt)_2 \quad 39\% \\ + \\ (EtO)_2P(O)CF_2C(O)CF_2P(O)(OEt)_2 \\ 9\% \end{array}$$

Problems resulting from abnormal reactivity are not encountered when zinc instead of lithium derivatives were used in the acylation process. The zinc derivatives are readily acylated with acyl chlorides at room temperature.[55] Ethoxycarbonylation with ethyl chlorocarbonate occurred only in the presence of cuprous bromide catalyst.[56]

$$(EtO)_2P(O)CF_2ZnBr \xrightarrow[\text{monoglyme, CuBr, r.t.}]{ClCO_2Et,\ CH_3CN} (EtO)_2P(O)CF_2CO_2Et \quad 50\%$$

3. Syntheses Starting from Halogenomethylenebisphosphonates

The Wadsworth-Emmons reaction of the carbanion obtained from tetraethyl chloromethylenebisphosphonate was used in the syntheses of α-chlorovinylphosphonates.[45] The same olefination process was used to synthesize α-fluorovinylphosphonates.[57]

Successful catalytic hydrogenation of fluorovinylphosphonates extended the scope of this approach to include the preparation of saturated dialkyl 1-fluoroalkyl phosphonates.[57]

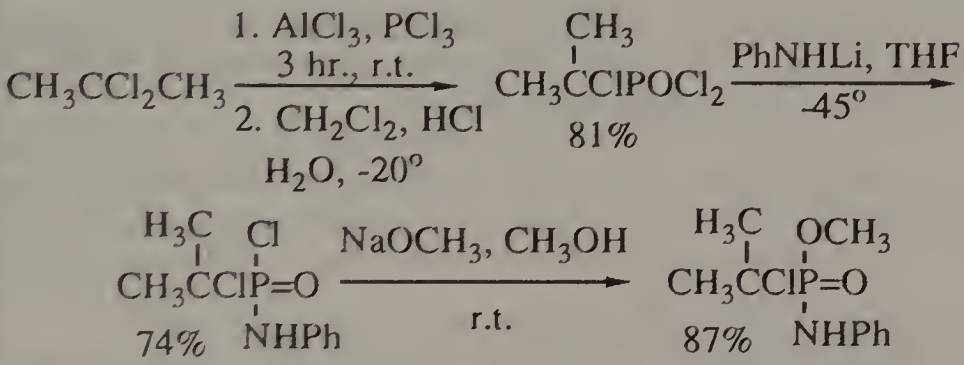
The utility of the Wadsworth-Emmons olefination for the synthesis of more complex α-fluoroalkylphosphonates was recently demonstrated by stereospecific syntheses of optically active fluoromethylenephosphonate analogues of the glycolytic intermediates, 3-phospho-D-glyceric acid[58] and 2-phospho-D-glyceric acid.[59] Tetraethyl fluoromethylenebisphosphonate was used in these syntheses and the initial chirality was secured by using sugar

substrates in the olefination step.

D. Syntheses by Modification of Phosphorus-Containing Functional Groups

1. Syntheses from Phosphonochloridates

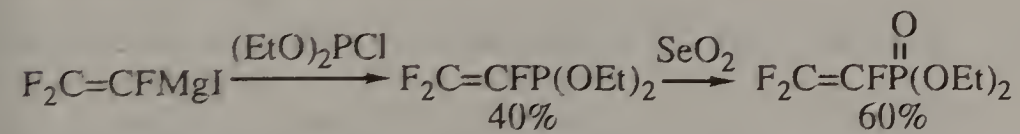
In some instances the Cl-C-P linkage is conveniently made using the Kinnear-Perren reaction of geminal dihaloalkanes with aluminum chloride and phosphorus trichloride.[5] The phosphonic dichlorides resulting from this reaction were recently used in a synthesis of methyl *N*-phenylphosphonamidates derived from 1-chloroalkylphosphonic acids.[60]



2. Syntheses Accomplished by Oxidation of the Phosphorus Function

Perfluoroalkylphosphonates were obtained from perfluoroalkyl iodides *via* a reaction sequence including a peroxide-catalyzed reaction with tetraethyl pyrophosphite followed by oxidation with *t*-butyl peroxide.[10,61]

An oxidation step is also involved in the synthesis of diethyl trifluorovinylphosphonate from trifluorovinylmagnesium iodide and diethyl phosphorochloridite.[13]



III. Phosphonates with the P-C-S Bond System

A. α-Phosphorylated Thiols

1. Syntheses by Formation of P-C Bonds

The described syntheses of 1-mercaptoalkylphosphonates *via* P-C bond forming reactions are limited to only very few examples, one of them being the preparation of diethyl mercaptomethylphosphonate by the Arbuzov reaction.[62]

$$CH_3C(O)SCH_2Br \xrightarrow[130^\circ,\ 2\ hr.]{(EtO)_3P} \underset{60\%}{CH_3C(O)SCH_2P(O)(OEt)_2}$$

$$\xrightarrow[r.t.,\ 1\ hr.]{NaOH,\ EtOH} \underset{80\%}{HSCH_2P(O)(OEt)_2}$$

The intermediate, (diethylphosphoryl)methyl thioacetate, was obtained also from diethyl iodomethylphosphonate by iodine substitution with the thioacetate anion.[63]

The syntheses based upon the addition of P-H entities to the carbon-sulfur bonds are not practical because thiocarbonyl compounds are not readily available and the addition is complicated by undesired side reactions.[64,65]

2. Syntheses by Formation of C-S Bonds

A general and very satisfactory synthesis of dialkyl 1-mercaptoalkylphosphonates was developed by Mikolajczyk, *et al.* In this synthesis alkylphosphonates are lithiated and treated with elemental sulfur to produce the target compounds in yields >80%.[63]

A mechanistically intriguing process of sulfur transfer from phosphorus to the neighbouring carbon atom was observed during solvolysis of mesylate esters of diethyl 1-hydroxy-1-arylmethylthiophosphonates. In 70% aqueous acetone the 1-mercaptophosphonates were formed as the only products.[66] The reaction has not beeen adapted to preparative purposes.

B. α-Phosphorylated Sulfides

1. Syntheses by Formation of P-C Bonds

The simplest compounds of this class, *i.e.* those derived from methylphosphonic acid, are obtainable by the Arbuzov reaction of suitable halogenomethyl sulfides.[5,67-69] The Michaelis-Becker reaction was used much less frequently.[22]

Tetraalkyl alkylthiomethylenebisphosphonates were prepared

from trialkyl phosphonodithioformates and trialkyl phosphites.[70]

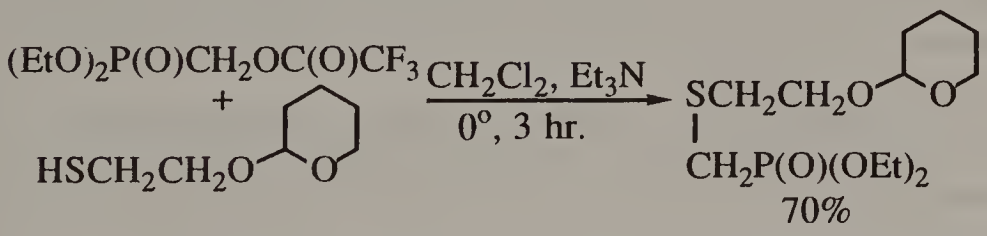
$$(RO)_2P(O)CS_2R' \xrightarrow[\substack{20^\circ \\ 2.\ CH_2Cl_2,\ HCl \\ 0^\circ}]{1.\ 2\ (RO)_3P,\ THF} (RO)_2P(O)\underset{\displaystyle SR'}{\underset{|}{C}}HP(O)(OR)_2 \quad 100\%$$

An interesting and complex process was observed when trialkyl phosphites were treated with thiophosgene. Instead of the expected tetraalkyl thiocarbonylbisphosphonates, the reaction gave good yields of tetraalkyl (diethylphosphorylthio)methylenebisphosphonates. As in the preceding example, the initially formed material was an ylid.[71] The tetraalkyl thiocarbonylbisphosphonates remain unknown.

2. Syntheses by Formation of C-S Bonds

Syntheses of α-phosphorylated sulfides by C-S bond formation are accomplished either by alkylation of the SH function or by creation of the P-C-S linkage from P-C systems.

α-Phosphorylated thiols are readily alkylated in good yields in two-phase catalytic systems[63] or by refluxing their sodium salts and alkyl halides in ethanol.[72] Thiols were alkylated also using suitably substituted derivatives of methylphosphonic acid.[48]

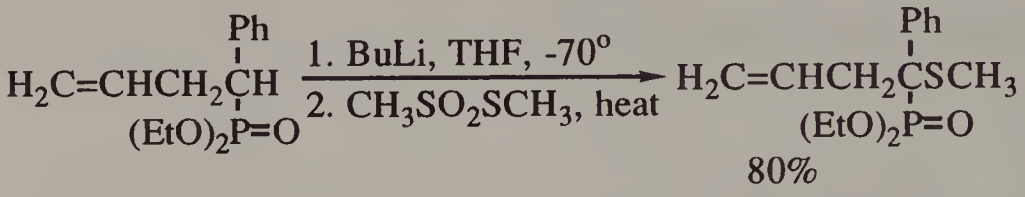


The SH group in diethyl mercaptomethylphosphonate was alkylated also by Michael addition.[73,74]

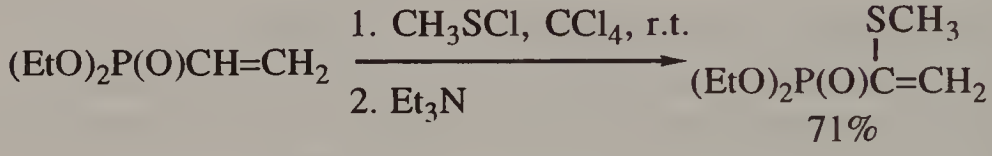
Intramolecular alkylation of thiols generated by sulfur addition to carbanions was used in syntheses of phosphorylated isopenams and isocephams.[75]

The most general and most frequently used method for the formation of α-phosphorylated sulfides is based on the reaction of carbanions with sulfenylating agents, R-S-Y, where Y is a sufficiently active leaving group and R is alkyl or aryl. The successfully

used R-S-Y agents include dialkyl and diaryl disulfides[76,77] as well as S-alkyl and S-aryl thiosulfonates.[78,79]



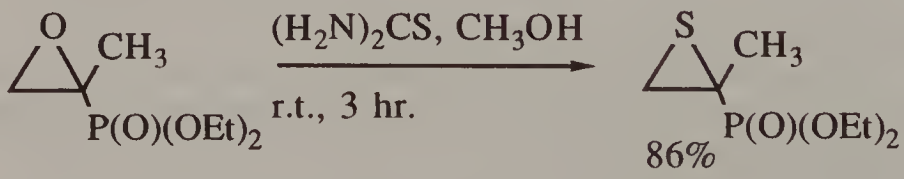
Other published approaches are inherently less general or have not been sufficiently developed to make possible an assessment of their scope of application. The addition of sulfenyl halides to carbon-carbon double bonds may represent a general reaction, but the only example described so far is the addition of methylsulfenyl chloride to diethyl vinylphosphonate.[80]



A study of sulfenylation of methylenebisphosphonates with trihalogenomethylsulfenyl halides revealed a complex reaction producing mixtures of several products.[81]

Diethyl 1-phenylthioalkylphosphonates were obtained from the readily available 1-hydroxyalkylphosphonates and thiophenol using the triphenylphosphine/diethyl azodicarboxylate system to promote the reaction.[82] The yields are only moderate and the reaction is not general.

A replacement of oxygen with sulfur takes place when 1,2-epoxyalkylphosphonates react with thiourea. The reaction is remarkably easy and affords high yields of 1,2-epithioalkylphosphonates.[83]

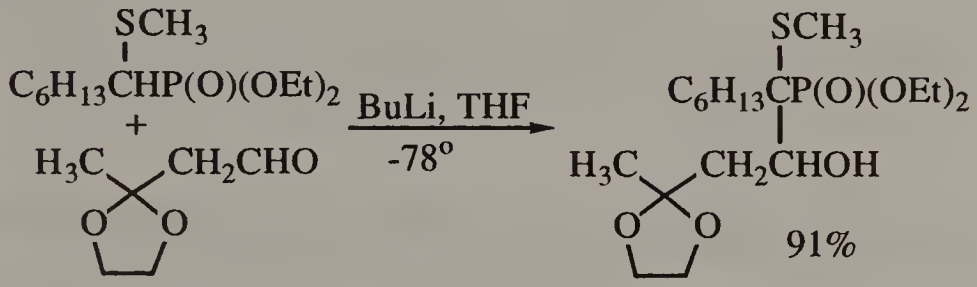


3. Syntheses by Formation of C-C Bonds

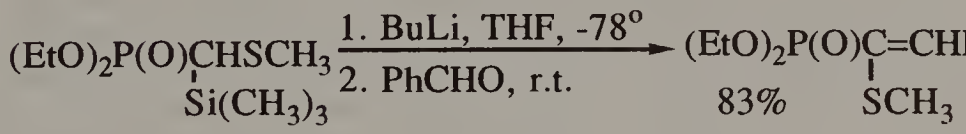
More complex α-phosphoryl sulfides were frequently obtained from the simpler ones by alkylation or arylation at the carbon

atom of the P-C-S system. The alkylation was usually performed by lithiation of α-phosphoryl sulfides followed by the treatment of the resulting carbanions with appropriate alkylating agents. Both the carbanion generation and alkylation proceed readily and afford good yields of products with elaborated carbon chains. Alkylation may be performed in THF at temperatures from -78° to reflux[77,84-87] or in toluene.[79] Work prior to 1982 has been reviewed.[88]

Carbon chain extension takes place also when the carbanions of α-phosphoryl sulfides react with aldehydes and ketones. The addition products, *i.e.* the 2-hydroxy-1-alkylthioalkylphosphonates are stable enough to be isolated.[84,85] Their conversion to Wadsworth-Emmons products is also possible.[85,89]



Unsaturated α-phosphoryl sulfides were prepared from diethyl (methylthio)(trimethylsilyl)methylphosphonate by Peterson reaction with aldehydes.[77] The reaction failed with ketones.



Elaboration of the carbon skeleton of α-phosphoryl sulfides is possible also by means of reactions in which the α-carbon atom displays carbocationic reactivity. The activation sufficient for such reactivity to appear is achieved by chlorination. The chlorinated sulfides readily react with arenes in the presence of stoichiometric amounts of Sn(IV) chloride to give high yields of dialkyl 1-alkylthio-1-arylmethylphosphonates.[34,90]

Electrophilic species able to react with arenes were obtained also by oxidation of sulfides to sulfoxides followed by treatment

with trifluoroacetic anhydride. Under these conditions sulfoxides rearrange to the very reactive α-trifluoroacetoxyphosphoryl sulfides (Pummerer rearrangement). The isolation of the rearranged intermediates is not necessary. Successful arylation was accomplished in very good yields when the Pummerer reaction was performed in the presence of aromatic substrates and Sn(IV) chloride.[91,92]

Another potentially even more useful application of electrophilic α-phosphoryl sulfides results from their reaction with double bonds of terminal alkenes. The reaction takes place under very mild conditions and affords good yields of products with extended carbon chains.[90]

Chain extension was accomplished also by the Michael addition of carbanions to diethyl 1-(methylthio)vinylphosphonate.[93,94]

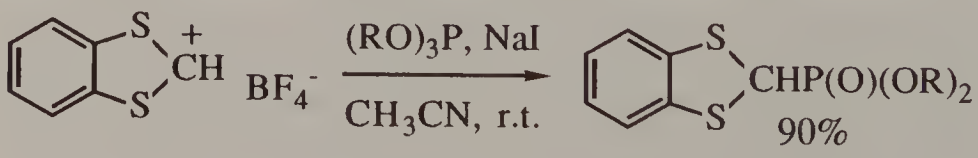
$$(EtO)_2P(O)\underset{\displaystyle SCH_3}{\overset{\displaystyle |}{C}}=CH_2 \xrightarrow[\text{base}]{\text{acetone}} (EtO)_2P(O)\underset{\displaystyle SCH_3}{\overset{\displaystyle |}{C}}HCH_2CH_2C(O)CH_3 \quad 51\%$$

A synthesis of a complex α-phosphoryl sulfide by carbene insertion into a carbon-sulfur bond has been described.[95]

C. Dithioacetals and Derivatives of Formylphosphonates

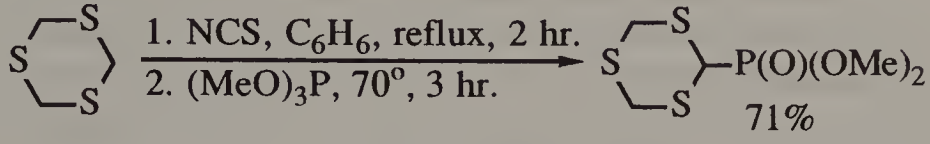
1. Syntheses by Formation of P-C Bonds

The first ever described dithioacetal derivatives of formylphosphonates were prepared by the Arbuzov reaction of benzodithiolium tetrafluoroborate with trialkyl phosphites. Because of the very low nucleophilicity of the tetrafluoroborate anion it was necessary to add sodium iodide to effect the nucleophilic displacement occurring in the second step of the Arbuzov process.[96,97]



The utility of the Arbuzov reaction is limited by the availability of substrates with two suitably arranged C-S linkages and a leaving group. The described examples include both cyclic and

open-chain α-phosphorylated dithioacetals as well as cyclic O,S-acetals.[98-100]



Various attempts have been made to overcome the limitations of the Arbuzov reaction.[101]

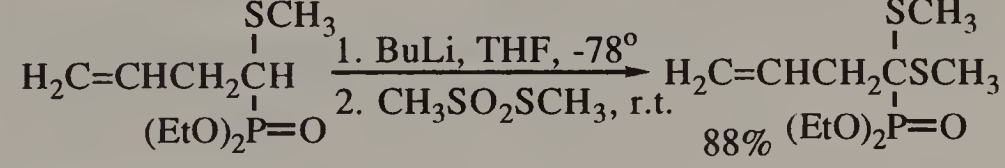
Moderate yield of 2-diethylphosphoryl-1,3-dithiane was obtained by phosphorylation of the lithium salt of 1,3-dithiane with diethyl phosphorochloridate.[102]

Direct preparation of dialkyl bis(ethylthio)methylphosphonates from triethyl trithioorthoformate is possible *via* phosphorylation with dialkyl phosphonates.[103]

$$(PrO)_2PHO + HC(SEt)_3 \xrightarrow[30\ hr.]{150^\circ} (EtS)_2CHP(O)(OPr)_2 + EtSH$$
63%

2. Syntheses by Formation of C-S Bonds

The lithiation/sulfenylation procedure (III.B.2) converts α-phosphoryl sulfides to α-phosphoryl dithioacetals.[63,76,77,87]



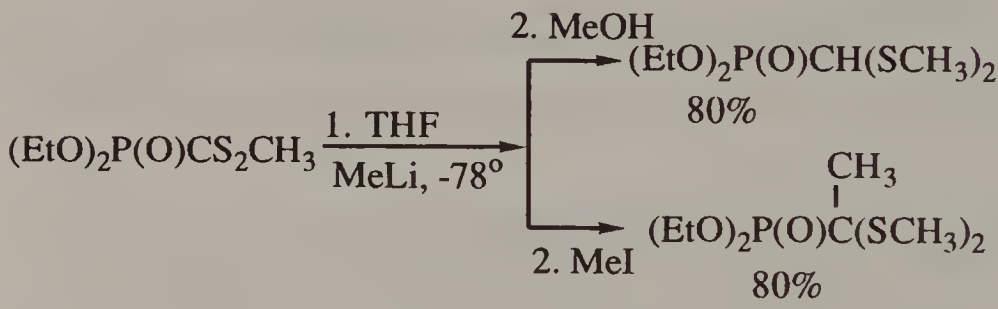
The same procedure was used to prepare O,S-acetals from alkoxymethylphosphonates.[63] Other syntheses of O,S-acetals include chlorination of α-phosphoryl sulfides followed by solvolytic chlorine substitution with the alkoxy groups,[104] electrochemical methoxylation of α-phosphoryl sulfides,[105] and alkoxylation by the Pummerer reaction of α-phosphoryl sulfoxides. The Pummerer reaction was performed by refluxing the sulfoxides in alcohols in the presence of equimolar amounts of iodine.[106]

$$(EtO)_2P(O)CH_2SPh \xrightarrow[50\ min.]{I_2,\ EtOH,\ reflux} (EtO)_2P(O)CHSPh \quad 78\%$$

Other examples of this reaction have been reported.[106,107]

Efficient syntheses of symmetrical and unsymmetrical α-phosphoryl dithioacetals are based upon chlorination of diethyl arylthiomethylphosphonates and subsequent chlorine displacement with thiols. The displacement reaction is catalyzed by Sn(IV) chloride.[108] The displacement of alkoxy substituents with thiols converts bis(alkoxy)methylphosphonates to bis(alkylthio)methylphosphonates. The reaction occurs at 0° in a 1:1 mixture of acetic acid and conc. HCl.[101]

Trialkyl phosphonodithioformates, readily accessible from dialkyl phosphonates and carbon disulfide, were recently found to be useful as substrates for the preparation of α-phosphoryl dithioacetals. The thiophilic addition of alkylmagnesium bromide or, preferably, organolithium reagents gives bis(alkylthio)methylphosphonates. Higher homologues are obtained by C-alkylation of the metallated intermediates.[109]



D. α-Phosphoryl Sulfoxides, Sulfones, and Sulfonic Acids

1. Syntheses by Oxidation at Sulfur

Sulfoxides and sulfones are obtained in high yields by oxidation of α-phosphoryl sulfides. The reagents used for selective oxidation to sulfoxides include stoichiometric amounts of hydrogen peroxide in methanol,[68,73,110] sodium metaperiodate in aqueous acetone,[72,110,111] and bromine in the two phase system methylene chloride/aqueous $KHCO_3$.[112] Excess hydrogen peroxide oxidizes sulfides directly to sulfones.[33,73] Oxidation to sulfones

was performed also with *m*-chloroperbenzoic acid,[33,72] potassium permanganate,[113-116] and with persulfates.[67,116]

Oxidation at sulfur was used also in syntheses of α-phosphorylated sulfonic acids.[10,117] Sulfodifluoromethylphosphonic acid, recently described for the first time, was prepared *via* the following sequence.[118]

$$(i\text{-PrO})_2P(O)CF_2I \xrightarrow[NaHCO_3]{Na_2S_2O_4} (i\text{-PrO})_2P(O)CF_2SO_2Na$$

CH_3CN, 50°, 4 hr. — 70%

$$\xrightarrow[\text{r.t., 30 min}]{30\%\ H_2O_2} (i\text{-PrO})_2P(O)CF_2SO_3Na \xrightarrow[80°,\ 6\ hr.]{\text{conc. HCl}} H_2O_3PCF_2SO_3H$$

89% — 85%

2. Syntheses by Formation of C-S Bonds

A general synthesis of α-phosphoryl sulfoxides uses the C-S bond formation reaction of carbanions with esters of sulfinic acids.[119] Sulfinylation with stereochemically defined menthyl esters of arylsulfinic acids was extensively used in syntheses of optically active α-phosphoryl sulfoxides.[110,120-123] Chemical resolution of racemic sulfoxides was also described.[119] Stereoisomers of a sulfoxide with two chiral centers, located at the α-carbon atom and in the sulfinyl group, were obtained by sulfinylation of lithiated dialkyl ethylphosphonates with menthyl *p*-tolylsulfinate having the *S* configuration at the sulfur atom.[110]

$$(MeO)_2P(O)CHLiCH_3 + p\text{-}CH_3C_6H_4SO_2Men \xrightarrow[-78°,\ 15\ min]{THF} (MeO)_2P(O)\underset{CH_3}{\overset{|}{C}}HS(O)C_6H_4CH_3\text{-}p$$

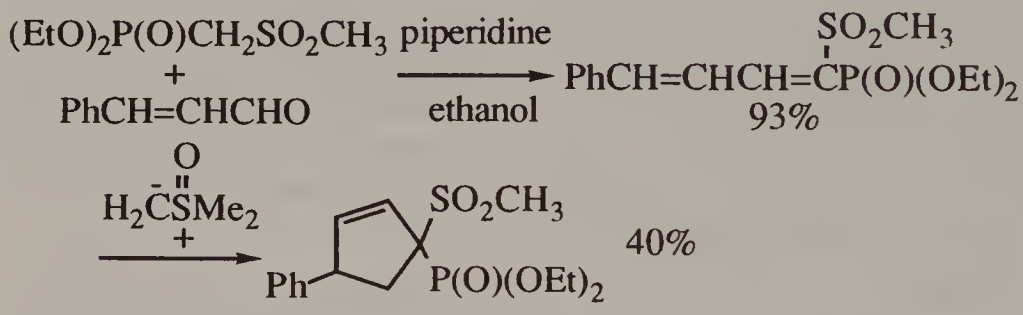
85%

The formation of C-S bonds to the α-carbon atom of phosphonates occurs also in syntheses of α-phosphoryl sulfinic acids from α-halogenoalkylphosphonates and sodium sulfite or sodium dithionite.[10,117,118] Another procedure is based on the reaction of sulfur dioxide with (dialkylphosphoryldifluoromethyl)cadmium bromide.[118]

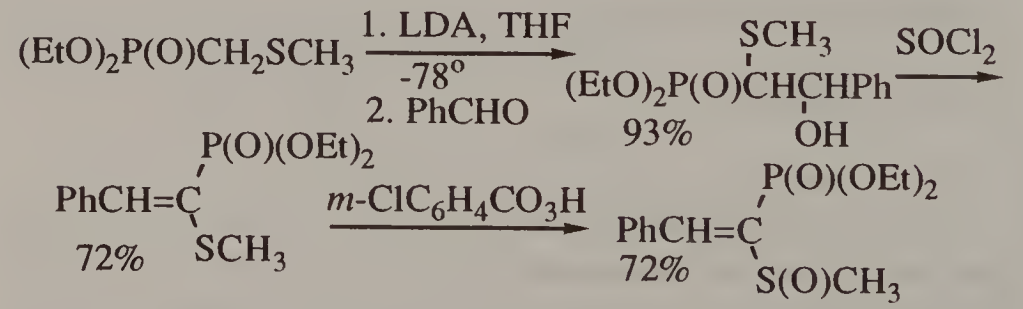
3. Syntheses by Formation of C-C Bonds

Carbanions of α-phosphoryl sulfoxides and sulfones can be alkylated by the usual procedures, but only a few examples of such alkylations were described. Diethyl (phenylsulfonyl)methylphosphonate was alkylated in 82% yield with allyl bromide under phase transfer conditions.[67] In another example the optically active (dimethylphosphoryl)methyl *p*-tolyl sulfoxide was lithiated and treated with methyl iodide to give dimethyl 1-(*p*-tolylsulfinyl)ethylphosphonate as a mixture of diastereoisomers.[110] The simplest unsaturated α-phosphoryl sulfone was obtained from diethyl (methylsulfonyl)methylphosphonate in two steps.[94]

A more extensive elaboration of carbon skeleton was performed by Knoevenagel condensation with cinnamaldehyde and subsequent reaction with a sulfur ylid.[124]



Unsaturated α-phosphoryl sulfoxides and sulfones were obtained by oxidation of α,β-unsaturated sulfides prepared by carbon chain extension reactions of simpler substrates.[89]



Diazomethane addition to diethyl (1-methylsulfonylethenyl)-phosphonate provided a derivative with a cyclopropane ring. The intermediate pyrazoline was too unstable to be isolated.[94]

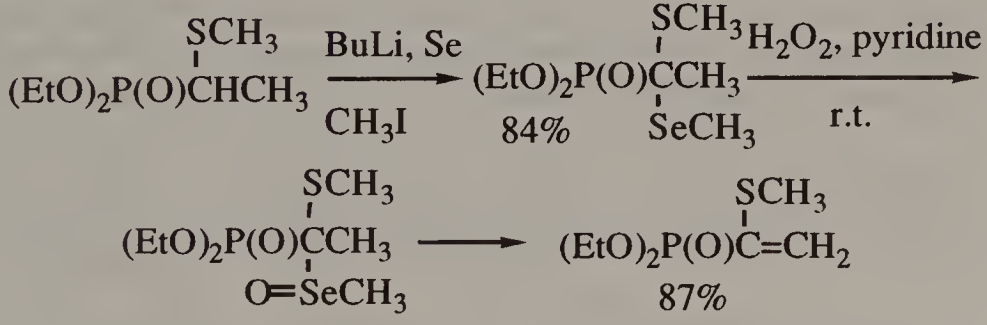
E. α-Phosphoryl Organoselenium Compounds

The α-phosphoryl selenides were prepared for use in the Wadsworth-Emmons reactions where they supplement the more widely used sulfides.[125] From the point of view of organic synthesis, perhaps more interesting is the formation of α,β-unsaturated phosphonates by selenoxide elimination from α-phosphoryl selenoxides generated by oxidation of selenides. The intermediate selenoxides are virtually unknown as they undergo spontaneous elimination.

The P-C-Se bond system is formed either from iodomethylphosphonates by iodine displacement with selenium reagents or by selenylation of carbanions. The reagents used for iodine displacement include sodium phenylselenide and disodium selenide.[125]

The carbanions of dialkyl alkylphosphonates were selenylated with phenylselenyl bromide,[26,79,126] diphenyl diselenide,[79] and with elemental selenium. In the latter procedure the initially formed selenols were alkylated to selenides without isolation.[94]

Selenylation of dialkyl (1-alkylthio)alkylphosphonates coupled with selenoxide elimination represents a general method for the synthesis of dialkyl 1-(alkylthio)-1-alkenylphosphonates. Noteworthy is the selective oxidation of the intermediate S,Se-acetals at the selenium atom.[94]



IV. Phosphonates with the P-C-O Bond System

A. 1-Hydroxyalkylphosphonates

1. Syntheses by Formation of P-C Bonds (Addition of P-H Reagents to Carbonyl Groups)

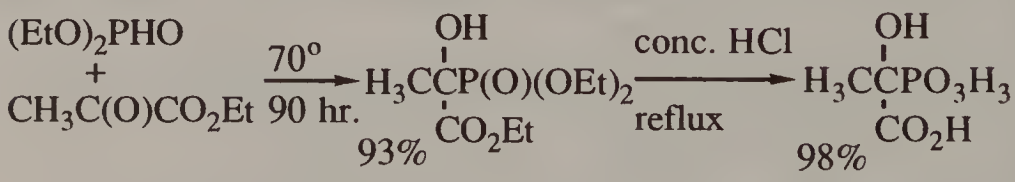
The formation of P-C bonds by addition of phosphorus reagents to the carbonyl group of aldehydes and ketones, known for

about forty years, was developed into a most general, very efficient and most frequently used synthesis of α-phosphoryl alcohols. The range of phosphorus compounds capable of addition to the carbonyl group includes virtually any species with a P-H bond. Dialkyl phosphonates were used most frequently but the additions of other compounds derived from trivalent phosphorus and from phosphorus at lower oxidation states are also known.[5,6] The addition of the P-H function represents a simple case of nucleophilic addition to the carbonyl group and follows general rules applying to the reactivity of aldehydes and ketones toward nucleophiles.

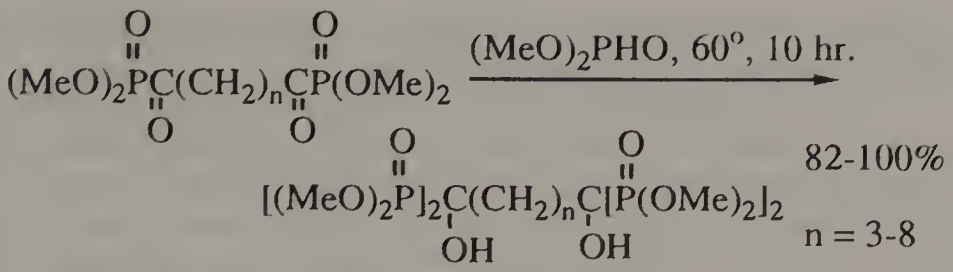
Some limitations, *e.g.* those observed with α-halogenoketones or α,β-unsaturated carbonyl compounds, are avoided when silylated P(III) reagents are used. The reactions are less straightforward because the desilylation step is necessary to remove the silyl groups from the initially formed silyloxyphosphonates.

Detailed discussions of the formation of 1-hydroxyalkylphosphonates by addition of P-H compounds to the carbonyl group are found in older, comprehensive reviews.[5,6,127] Recent contributions by Russian workers were also reviewed.[128]

The addition of dialkyl phosphonates to aldehydes and ketones is most frequently performed in the presence of basic catalysts. Acid catalysis was applied rather less frequently and only few examples were described of non-catalyzed additions.[44] Reactions without catalysis are slow but workable, and occassionally may provide excellent yields of desired products, as in the synthesis of 1-hydroxy-1-carboxyethylphosphonic acid from ethyl pyruvate.[129]



In another example of non-catalyzed addition, dimethyl phosphonate was added to both carbonyl groups of α,α-dioxobisphosphonates.[130] Much less efficient (yields < 13%) was the addition of dialkyl phosphonates to both carbonyl groups of glyoxal.[131] On the other hand, paraformaldehyde and diethyl phosphonate gave a 90% yield of diethyl hydroxymethylphosphonate in an exothermic reaction without catalyst.[132]



Very effective catalysis under neutral conditions is provided by alkali metal fluorides,[133] alumina,[134] and potassium fluoride on alumina.[135] The additions of dialkyl phosphonates in the presence of these catalysts are performed without solvents and are sufficiently rapid at ambient temperatures. The yields are generally high. Catalysis by potassium fluoride was recently used in the synthesis of 1-hydroxyalkylphosphonates derived from sugars.[136]

Examples of acid-catalyzed addition of P-H substrates to the carbonyl group are found in older literature.[5] In a more recent work hydrogen chloride was used to promote the formation of α-phosphoryl alcohols from triethyl phosphite and aldehydes.[129,137] The function of HCl is to assist in the dealkylation step following the initial nucleophilic attack of phosphorus on the carbonyl carbon.

A great number of 1-hydroxyalkylphosphonates were prepared from aldehydes and ketones by addition of P-H reagents in the presence of triethylamine. The yields vary from good[138,139] to excellent[140] and depend mainly on the structure of the carbonyl reagents.[66] Triethylamine is sufficiently effective under mild conditions to permit its use in syntheses of complex, polyfunctional 1-hydroxyalkylphosphonates, such as in the formation of a phosphonic analogue of an anhydronucleotide.[141] More complex organic bases, *e.g.* DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene), were also used to catalyze the addition of P-H reagents to carbonyl groups.[142,143]

The amount of amine used to catalyze the addition may have a dramatic effect upon the reaction course when the addition products readily undergo the phosphonate-phosphate rearrangement. For example, catalytic amounts of diethylamine bring about a smooth addition of dimethyl phosphonate to the carbonyl group of acylphosphonates whereas with stoichiometric amounts of the same catalyst only the rearranged products are obtained under otherwise the same conditions.[144] 1-Hydroxy-1,1-bisphosphonates are

rearranged to phosphonate-phosphates at room temperature with catalytic amounts of triethylamine.[145]

The phosphonate-phosphate and other similar rearrangements were reviewed.[146] The reverse process, *i.e.* the formation of 1-hydroxyphosphonates from phosphate esters, is also known. It is not important in synthetic organophosphorus chemistry but attracts attention from the point of view of reaction mechanisms and because of the involvement of the phosphate-phosphonate rearrangement in the biosynthesis of natural phosphonates. It was found that the base-induced formation of hydroxyphosphonates from phosphates takes place with retention of configuration at the carbon atom to which the phosphonate group migrates.[147] Both enantiomers of hydroxyphosphonates resulting in this rearrangement were obtained also by chemical resolution and their absolute configurations were determined by X-ray crystallography.[147] Several aliphatic and aromatic α-hydroxyalkylphosphonates were resolved to pure enantiomers by crystallization of their salts with α-methylbenzyl amine or amphetamine[148] and ephedrine.[149]

The synthesis of optically active α-hydroxyalkylphosphonates was accomplished also by addition of dialkyl phosphonates to aromatic aldehydes in the presence of chiral bases (quinine, quinidine). The degree of asymmetric induction was quite high (to 85%) and the products were easily crystallized optically pure.[150] The absolute configuration of dimethyl (*o*-chlorophenyl)hydroxymethylphosphonate was determined by X-ray analysis.[151] The list of optically active 1-hydroxyalkylphosphonates of known configuration includes also 1-hydroxyethyl- and 1-hydroxypropylphosphonic acids[152,153] and the natural product 1-hydroxy-2-aminoethylphosphonic acid.[143]

The application of silylated phosphorus reagents in the synthesis of α-hydroxyalkylphosphonates was reviewed.[127,154] In the addition of P(III) silyl esters to the carbonyl group the phosphorus atom forms a bond with the carbonyl carbon and the silyl group is transferred to the carbonyl oxygen. No catalyst is required and the reaction is usually sufficiently rapid at room temperature. The necessity of separate preparation of silylated reagents can be avoided in one-pot procedures where mixtures of P-H substrates with commercially available silylating reagents are treated with carbonyl substrates. An example is the synthesis of γ-hydroxy-

phosphinothricin. The key step in this synthesis is the reaction of the aldehyde derived from homoserine with a mixture of ethyl methylphosphinate and bis(trimethylsilyl)acetamide.[155]

Phosphorus reagents in which the phosphorus atom is less oxidized than in P(III) species are capable of multiple additions to the carbonyl group. This property was used in a synthesis of bis-(hydroxyalkyl)phosphinic acids from aldehydes and ketones by addition of bis(trimethylsilyloxy)phosphine.[156]

$$\begin{array}{l}(Me_3SiO)_2PH \\ + \\ 2\ PhCHO\end{array} \xrightarrow[C_6H_6,\ reflux,\ 2\ hr.]{Me_3SiCl,\ Et_3N} Me_3SiOP(O)(CHPhOSiMe_3)_2 \quad 92\%$$

Examples of primary phosphine addition are also known. Particularly interesting are the intramolecular additions of the PH_2 function to the carbonyl group in sugar derivatives. Such additions were used to synthesize sugar analogues with a phosphorus atom in the ring.[157]

The addition of dialkyl phosphonates to the carbonyl groups in sugar molecules was used also in syntheses of phosphonate analogues of sugar phosphates. Stereochemical analysis and configuration assignment of products obtained by addition of dimethyl phosphonate to threose and erythrose were reported.[158] In some cases the addition is complicated by interaction of the functional groups in the sugar moieties with the introduced phosphonate group. For example, a phostone rather than the expected addition product was formed in base-catalyzed reaction of dimethyl phosphonate with diisopropylidene mannofuranose.[159]

The hydroxy group in 1-hydroxyalkylphosphonates is readily esterified by standard methods with no interference from the phosphonate group.[66,131,141,143,155,160,161]

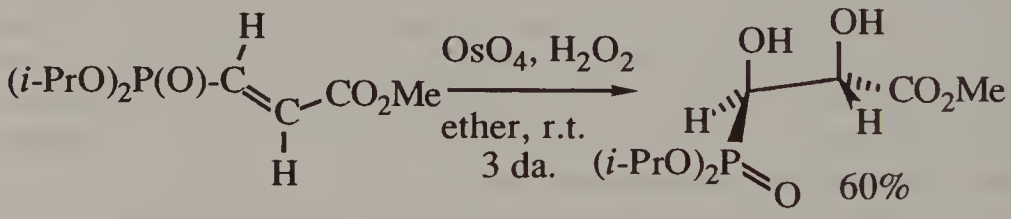
2. Syntheses by Oxidation-Reduction

The reduction of the carbonyl group in acylphosphonates was rather infrequently used to produce 1-hydroxyalkylphosphonates. Catalytic hydrogenation works well in simple cases but complications may arise with more complex substrates.[155] The reduction with borohydrides is feasible but the yields are low because of competing P-C bond cleavage typical for 1-hydroxyalkylphosphonates in alkaline media.[160,162] The reduction of diethyl benzoylphosphonate with a complex chiral borohydride afforded

optically active diethyl (phenyl)hydroxymethylphosphonate.[160]

Hydroboration-oxidation of α,β-unsaturated phosphonates appears to be useful for regiospecific introduction of the OH group into the α-position. The (1*R*,3*S*) and (1*S*,3*S*) diastereoisomers of 1,3,4-trihydroxybutyl-1-phosphonic acid were obtained from a chiral unsaturated substrate using optically active boranes. The (+) enantiomer of diisopinocampheylborane generated the *S* configuration at the α-position and the (-) enantiomer gave the *R* configuration.[163] A different regiospecificity was also reported; hydroboration-oxidation of 2-dialkylphosphoryl-1-alkenes gave 1-hydroxyphosphonates.[164]

Oxidation of α,β-unsaturated phosphonates was frequently used to prepare 1,2-dihydroxyphosphonates[161,165-168] needed either as analogues of natural products[168] or as substrates for the preparation or other target molecules.[161,165] The oxidation was performed with osmium tetroxide in the presence of auxiliary oxidants such as hydrogen peroxide,[161,165,166] *t*-butylhydroperoxide,[166,168] or 4-methylmorpholine-4-oxide.[167,169] The stereochemistry is governed by the usual rules applying to *syn*-dihydroxylation.



It is also possible to obtain 1,2-dihydroxyalkylphosphonates by hydrolytic ring opening in 1,2-epoxyalkylphosphonates[170] available directly by oxidation of α,β-unsaturated phosphonates. Epoxide ring opening with ammonia was used to prepare 1-hydroxy-2-aminoalkylphosphonates.[170]

3. Syntheses by Formation of C-C Bonds

The preparation of 1-hydroxyalkylphosphonates by reactions in which C-C bonds are formed is possible either by addition of carbanions to the carbonyl group of α-ketophosphonates[171,172] or by alkylation[173,174] and acylation[175] of α-carbanions obtained

by deprotonation of 1-silyloxyphosphonates. The first approach was used to prepare several 1-hydroxyalkylphosphonates including 1-hydroxy-2-alkynyl derivatives.[171]

$$\begin{matrix} CH_3C(O)P(O)(OEt)_2 \\ + \\ PhC{\equiv}CH \end{matrix} \xrightarrow[2.\ CH_3CO_2H]{1.\ BuLi,\ toluene,\ -78^\circ} PhC{\equiv}C\overset{OH}{\overset{|}{C}}P(O)(OEt)_2 \quad \begin{matrix} Ph \\ 81\% \end{matrix}$$

Similarly, nitromethane addition yields 1-hydroxy-2-nitroethylphosphonates.[176]

$$PhC(O)P(O)(OPr\text{-}i)_2 \xrightarrow[60^\circ,\ 10\ hr]{CH_3NO_2,\ Et_3N} O_2NCH_2\overset{OH}{\overset{|}{C}}P(O)(OPr\text{-}i)_2 \quad \begin{matrix} Ph \\ 67\% \end{matrix}$$

The 1-silyloxyalkylphosphonates serve as acyl anion equivalents in organic synthesis. They are readily C-alkylated and both the phosphoryl and silyl groups are readily removed by alkaline treatment.[173-175]

$$\begin{matrix} OSiMe_3 \\ | \\ PhCHP(O)(OEt)_2 \end{matrix} \xrightarrow[2.\ MeI,\ -78^\circ,\ 30\ min.\\ 3.\ NaOH,\ EtOH,\ H_2O,\ r.t.,\ 20\ min.]{1.\ LDA,\ THF,\ -78^\circ} \begin{matrix} O \\ \| \\ PhCCH_3 \\ 86\% \end{matrix}$$

B. α-Phosphoryl Ethers

1. Syntheses by Formation of P-C Bonds

In recent years there have been developed synthetic sequences leading to numerous complex, polyfunctional compounds containing the α-phosphoryl ether function along with acyclic[178] or heterocyclic base moieties,[179] among others. The synthesis of α-phosphoryl ethers *via* the classical Arbuzov and Michaelis-Becker reactions is practical only when the required α-halogenated ethers are not too difficult to obtain.[180-182] The Arbuzov reaction was more frequently used than the Michaelis-Becker procedure. In both instances the best results were obtained with chloromethyl ethers. In a recent work the Arbuzov

reaction was used to prepare the desired product from a chloromethyl ether containing two halogen atoms of different reactivities.[48]

$$BrCH_2CH_2CH_2OCH_2Cl \xrightarrow[-78^\circ]{(EtO)_2PONa,\ pentane} \underset{90\%}{BrCH_2CH_2CH_2OCH_2(EtO)_2P{=}O}$$

On the other hand, the Arbuzov reaction was used successfully in a similar synthesis.[183]

$$ClCH_2CH_2OCH_2Cl \xrightarrow[4\ hr.]{(EtO)_3P,\ 125^\circ} \underset{90\%}{ClCH_2CH_2OCH_2(EtO)_2P{=}O}$$

A useful alternative to the α-halogenated ethers are the more readily available acetals. In the presence of Lewis acids the acetals readily react with trialkyl phosphites with the formation of phosphorylated ethers.[184] The reaction involves the generation of oxygen-stabilized carbocation from acetals, electrophilic attack on the phosphorus atom, and dealkylation of the quasi-phosphonium intermediates typical of the Arbuzov reaction. The reaction occurs even more readily with mixed trimethylsilyl alkyl phosphites.[185]

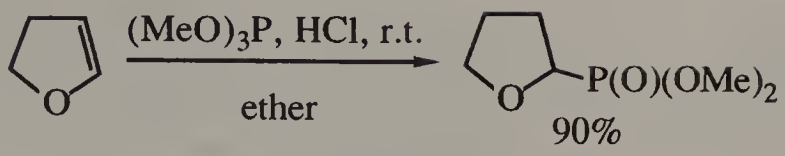
$$\underset{+\ Me_3SiOP(OEt)_2}{ArCH(OR)_2} \xrightarrow[r.t.]{CH_2Cl_2,\ SnCl_4} \underset{84\text{-}95\%}{ArCHP(O)(OEt)_2 \\ OR}$$

Alkoxymethylphosphonates with primary, secondary, tertiary and allylic alkyl groups at oxygen were obtained by the Arbuzov reaction of alkoxyphenoxymethanes in the presence of titanium tetrachloride.[180]

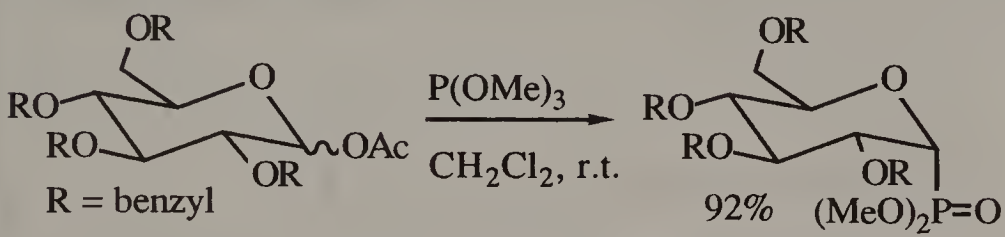
$$ROCH_2OAr \xrightarrow[CH_2Cl_2,\ -78^\circ]{P(OEt)_3,\ TiCl_4} \underset{76\text{-}90\%}{ROCH_2P(O)(OEt)_2}$$

Ar = *p*-chlorophenyl

The formation of P-C bonds by addition to carbon-carbon double bonds occurs when unsaturated ethers react with trialkyl phosphites and hydrogen chloride.[181] The function of acid, apart from its role in the dealkylation step, is to generate carbocations from the unsaturated ethers.



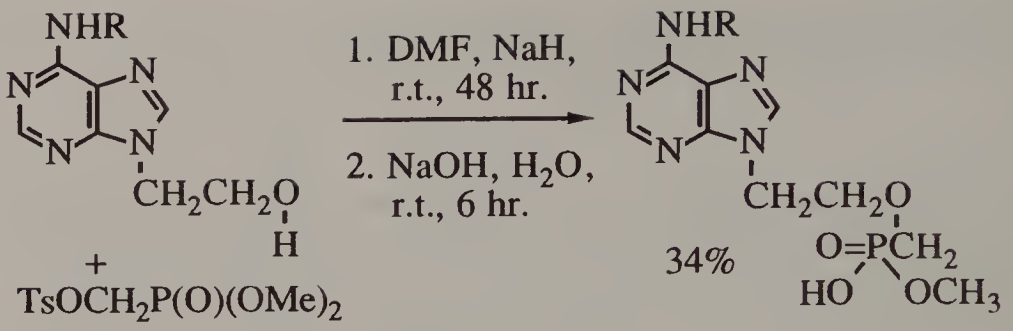
The carbocation approach was used also to prepare more complex ether-type products in which the phosphonate function is linked to the anomeric carbon atom in monosaccharides. The treatment of protected 1-acetoxyglucopyranoses with trialkyl phosphites and trimethylsilyl trifluoromethylsulfonate as the carbocation-generating reagent yielded preferentially the *cis*- configurated α-D-glucopyranosylphosphonates.[186]



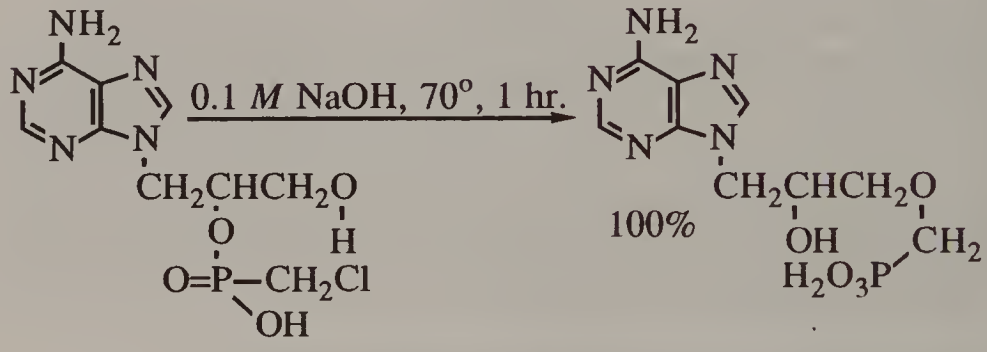
By the same approach there were prepared several non-isosteric analogues of sugar phosphates[187,188] including some very complex glycolipid derivatives.[189]

2. Syntheses by Formation of C-O Bonds

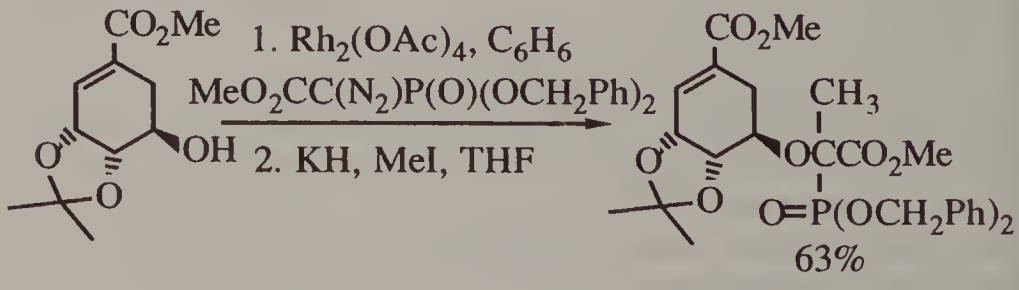
The preparation of 1-alkoxyalkylphosphonates by C-O bond forming reactions is possible either by alkylation of 1-hydroxyalkylphosphonates or by replacement of α-substituents with alkoxy or aryloxy groups. Virtually all described examples of both approaches are limited to ethers containing P-CH_2O linkages, *i.e.* to derivatives of hydroxymethylphosphonates.[177] One of the approaches to their synthesis is based on nucleophilic substitution of suitably derivatized methylphosphonates. The well known inertness of halogenomethylphosphonates toward nucleophiles precludes their use when mild reaction conditions are necessary. However, satisfactory results were obtained with dialkyl phosphonomethyl tosylates[190,191] and trifluoromethylsulfonates.[175] In fact, the tosylates were routinely used by Holy in numerous syntheses of several phosphonomethyl ether analogues of acyclic nucleotide mimics.[192]



The low reactivity of chloromethylphosphonates toward oxygen nucleophiles does not apply to intramolecular substitutions. Thus, even moderate heating in dilute alkali quantitatively converts the chloromethylphosphonate esters of 1,2-glycols into phosphonomethyl ethers.[193-195]

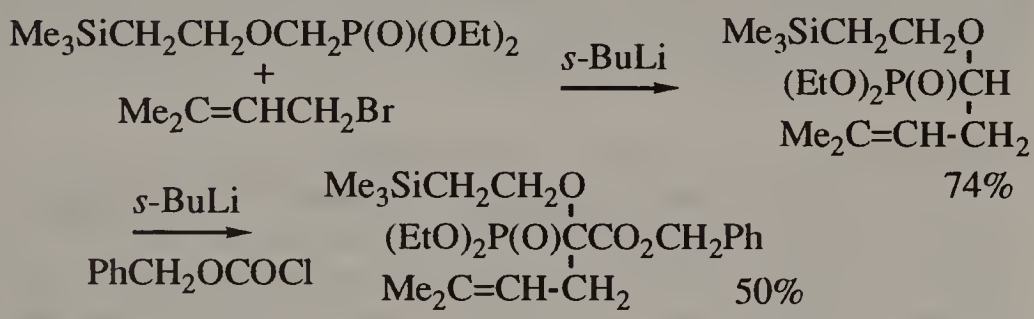


An interesting example of modern chemistry in the synthesis of complex α-phosphoryl ethers is provided by the synthesis of an ether-type analogue of 5-enolpyruvylshikimate. The key step, the formation of the ether linkage, was accomplished by rhodium-catalyzed reaction of shikimic acid with a derivative of diazophosphono acetic acid.[196]



3. Syntheses by Formation of C-C Bonds

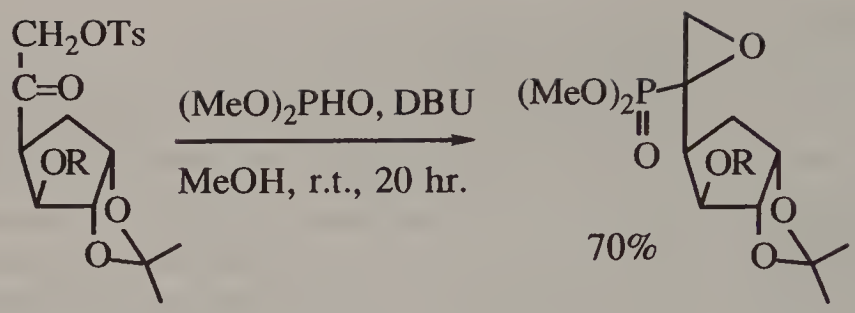
The last reaction sequence in the preceding section includes alkylation of a carbanion generated from a complex α-phosphoryl ether. Similar alkylations were performed on simple α-phosphoryl ethers[197] but were never extensively used[88] because the deprotonation is difficult and the carbanions are unstable due to the destabilizing effect of the neighbouring oxygen atom.[182,198] However, very extensive elaboration of the carbon skeleton of α-phosphoryl ethers was reported by Zbiral.[198] Noteworthy is the use of *s*-butyl lithium (a stronger base than the more commonly used *n*-butyl lithium) in the deprotonation step.[199]



C. 1,2-Epoxyphosphonates

1. Syntheses by Formation of P-C Bonds

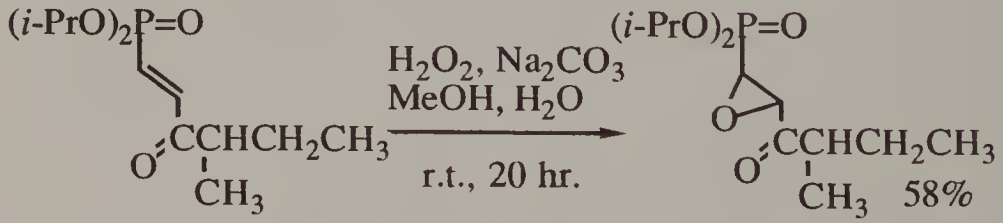
Syntheses in which a P-C bond is formed to a pre-existing oxirane ring have not yet been described. Reactions are known, however, in which the formation of a P-C bond is immediately followed by the closure of an epoxide ring. Such is the case when dialkyl phosphonates react with aldehydes or ketones bearing a halogen atom or other good leaving group adjacent to the carbonyl group. The reactions require basic catalysis to generate the alkoxide anions from the initially formed 1-hydroxyphosphonates and thus to effect ring closure by intramolecular nucleophilic substitution.[200] Similar reactions catalyzed with KF gave diethylphosphoryloxiranes in ~50% yields.[201] Good results are obtained also when 1-tosyloxyketones are treated with dialkyl phosphonates and bases.[203]



A rare example of triphenylphosphine acting as the leaving group is provided by the synthesis of epoxides from phosphorus ylids, trifluoroacetic anhydride, and dialkyl phosphonates. The reaction occurs by either triphenylphosphine elimination after the addition of the phosphonate anion to yield the epoxide, or the more usual elimination of triphenylphosphine oxide to produce the unsaturated phosphonates. The outcome depends on reaction conditions and the structure of the reactants.[204]

2. Oxidation of 1-Alkenyl Phosphonates

The epoxidation of 1-alkenylphosphonates[202] was performed with hydrogen peroxide,[205-207] *t*-butylhydroperoxide,[206] or trifluoroperacetic acid.[208] None of these procedures is very efficient and the isolated yields are in the range of 70% at best. The usual stereochemistry is observed, *i.e. trans*-alkenes yield *trans*-epoxides. The oxidations with hydrogen peroxide were usually performed in the presence of sodium tungstate catalyst. However, the apparently rather reactive 3-oxo-1-alkenylphosphonates were oxidized without catalyst.[205]



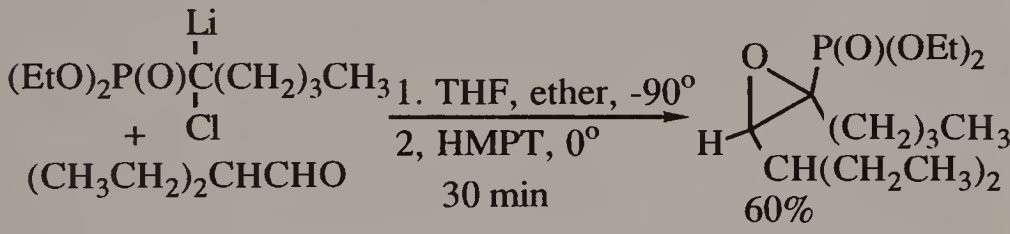
3. Syntheses from Halohydrins

Halohydrins are efficiently prepared from α,β-unsaturated phosphonates and are readily cyclized with basic reagents to 1,2-epoxyphosphonates.[41] Epoxides were prepared also from 1,2-dihydroxyphosphonates by tosylation of one of the hydroxy groups and silylation of the other, followed by treatment with fluoride ion

to generate the alkoxide anions at the initially silylated oxygens.[161] The synthesis from halohydrins is exemplified by the recent preparation of enantiomerically pure fosfomycin using (*S,S*)- tartaric acid as the chiral auxiliary.[209]

4. Syntheses Involving the Formation of C-C Bonds and Epoxide Ring Closure

The synthesis of 1,2-epoxyphosphonates by the Darzens condensation of carbanions with carbonyl compounds was initially limited to ketones and aromatic aldehydes. Moreover, the yields were rather low or at best moderate.[202] By procedural improvements consisting mainly of the use of THF/hexane in place of protic solvents it was possible to extend the scope to include also the aliphatic aldehydes and to increase the yields to 60-90%.[210] It was also found that the Darzens reaction works equally well with the homologues of dialkyl chloromethylphosphonates.[211]



Remarkably, the intermediate lithium salts of halohydrins are stable even in boiling ether and are not converted to epoxides unless one equivalent of HMPT is added.

D. 1-Oxophosphonates (Acylphosphonates)

1. Synthesis by Formation of P-C Bonds

Older literature on the preparation and properties of 1-oxoalkyl phosphonates was reviewed.[212] Practical syntheses of the vast majority of acylphosphonates were performed by the Arbuzov reaction of acyl chlorides with P(III) nucleophiles bearing at least one alkoxy or silyloxy group. Bis(trialkylsilyl) acylphosphonates were obtained by the Arbuzov reaction of acyl chlorides with tris-(trialkylsilyl) phosphites[154] as well as by silylation of the alkyl esters of acylphosphonic acids.[213]

There appears to be a considerable leeway as concerns the experimental conditions of the Arbuzov reaction of simple acyl chlorides with trialkyl phosphites. Comparable and almost always

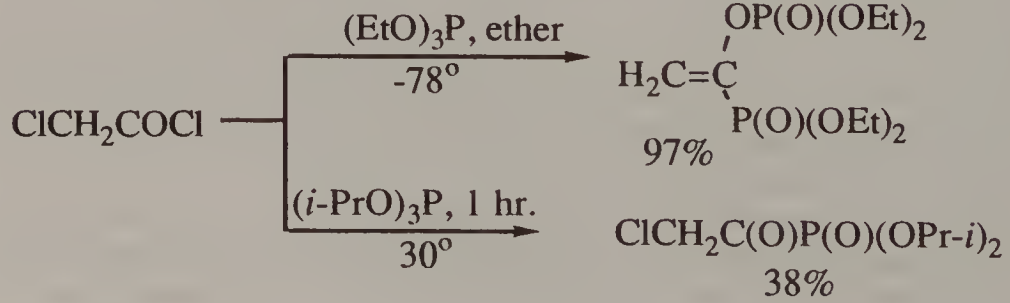
good or very good yields of dimethyl and diethyl acylphosphonates were obtained whether the reactions were performed at room temperature[130,140,162,164,214] or with gentle heating,[164,215] without solvent[130,140,162,164,215] or in solution,[145,214] with stoichiometric amounts of substrates[130,140,145,162] or using an excess of either of the reagents.[164,215] However, a more rigorous control is required and the yields are reduced when the acyl chlorides contain other reactive groups, as in the following example.[216]

$$R'O_2CCH_2COCl \xrightarrow{(RO)_3P,\ -10^\circ,\ 2\ hr.} R'O_2CCH_2C(O)P(O(OR)_2$$

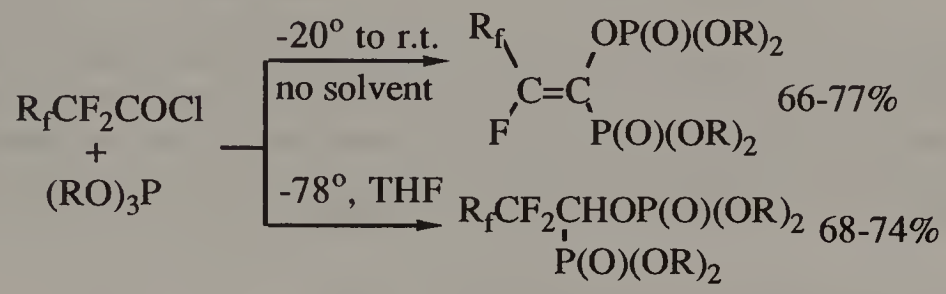
R, R' = alkyl 20-60%

The stoichiometry determines the outcome of the reaction of α,β-unsaturated acyl chlorides. Thus, the reaction of trimethyl phosphite with a three-fold excess of *trans*-but-2-enoyl chloride affords a 50% isolated yield of the expected Arbuzov product whereas a compound with two P-C bonds is obtained as the main product when the reaction is performed using an equimolar proportion of substrates, other conditions being essentially the same.[217] A plausible mechanism assumes the formation of a cyclic intermediate resulting from the reaction of trimethyl phosphite with the primary "normal" product. On the other hand, the Arbuzov reaction of the even more unsaturated acyl chlorides with conjugated 1,3-dienes gave excellent yields of the normal products.[214]

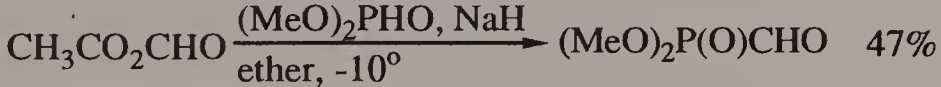
The nature of the phosphite reagent is crucial for the reaction with chloroacetyl chloride. Trimethyl and triethyl phosphites give only the 2:1 adducts regardless of the ratio of substrates while with the more bulky triisopropyl phosphite it is possible to obtain the normal Arbuzov product. Apparently, the bulkiness retards the reaction of the phosphite with the carbonyl group of the initially formed quasi-phosphonium intermediate.[218]



The formation of 2:1 adducts appears to be the normal reaction course of perfluoroalkanoic acid chlorides with trialkyl phosphites. Attempts to obtain perfluoroacylphosphonates were met with failure regardless of the ratio of reagents, mode of addition, and reaction temperature.[219]



The Arbuzov reaction of acid anhydrides with trialkyl phosphites and the Michaelis-Becker reaction of acid chlorides with the sodium salts of dialkyl phosphonates were described but are not recommended for the preparation of acylphosphonates because of low yields.[212] However, Vasella, *et al.* reported a successful synthesis of diethyl formylphosphonate from the mixed formic acetic anhydride and sodium dimethyl phosphonate.[220] In view of the interest in this rather elusive compound it is remarkable that its preparation was not confirmed as of the date of this writing. Russian workers reported a failure of diethyl formylphosphonate synthesis by Arbuzov reaction of formic acetic anhydride with triethyl phosphite.[221]



2. Other Syntheses of Acylphosphonates

There is very little information on the synthesis of acylphosphonates apart from the material discussed in the preceding section. Carbonyldiphosphonate, an interesting antagonist of pyrophosphate in biological systems, was recently prepared by alkaline hydrolysis of dichloromethylenebisphosphonic acid.[222]

The stability of carbonyldiphosphonate under drastic alkaline conditions is remarkable in view of the reactivity of the P-C bond in dialkyl acylphosphonates toward nucleophiles. However, it appears to be in line with the much higher stability of free acylphosphonic acids relative to their esters in reactions with nucleophiles.[162]

The potentially useful oxidation of 1-hydroxyphosphonates to ketophosphonates is virtually unknown. According to the only published report, the oxidation of 1-hydroxyalkylphosphonates in the carbohydrate series with the dimethyl sulfoxide/acetic anhydride system gave complex mixtures.[223]

A characteristic modern trend in organophosphorus chemistry is the synthesis of complex phosphonates either as target molecules or as intermediates in the synthesis of non-phosphonate products. An intriguing application is the synthesis and further transformations of nucleoside acylphosphonates. The acylphosphonate constitutes a masked P-H function and is used to prepare complex synthetic intermediates bearing the P-H bond.[224]

E. The Acetals of Acylphosphonates

1. Syntheses by Formation of P-C Bonds

Dialkoxymethylphosphonates and phosphinates are of interest as they serve as equivalents of P-H compounds.[225,226] Dialkyl alkoxymethylphosphonates are most frequently prepared from orthoformates. Syntheses by Arbuzov reaction of suitably substituted dialkoxymethanes are limited by the availability of substrates. In one of the reported syntheses, trialkyl phosphites were treated with dialkoxymethyl acetates.[227]

$$\begin{matrix}(RO)_2POR' \\ + \\ CH_3CO_2CH(OEt)_2\end{matrix} \longrightarrow \underset{60\%}{(RO)_2P(O)CH(OEt)_2} + CH_3CO_2R'$$

R = alkyl; R' = alkyl, trimethylsilyl

More practical are the preparations from trialkyl orthoformates and phosphorus trichloride or phosphorous acid.[6]

$$\begin{matrix}H_3PO_3 \\ + \\ 3\ CH(OEt)_3\end{matrix} \xrightarrow{100^\circ} \underset{70\%}{(EtO)_2CHP(O)(OEt)_2} + 3\ EtOH + 2\ HCO_2Et$$

The reaction of orthoformates with dialkyl phosphonates requires drastic heating and gives rather poor yields. However, yields of up to 90% were obtained using boron trifluoride as catalyst.[228] Trialkyl phosphites, and even dialkyl trimethylsilyl phosphites, are totally unreactive toward orthoformates unless an

electrophilic catalyst is added. In the presence of boron trifluoride an exothermic reaction occurs, but the yields are only moderate.[229]

$$\begin{matrix}(EtO)_2POSiMe_3 \\ + \\ CH(OEt)_3\end{matrix} \xrightarrow{BF_3} \underset{50\%}{(EtO)_2CHP(O)(OEt)_2} + EtOSiMe_3$$

Hypophosphorous acid enters a multi-step reaction with trimethyl or triethyl orthoformate in the presence of boron trifluoride. Dialkoxymethylphosphonites are obtained in fair yields after several hours at room temperature upon catalyst inactivation by addition of triethylamine. Otherwise, further reaction takes place and bis(dialkoxymethyl)phosphinates are formed.[230]

The addition of dialkyl phosphonates to the double bond of 1,1-dialkoxyethenes provides access to dialkyl 1,1-dialkoxyethylphosphonates in good yields.[231] The formation of P-C bonds by addition of P-H compounds to carbon-carbon double bonds was used also in syntheses of products containing two carbon-phosphorus bonds.[225]

$$\begin{matrix}H \\ | \\ (EtO)_2CHP(O)OEt \\ + \\ RCH{=}CHCN\end{matrix} \xrightarrow[0^\circ \text{ to r.t.}]{NaOEt,\ EtOH} \underset{51\text{-}66\%}{\begin{matrix}OEt \\ | \\ (EtO)_2CHP{-}CHCH_2CN \\ \| \\ O \quad R\end{matrix}}$$

2. Syntheses by Formation of C-C Bonds

Ethyl (diethoxymethyl)methylphosphinate, easily prepared from methyldichlorophosphine and triethyl orthoformate, is deprotonated selectively at the methyl group and the resulting carbanion undergoes typical addition to activated double bonds.[225] Deprotonation at the carbon atom bearing the alkoxy substituents is not favoured because of the vicinity of the oxygen atoms.[199]

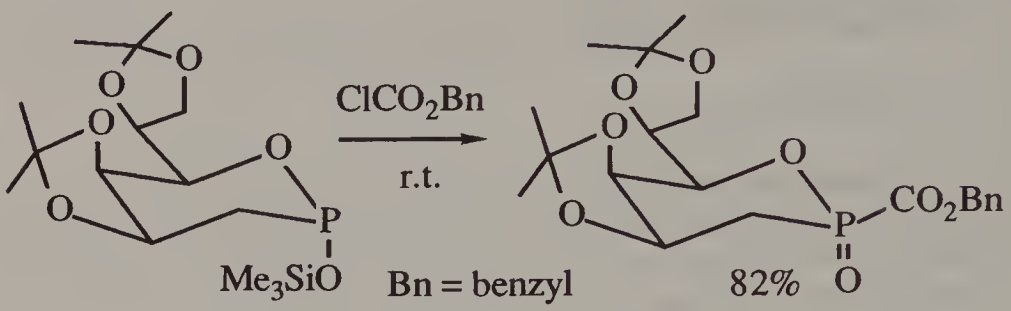
F. Derivatives of Phosphonoformic Acid

1. Syntheses by Formation of P-C Bonds

Phosphonoformates have been used as synthetic equivalents of P-H entities.[224,232] Complex P-esters of phosphonoformic acid were recently prepared as potential antiviral agents.[233-236]

Simple esters of phosphonoformic acid are prepared by the Arbuzov reaction of trialkyl phosphites with chloroformates.[5]

Mixed dialkyl trimethylsilyl phosphites are preferred when very mild reaction conditions are of importance.[235]



Bis(trimethylsilyl) alkoxycarbonylphosphonates are prepared in near quantitative yield from alkyl chloroformates and tris(trimethylsilyl) phosphite.[233] Syntheses of phosphonoformates by the Michaelis-Becker reaction are known but are not important.[237]

2. Other Synthetic Approaches

Moderate to good yields of alkyl trialkoxymethylphosphonates were obtained by anodic methoxylation of the acetals of formylphosphonates.[105]

Many complex phosphonoformates were prepared by transformations at the phosphorus atom and in the carboxylic group. A classical example is the synthesis of a nucleoside phosphonoformate from the parent protected nucleoside.[233]

V. Phosphonates with the P-C-N Bond System

A. 1-Aminoalkylphosphonates

1. Syntheses Involving P-C Bond Formation by Substitution Reactions

Many synthetic aspects have been reviewed.[238-241] A recent review by Dhavan and Redmore is devoted to methods of preparation of optically active 1-aminoalkylphosphonic acids.[242]

The structural types discussed under this heading include compounds with free as well as with substituted amino groups. Further subdivision should distinguish between *N*-alkyl or *N*-aryl and the *N*-acyl derivatives. The latter are particularly important as they include phosphonopeptides, *i.e.* compounds in which the amino group of the phosphonate moiety is substituted with aminoacyl groups. Although the synthesis of phosphonopeptides is very

actively pursued at present, it is too specialized to be discussed in this Chapter. Interested readers are referred to a review.[243]

The history of 1-aminoalkylphosphonates began in 1942 with the preparation of aminomethylphosphonic acid from *N*-hydroxymethylamides of carboxylic acids and phosphorus trichloride.[244] In this synthesis the formation of the P-C bond occurs by substitution of the hydroxy group by a phosphorus nucleophile whose nature depends on experimental conditions and was never determined. The original procedure of Engelmann and Pikl is not very practical, but experimental details were sufficiently refined during the last decade to allow easy preparation of aminomethylphosphonic acid.[245,246] The highest yield is obtained from *N*-hydroxymethylbenzamide when the reaction with phosphorus trichloride is performed in acetic acid.[245]

$$PhC(O)NHCH_2OH \xrightarrow[\text{2. hydrolysis}]{\text{1. } PCl_3,\ AcOH,\ \text{reflux, 1 hr.}} H_2NCH_2PO_3H_2 \quad 85\%$$

The mechanism probably involves the reaction of *N*-acyliminium ions with such phosphorus nucleophiles as may be present in the respective reaction mixtures. Similar procedures were used to synthesize *N*-alkylaminomethylphosphonic and phosphinic acids.[247,248] The latter are formed when alkyldichlorophosphines are used in place of phosphorus trichloride.[249]

The classical Arbuzov and Michaelis-Becker reactions of P(III) nucleophiles with alkyl halides are not frequently used for the preparation of 1-aminoalkylphosphonates. The utility of these reactions is limited to the relatively few cases where the required substrates, *i.e.* the α-halogenated amine derivatives, are readily available. Older examples were thoroughly discussed by Redmore.[239] More recently the Arbuzov reaction was used in efficient syntheses of 1-amino-2-chloroalkylphosphonates and aminophosphonoacetates. The latter were prepared from *N*-protected bromoglycine derivatives. Deprotection yielded triethyl aminophosphonoacetate, a useful synthon for the preparation of the cephalosporin ring system.[250]

$$RC(O)NHCHCO_2Et \xrightarrow[\text{r.t., 1 hr.}]{(EtO)_3P,\ CH_2Cl_2} RC(O)NHCHP(O)(OEt)_2$$
(Br; 65-98%; CO_2Et)

R = benzyloxycarbonyl, trichloroethoxycarbonyl

In another synthesis the *N*-protected aminophosphonoacetates were obtained by the Arbuzov reaction of chloroglycine esters prepared *in situ* from α-methoxyglycine derivatives.[251]

$$CBZNHCHCO_2Me \xrightarrow[\text{2. } P(OMe)_3,\ 2\text{ hr., } 70^\circ]{\text{1. } PCl_3,\ \text{toluene, } 70^\circ,\ 18\text{ hr.}} CBZNHCHCO_2Me$$
(OMe; 80%; $P(O)(OMe)_2$)

The phosphonic analogue of β-chloroalanine was obtained by the Arbuzov reaction of 1,2,2,2-tetrachloro-*N*-acylethylamines, reductive removal of two chlorine atoms with tributyltin hydride, and final deprotection.[252]

$$RNHCHCCl_3 \xrightarrow[\text{2. } Bu_3SnH\ \text{3. hydrolysis}]{\text{1. } P(OR')_3,\ CCl_4,\ \text{reflux, 1 hr.}} ClCH_2CHPO_3H_2$$
(Cl; NH_2; 65-98%)

R = phenylsulfonyl, benzyloxycarbonyl, ethoxycarbonyl, formyl
R' = methyl, ethyl

The same approach was used to prepare *P*-methyl and *P*-phenylphosphinic analogues of β-chloroalanine.[253]

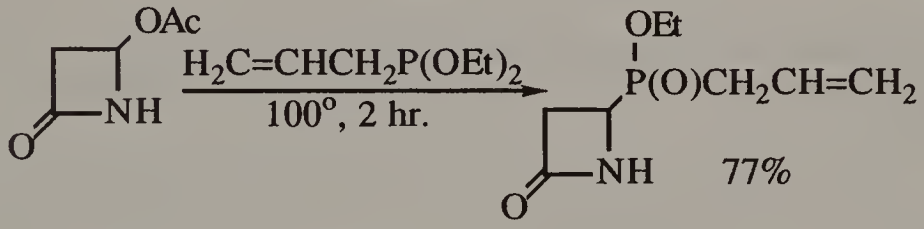
The Michaelis-Becker reaction of *N*-protected α-aminoalkyl bromides was used in a reaction sequence to convert amino acids and simple peptides to corresponding phosphonic acids. The bromides were prepared by Hunsdiecker decarboxylative bromination of silver salts and were treated without isolation with sodium diethyl phosphonate using excess phosphonate as solvent. Unfortunately, the yields are acceptable only for derivatives of glycine (35-54%). The yields of phosphonic acids obtained from other aminocarboxylic acids and from peptides were in the range of only 10 to 20%.[254]

Arbuzov reactions are possible also with imidoyl chlorides. Interesting applications for the synthesis of fluorinated phosphonate analogues of alanine were described by Flynn, *et al.*[255]

Arbuzov reactions of reactive quaternary ammonium salts are also known. An example is provided by the efficient preparation of diethyl formylaminomethylphosphonate.[256]

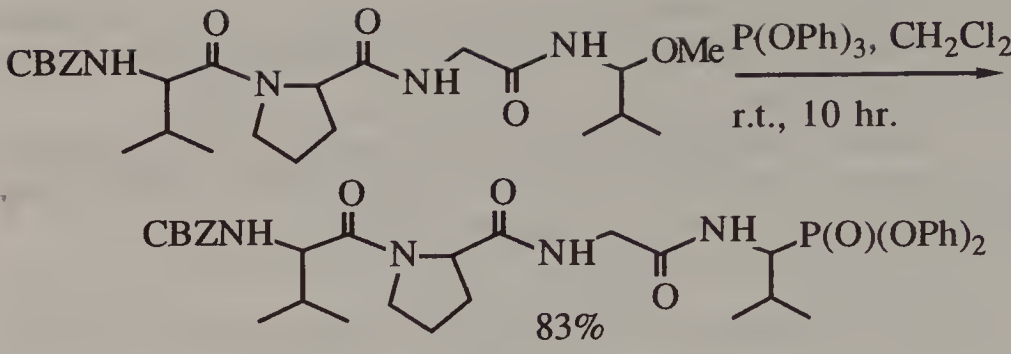
$$(Me_3\overset{+}{N}CH_2NHCHO)\ I^- \xrightarrow[\text{reflux, 4 hr.}]{P(OEt)_3,\ EtOH} OHCNHCH_2P(O)(OEt)_2 \quad 90\%$$

Nucleophilic displacements of less reactive leaving groups, such as the acetoxy and even the methoxy groups, are readily accomplished when these groups are involved in structures of the N,O-acetal type. Displacement of the acetoxy group with P(III) nucleophiles found interesting applications in the chemistry of β-lactams. For example, the first step in the synthesis of a cephalosporin analogue with the phosphorus atom in the six-membered ring involves the reaction of 4-acetoxy-2-azetidinone with diethyl allylphosphonite.[257,258]

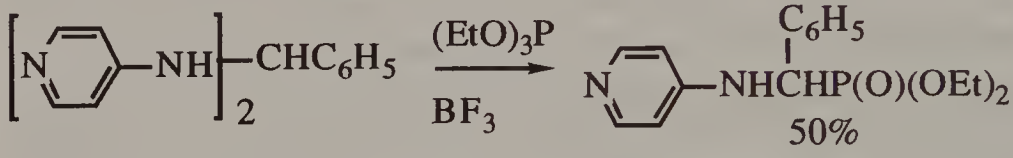


Similar reactions were used by Campbell, *et al.* to prepare the phosphonic and phosphinic analogues of aspartic and 2,3-diaminosuccinic acids.[259]

The N,O-acetals obtained from amino acids and peptides by electrochemical oxidative decarboxylation are emerging as promising substrates for the preparation of 1-aminoalkylphosphonates and phosphonopeptides.[260-262] The displacement of the methoxy group from N,O-acetals by Arbuzov reaction takes place under sufficiently mild conditions to be applicable to a wide range of highly functionalized substrates. The following high yield preparation of a phosphonopeptide illustrates the utility of these reactions.[262]



The displacement of amines from geminal diamino compounds by phosphorus nucleophiles was only occassionally used to prepare 1-aminoalkylphosphonates. A recent application was described by Burkhouse and Zimmer.[263]



In a similar process hypophosphorous acid displaces the acetamido group from geminal bisamides.[264]

2. Syntheses Involving the Formation of P-C Bonds by Addition of P(III) Reagents to Carbon-Nitrogen Double Bonds

The oldest of general methods for the preparation of 1-aminoalkylphosphonates is based on the addition of dialkyl phosphonates to the double bond of imines.[5] The scope of this reaction is rather wide because the additions occur more or less readily with virtually any phosphorus entity containing the P-H function, and, moreover, there are very few limitations concerning the structure of the imine substrate. In this section we illustrate the synthetic potential of these addition reactions. The syntheses reported over the past decade are too numerous to be given full coverage. A more detailed account of work published before 1985 is available.[127]

The addition of dialkyl phosphonates to imines derived from ammonia affords directly 1-aminoalkylphosphonates with a free amino group. Unfortunately, the reaction is limited to the few instances where the imines are sufficiently stable to be isolated.[265] Hexafluoroisopropylimine is stable enough, but it is not sufficiently reactive to allow the addition of dialkyl phosphonates. However,

the reaction occurs with the more reactive phosphonites.[266]

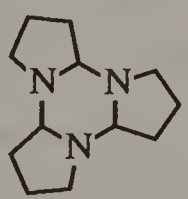
$$(CF_3)_2C{=}NH + \underset{i\text{-BuO}}{CH_3PHO} \xrightarrow[20\ hr.]{70^\circ} \underset{i\text{-BuO}}{\overset{NH_2}{(CF_3)_2CP(O)CH_3}}\quad 55\%$$

Simple 1-aminoalkylphosphonic acids were obtained in acceptable overall yields from nitriles by a one-pot procedure which involves *in situ* addition of diethyl phosphonate to aldimine salts formed by reduction of nitriles with Sn(II) chloride.[267]

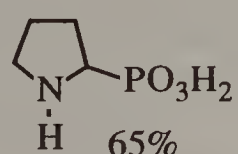
$$RCN \xrightarrow[\text{ether, r.t., 4 da.}]{SnCl_2,\ HCl} \xrightarrow[2.\ \text{hydrolysis}]{1.\ (EtO)_2PHO,\ 80^\circ,\ 3\ hr.} \underset{NH_2}{RCHPO_3H_2}\quad 43\text{-}71\%$$

Similar yields were obtained with a considerably shorter procedure (hours rather than days) when the reduction of nitriles was performed with diisobutyl aluminum hydride.[268]

Unlike monomeric aldimines, their trimeric forms, the hexahydrotriazines, are stable and readily obtainible. They retain much of the reactivity of their monomers and were successfully used to prepare 1-aminoalkylphosphonates by ring opening reactions with dialkyl phosphonates and other P-H reagents.[269-273] The method is applicable to unsubstituted triazines as well as to their derivatives with substituents at the nitrogen and/or carbon atoms and is thus quite versatile. The reactions are usually performed by gentle heating of stoichiometric mixtures of substrates for a few hours without solvent or catalyst. The yields are moderate to very good. The reaction mechanism may involve simple addition of dialkyl phosphonates to imines which exist in equilibrium with their triazines. However, there is evidence for nucleophilic ring opening by direct attack of the phosphorus reagent on triazine carbon atoms.[245,271] No mechanistic studies were thus far reported. Among the more interesting applications is the synthesis of the phosphonic analogue of proline.[269]



$$\xrightarrow[2.\ \text{aq. acid.}]{1.\ (EtO)_2PHO,\ 85^\circ,\ 90\ min.}$$



65%

A useful recent procedure for the preparation of aminomethylphosphonic acid is based on the reaction of *N*-acyltriazines with phosphorus trichloride in acetic or propionic acid, followed by hydrolysis. In this instance the triazine ring is probably attacked by the phosphorous acid formed *in situ*..[245]

The addition of P-H compounds to imines (Schiff's bases) derived from a very broad spectrum of amines and carbonyl compounds is described in well over one hundred publications. The most frequently used phosphorus reagents were the dialkyl and diaryl phosphonates. Phosphorous acid also undergoes addition reactions with Schiff's bases but competing side reactions prevent its use in practice.[274] In most cases the addition of dialkyl and diaryl phosphonates was performed by heating substrate mixtures without solvent or catalyst and afforded good to very good yields of *N*-substituted 1-aminoalkylphosphonates. In one-pot procedures it may be convenient to perform the addition in the solvent used to prepare the imine, as in the synthesis od diphenyl 1-(*N*-aryl)arylmethylphosphonates reported by Smith, *et al.*[275]

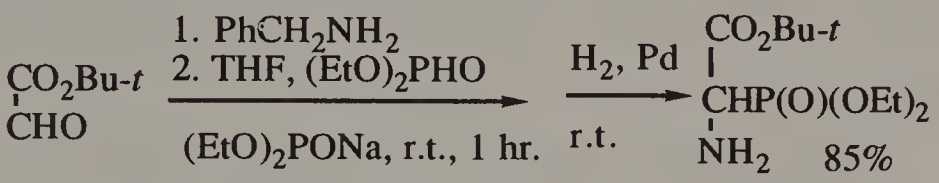
$$ArCHO + ArNH_2 \xrightarrow[\text{reflux}]{C_6H_6} \xrightarrow[C_6H_6,\ \text{reflux}]{(PhO)_2PHO} \underset{\displaystyle NHAr}{ArCHP(O)(OPh)_2}\ 60\text{-}80\%$$

Base or acid catalysis was often used in early studies.[238] It appears to offer no particular advantages, but examples of catalytic addition are found also in more recent papers. For example, boron trifluoride was used to catalyze the addition of a chiral cyclic phosphonate to a cyclic imine in the synthesis of optically active 1-amino-2-mercapto-2-methylpropylphosphonic acid, the phosphonic analogue of penicillamine.[276] It is noteworthy that the addition of diethyl phosphonate to the same cyclic imine (2,5-dihydro-2,2,5,5-tetramethylthiazoline) was performed without catalyst.[277]

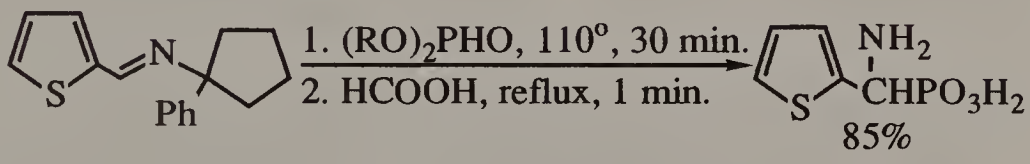
Schiff's bases with readily removable substituents at the nitrogen atom are rather useful in syntheses of 1-aminoalkylphosphonates containing free amino groups. *N*-Benzylimines were frequently used as they offer the advantages of easy preparation and mild removal of benzyl groups by hydrogenolysis.[278] The procedure is shown by a high-yield synthesis of a mixed ester of aminophosphonoacetic acid from *t*-butyl glyoxalate.[279]

Optically active imines prepared from both enantiomers of α-methylbenzylamine add dialkyl phosphonates with some degree

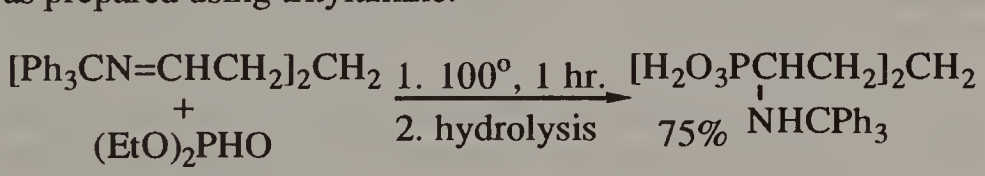
of asymmetric induction and were therefore used to synthesize optically active 1-aminoalkylphosphonic acids. This subject will not be discussed further because no relevant contributions appeared since the exhaustive review by Dhavan and Redmore.[242]



N-Protecting groups which are removable by mild acid treatment can be of advantage when the desired aminophosphonates contain reduction-sensitive functional groups. By simultaneous use of acid-labile protecting groups both at the nitrogen atom and in the phosphorus function it is possible to achieve total deprotection in one mild hydrolytic step.[280]

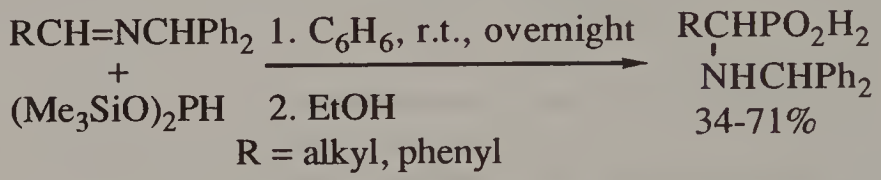


Acid-sensitive protection is possible also with the benzhydryl and trityl groups. The imines derived from tritylamine and benzhydrylamine are readily obtainable and undergo addition reactions with dialkyl phosphonates.[281-284] However, a report by Issleib, *et al.*[283] on the alleged facile preparation of diaminodiphosphonic acids from aliphatic dialdehydes using benzhydrylamine Schiff's bases was recently found to be erroneous.[284] The diphosphonic analogue of diaminopimelic acid (but not of lower homologues) was prepared using tritylamine.[284]

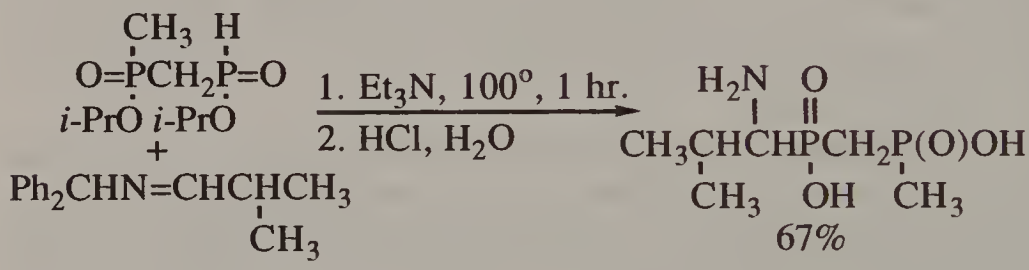


The imines prepared from aldehydes and benzhydrylamine were used to synthesize a series of 1-aminoalkylphosphonous acids related structurally to protein amino acids.[285] The syntheses were accomplished by addition of hypophosphorous acid to the imines in ethanol or by direct reaction of aldehydes with hypophosphorous acid and benzhydrylamine. The yields in either of these procedures

are low to moderate. The diphenylmethyl group was cleaved by treatment with acids. Oxidation of 1-aminoalkylphosphonous acids with bromine or mercuric chloride yielded the 1-aminoalkylphosphonic acids. An α-phosphonous analogue of α-methylaspartic acid was obtained from ethyl acetoacetate using basically the same procedure.[286] In another approach the benzhydrylamine imines were treated with bis(trimethylsilyl) phosphonite.[287]



Interesting aminophosphonates related to methylenebisphosphonic acid were synthesized by Tarusova, *et al.* by addition of a rather unusual P-H reactant to aldimine and deprotection by acid hydrolysis.[282]



Aminoalkylphosphonates were prepared also by addition of dialkyl phosphonates to imines bearing acyl or sulfonyl substituents at the nitrogen atom.[288] An example of this approach is the asymmetric synthesis of pure enantiomers of the phosphonic analogue of phenylalanine in which a camphanic acid function was attached at nitrogen as an amide.[289]

A considerable amount of new chemistry was developed around the addition of phosphorus reagents to the carbon-nitrogen double bonds of carbohydrate nitrones.[290,291] The nitrones were found to be highly reactive toward dialkyl phosphonates[220] and their anions, although the reactions depended strongly on the counter-cation; lithium dialkyl phosphonates were more useful than the potassium salts.[292] In some cases it was necessary to use the more reactive tris(trimethylsilyl) phosphite for effective addition.[293] The chirality of the sugar fragment induced a very

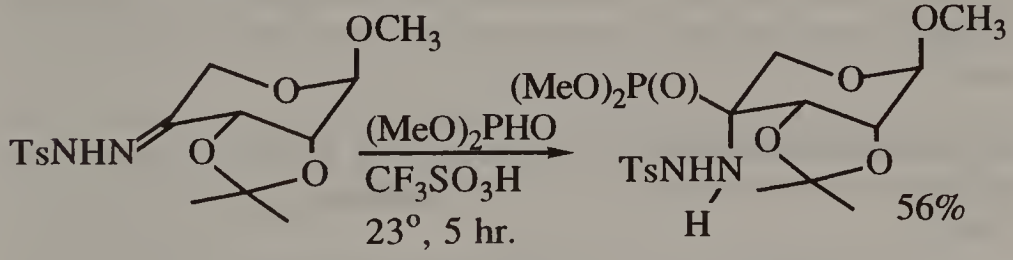
high degree of diastereoselectivity in the addition of the nitrone entity[294] and made possible elegant (although rather not practical) syntheses of optically active phosphonate analogues of alanine, serine, valine, methionine, and several other amino acids.[292,293] Some optically active *N*-hydroxy-1-aminoalkylphosphonates were also prepared and their absolute configurations were determined.[293]

The addition of P-H reagents to simple hydrazones was never systematically examined although it appears to be an obvious approach to the preparation of 1-hydrazinoalkylphosphonates and hence 1-aminoalkylphosphonates (the conversion of hydrazino to amino group is well known). In one of the few studies dealing with such additions the phenylhydrazone of acetone reacted as expected with diphenyl phosphonate without catalyst.[295]

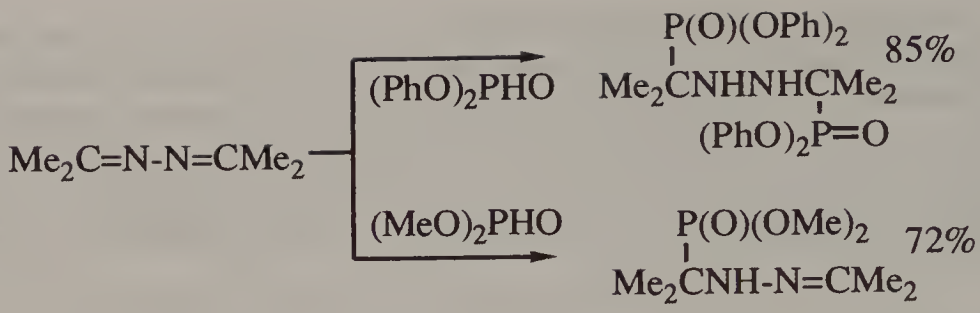
$$\begin{matrix} Me_2C{=}NNHPh \\ + \\ (PhO)_2PHO \end{matrix} \xrightarrow[5\ hr.]{60^\circ} \begin{matrix} Me_2CP(O)(OPh)_2 \\ | \\ NHNHPh \end{matrix} \qquad 60\%$$

Syntheses of hydrazinomethylphosphonates by addition of diethyl phosphonate to *N*-substituted hydrazones of formaldehyde were recently described by Diel and Maier.[296,297]

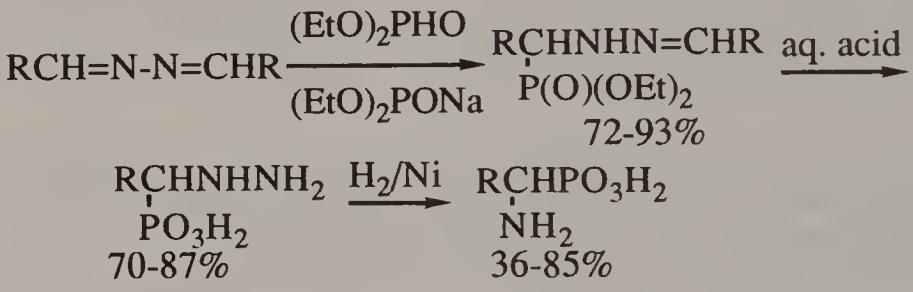
The addition of dialkyl phosphonates to *N*-tosylhydrazones of carbohydrates was used by Japanese workers to prepare phosphonate analogues of sugar phosphates. Acid-catalyzed addition occurs readily at room temperature.[157]



More information is available on the addition of P-H compounds to azines.[241] The reactions of dialkyl and diaryl phosphonates with aliphatic and aromatic azines occur readily under a variety of conditions and afford high yields of addition products. One or two moles of the P-H reagent are added depending upon the structure of substrates.[298]



The azines of aliphatic aldehydes react with only one mole of diethyl phosphonate regardless of experimental conditions and the amount of phosphonate. The products, diethyl 1-(*N*-alkylidene)hydrazinoalkylphosphonates were converted to 1-hydrazinoalkylphosphonic acids by hydrolysis, and to 1-aminoalkylphosphonic acids by hydrolysis and reduction.[299]

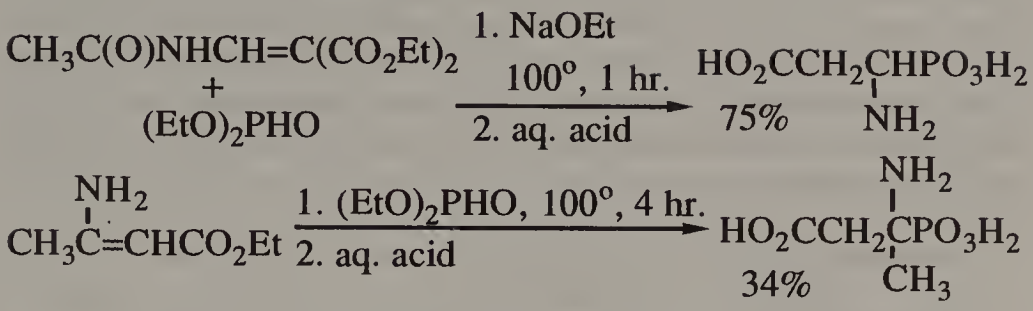


The addition of dialkyl phosphonates to the double bonds of oximes was never studied systematically. The reaction gives moderate yields of 1-(hydroxyamino)alkylphosphonates.[300] Moderate to good yields of 1-(benzyloxyamino)alkylphosphonic acids were obtained from *O*-benzyl oximes and phosphorus trichloride in acetic acid.[301]

3. Syntheses Involving the Formation of P-C Bonds by Addition of P(III) Reagents to Carbon-Carbon Double Bonds

It was known for some time that the addition of dialkyl phosphonates to enamines yields *N*-substituted 1-aminoalkylphosphonates.[241] The reaction does not require catalysis,[231,302] but base-catalyzed addition was used to prepare the α-phosphonic analogue of aspartic acid from diethyl acetamidomethylenemalonate.[380] A low yield of the α-phosphonic analogue of α-methylaspartic acid was obtained by addition of diethyl phosphonate to ethyl

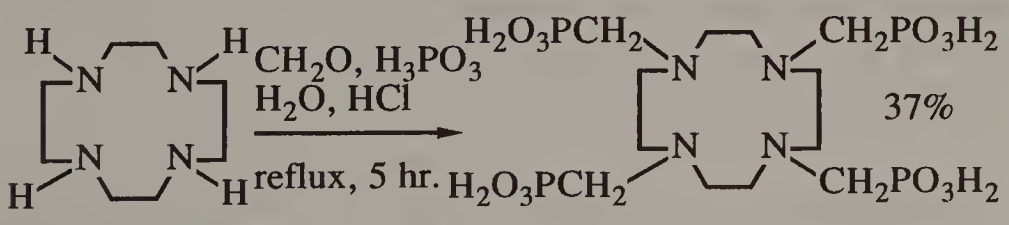
3-amino-2-butenoate.[302]



4. Syntheses by Simultaneous Formation of P-C and C-N Bonds

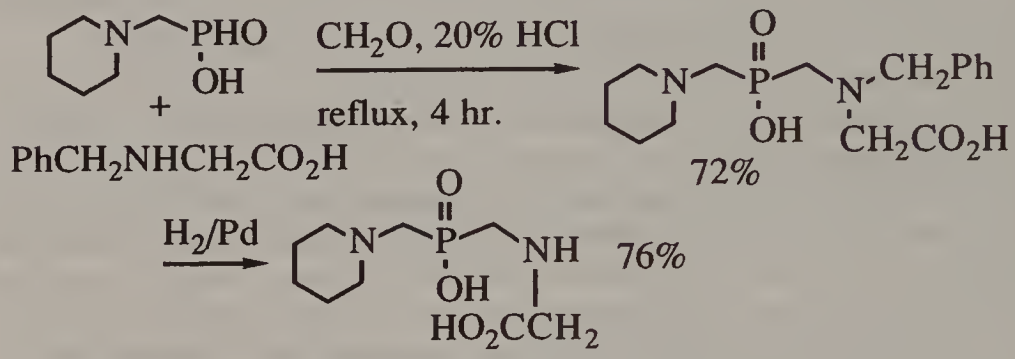
The syntheses discussed in this section are based on processes in which the P-C-N system is constructed from amines, carbonyl compounds, and phosphorus reactants in one overall reaction without isolation of intermediates. It is obvious that the formation of P-C and C-N bonds in such processes are not simultaneous in the mechanistic sense. It appears that reactive C-N systems are formed first and undergo nucleophilic displacement or addition reactions with the phosphorus reagents, as discussed in IV.A.1 and IV.A.2. Unfortunately, mechanistic considerations are only speculative at present as no rigorous studies of reaction mechanism have been published thus far.

Many derivatives of aminomethylphosphonic acid were prepared by the Mannich-type procedure of Moedritzer and Irani in which phosphorous acid reacts with formaldehyde and amines in strongly acidic solution.[6,239] A serious drawback of this procedure, apart from the requirement for low pH, is that only formaldehyde can be used as the carbonyl reagent.[274] The procedure is nevertheless very useful because no structural requirements concern the amine component. Modern practical applications are illustrated with the synthesis of azamacrocyclic derivatives of aminomethylphosphonic acid.[303]



Another drawback of the Moedritzer-Irani reaction results

from the fact that secondary amines react faster than primary. Consequently, it is practically impossible to prepare monophosphonylated derivatives from primary amines without suitable protection of one of the N-H bonds.[304] The following example illustrates the protection principle and demonstrates that acidic phosphorus species other than phosphorous acid also undergo aminomethylation with formaldehyde under typical conditions.[305]



Mannich-type condensations of hypophosphorous acid with amines and formaldehyde are also known.[306,307]

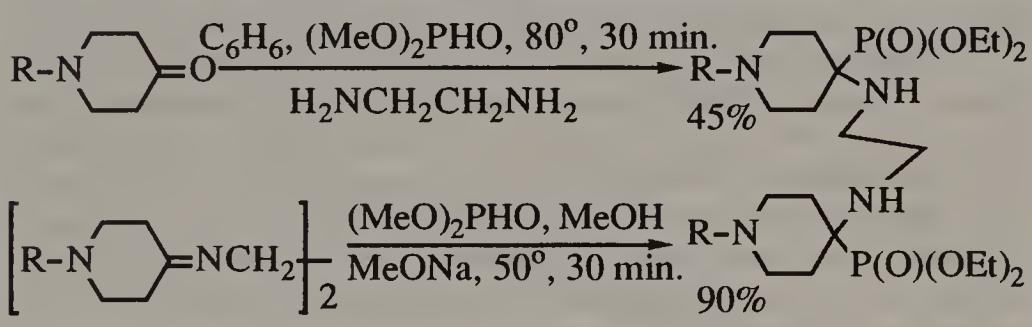
A similar Mannich-type process, known as the Kabachnik-Fields reaction, produces 1-aminoalkylphosphonates from P-H reactants, carbonyl compounds, and amines. This reaction, known since 1952, has a much wider scope than the Moedritzer-Irani procedure because it is applicable to a large variety of aliphatic and aromatic aldehydes and ketones. While dialkyl phosphonates were used most frequently, the reaction is possible also with other P-H species with the exception of phosphorous acid.[274] A thorough review of this reaction is available.[238]

The reaction was performed under a wide range of experimental conditions, very frequently without solvent. The yields vary within wide limits and appear to depend not only on the structure of substrates but also upon the exact experimental details, like the order of mixing of reactants. The reactions of dialkyl phosphonates with aldehydes or ketones and primary or secondary amines are strongly exothermic.[308] Heating was used in early syntheses, but recent work shows it not to be necessary.[309]

$$CH_3CHO + NH_3 + (EtO)_2PHO \xrightarrow[3\ da.]{liq.\ NH_3,\ r.t.} CH_3\underset{\displaystyle NH_2}{\underset{|}{C}}HP(O)(OEt)_2 \quad 76\%$$

The good yield claimed in the reaction shown above is rather exceptional for the Kabachnik-Fields reaction using ammonia as the amine component. Despite its apparent simplicity this reaction is neither general nor practical as a method for the preparation of dialkyl 1-aminoalkylphosphonates with an unsubstituted amino group because of erratic yields and difficulties encountered in the purification of products. A survey of recent literature shows that this reaction is not popular among practicing chemists. On the other hand, this reaction is the best of available procedures for the preparation of 1-(*N*,*N*-dialkylamino)alkylphosphonates.[308]

The most serious competing reaction appears to be the formation of 1-hydroxyalkylphosphonates which are inevitably formed when dialkyl phosphonates are mixed with amines and carbonyl compounds. In some cases the hydroxyphosphonates are formed as the principal products.[310] The relative merits of the Kabachnik-Fields reaction and the addition of dialkyl phosphonates to imines are illustrated by the following example.[311]



Several useful syntheses of 1-aminoalkylphosphonates from acid amides, aldehydes, and P(III) reagents were developed based on the seminal paper by Birum.[312] Ureas, thioureas, and other amides, including carbamates, react with trialkyl or triaryl phosphites yielding *N*-substituted 1-aminoalkylphosphonates. Quite unexpectedly, triphenyl phosphite enters these reactions more readily than the trialkyl phosphites. While unsubstituted urea or thiourea give diphosphonates predominantly, monophosphonates are obtained from *N*- substituted ureas.[312]

Birum did not hydrolyze the products to phosphonates with unsubstituted amino groups, but it was obvious that such hydrolysis should be possible. It was first accomplished by Huber and Middlebrooks who obtained the phosphonic analogues of alanine and phenylglycine from aldehydes, phenylurea, and triethyl phosphite in yields of ~40%.[313] A complete compilation of references

to work published before 1987 is available.[241] The following synthesis of the phosphonic analogue of methionine illustrates the use of acetic acid as solvent for ureidoalkylation of aldehydes.[314]

$$\begin{array}{l} MeSCH_2CH_2CHO \\ + \\ H_2NC(S)NH_2 \end{array} \xrightarrow[P(OPh)_3,\ HOAc]{2\ hr.,\ r.t.} \underset{86\%}{MeSCH_2CH_2\underset{\displaystyle NHC(S)NH_2}{\underset{|}{C}}HP(O)(OPh)_2} \xrightarrow[reflux,\ 7\ hr.]{conc.\ HCl,\ HOAc,} \underset{95\%}{MeSCH_2CH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HPO_3H_2}$$

Optically active 1-aminoalkylphosphonic acids were obtained by condensation of both enantiomers of *N*-(1-phenylethyl)urea with triphenyl phosphite and aldehydes. The procedure does not appear to be particularly useful owing to a low degree of asymmetric induction.[315,316] The Birum intermediates (1-thioureidoalkylphosphonates) were used to prepare a series of 1-guanidinoalkylphosphonates by conversion of the thioureido to a guanidino group.[317]

Practical syntheses of 1-aminoalkylphosphonates from aldehydes or ketones, P(III) compounds, and benzyl carbamate were developed at this author's laboratory following Birum's disclosure of the possibility of using carbamates in such syntheses. In one of the procedures the carbonyl compounds were treated with benzyl carbamate and phosphorus trichloride or with dichlorophosphines in acetic acid to give 1-aminoalkylphosphonic or -phosphinic acids in yields of ~50%.[249,318]

$$\begin{array}{l} RR'C{=}O + PCl_3 \\ + \\ PhCH_2OC(O)NH_2 \end{array} \xrightarrow[2.\ aq.\ HCl,\ reflux,\ 30\ min.]{1.\ HOAc,\ reflux,\ 40\ min.} \underset{52\text{-}65\%}{RR'\underset{\displaystyle NH_2}{\underset{|}{C}}PO_3H_2}$$

R, R' = H, alkyl, phenyl

The method works well also with more complex carbonyl compounds. For example, a 54% yield of the α-phosphonic analogue of α-methylaspartic acid was obtained from ethyl acetoacetate.[319] Other reported applications to specific synthetic problems include the syntheses of the phosphonic and phosphinic analogues of ornithine[320] and of aminodicarboxylic acids.[321] By the use of pivalic instead of acetic acid the yields were increased quite substantially.[321]

An interesting modification of the carbamate method affords satisfactory yields of the monoesters of *N*-protected aminoalkylphosphonic acids. In this modification the reaction is performed in the presence of thionyl chloride and the unidentified resulting product is treated with alcohol. Unfortunately, the reaction is limited to aromatic aldehydes.[322]

$$ArCHO + ZNH_2 \xrightarrow[2.\ ROH]{1.\ PCl_3,\ SOCl_2,\ r.t.,\ 2\ hr.} \underset{NHZ}{\overset{OH}{\underset{|}{\overset{|}{ArCHP(O)OR}}}}\ 41\text{-}68\%$$

Ar = phenyl, *p*-subst. phenyl; R = alkyl; Z = $PhCH_2OC(O)$

Another useful procedure developed in our laboratory is based on the reaction of aldehydes with benzyl carbamate and triphenyl phosphite. The reaction gives yields of ~50% of *N*-protected diphenyl esters which are almost quantitatively deprotected at nitrogen upon brief treatment with hydrogen bromide in acetic acid. Pure products are isolated as hydrobromide salts. This procedure opens an easy entry to diphenyl 1-aminoalkylphosphonates, compounds which are not readily available by other methods.[323]

$$RCHO + ZNH_2 + (PhO)_3P \xrightarrow[2\ hr.]{HOAc,\ 80^\circ} \underset{NHZ}{\overset{|}{RCHP(O)(OPh)_2}}\ 35\text{-}54\% \xrightarrow[HBr,\ 1\ hr.]{HOAc,\ r.t.} \underset{NH_2}{\overset{|}{RCHP(O)(OPh)_2}}\ 92\text{-}98\%$$

R = alkyl, phenyl

Vigorous hydrolysis gives 1-aminoalkylphosphonic acids, as in the synthesis of the phosphonic analogue of vinylglycine.[324]

$$\begin{matrix} PhSCH_2CH_2CHO \\ + \\ ZNH_2 + P(OPh)_3 \end{matrix} \xrightarrow[80^\circ,\ 1\ hr.]{HOAc} \underset{NHZ}{\overset{|}{PhSCH_2CH_2CHP(O)(OPh)_2}}\ 43\% \xrightarrow[HOAc]{H_2O_2} \underset{NHZ}{\overset{|}{\overset{O}{\overset{\|}{PhSCH_2CH_2CHP(O)(OPh)_2}}}}\ 90\% \xrightarrow[reflux,\ 24\ hr.]{xylene}$$

$$H_2C{=}CHCHP(O)(OPh)_2 \;(NHZ,\ 70\%) \xrightarrow[\text{reflux, 7 hr.}]{\text{conc. HCl}} H_2C{=}CHCHPO_3H_2 \;(NH_2,\ 42\%)$$
$$Z = PhCH_2OC(O)$$

The aminoalkylation of P(III) reactants with carbonyl compounds and acid amides appears to be open to many variations. For example, Chinese workers advocate the use of phosphoramidates in place of carboxylic amides[325] and find some merits in using dialkyl phosphonates as the P(III) species.[326] Simple carboxylic amides, *e.g.* acetamide, were also used with good results.[327]

5. Syntheses by Formation of C-N Bonds

The syntheses classified under this heading require that the substituents in the phosphonate substrate be replaced with an amino group (direct amination) or with a group which is converted to the amino function by reduction (indirect amination). While such transformations may be accomplished by any of the numerous methods of amine synthesis used in general organic chemistry, only a few are of practical significance in the synthesis of 1-aminoalkylphosphonates. For example, direct amination of carbanions with hydroxylamine derivatives[328] or with chloramine[329] was used in only a few cases and with moderate success.

An efficient preparation of aminophosphonoacetates was accomplished by indirect amination of trialkyl phosphonoacetates. The procedure involved the formation of diazo derivatives under standard diazo transfer conditions and reduction of the diazo group. Problems usually encountered in the hydrogenation of the diazo to amino group were overcome by performing the reduction in acidic medium.[329]

$$\underset{CO_2C(CH_3)_3}{\overset{|}{C}H_2P(O)(OEt)_2} \xrightarrow[\text{2. } TsN_3 \text{ r.t. 3 hr.}]{\text{1. DME, NaH}} \underset{CO_2C(CH_3)_3}{\overset{\|}{C}P(O)(OEt)_2}\ (N_2,\ 81\%) \xrightarrow[TsOH]{H_2/Pd} \underset{CO_2C(CH_3)_3}{\overset{|}{C}HP(O)(OEt)_2}\ (NH_2,\ 81\%)$$

Halogen displacement with ammonia or amines is generally not useful for the preparation of 1-aminoalkylphosphonates because the α-halogenated phosphonates are not readily available, and furthermore, the reaction requires rather severe conditions. For these reasons the practical utility of halogen displacement is limited to

syntheses of aminomethylphosphonates with only few exceptions. The followin example is quite typical for the reaction of chloromethylphosphonic acid with amine nucleophiles.[330] Monosubstitution was ensured by using a five-fold excess of amines.

$$\begin{matrix} H_2N(CH_2)_nNH_2 \\ + \\ ClCH_2PO_3H_2 \end{matrix} \xrightarrow[20\ hr.]{H_2O,\ 100^\circ} H_2N(CH_2)_nNHCH_2PO_3H_2 \quad n = 2\text{-}12 \quad 52\text{-}64\%$$

Intramolecular displacement of halogen is much easier. It was used as the key step in the synthesis of 2-aziridinephosphonic acid.[331]

$$H_2NCH_2\underset{Br}{C}HPO_3H_2 \xrightarrow[reflux,\ 5\ min.]{NaOH,\ H_2O} \underset{HN}{\triangle}PO_3H_2 \quad 74\%$$

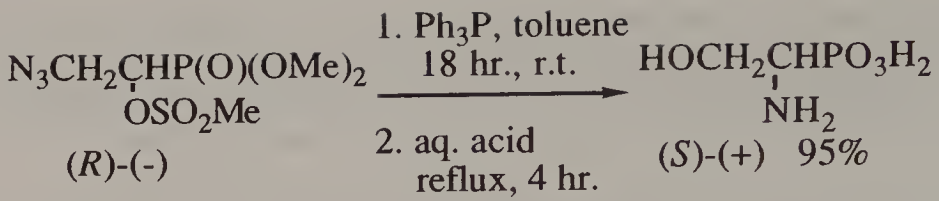
An apparently general method uses the Mitsunobu reaction to convert 1-hydroxyalkylphosphonates to 1-phthalimido- and hence to 1-aminoalkylphosphonates.[138] This approach does not offer any particular advantages over other methods and was not used since its introduction in 1982.

The (*R*)-(-) enantiomer of the phosphonic analogue of serine was obtained from optically active dimethyl 1-hydroxy-2-benzyloxyethylphosphonate by a variation of the Mitsunobu reaction using hydrazoic acid as the nitrogen source.[143] The substitution of hydroxy with the azido group took place with inversion of configuration.

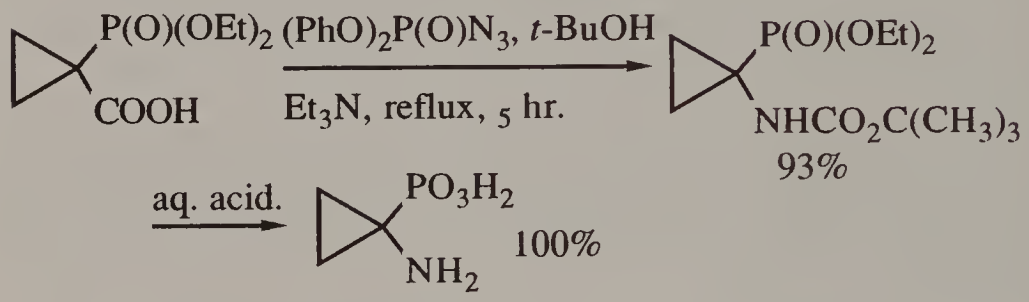
$$\begin{matrix} OCH_2Ph \\ | \\ CH_2\underset{OH}{C}HP(O)(OMe)_2 \\ (S)\text{-}(+) \end{matrix} \xrightarrow[r.t.,\ 1\ hr.]{\begin{matrix} Ph_3P,\ HN_3,\ THF \\ EtO_2CN{=}NCO_2Et \end{matrix}} \begin{matrix} OCH_2Ph \\ | \\ CH_2\underset{N_3}{C}HP(O)(OMe)_2 \\ (R)\text{-}(-)\ 70\% \end{matrix}$$

$$\xrightarrow[2.\ aq.\ acid]{1.\ H_2/Pd} HO\underset{NH_2}{C}H_2PO_3H_2 \quad (R)\text{-}(-)\ 88\%$$

The (*S*)-(+) enantiomer of 1-amino-2-hydroxyethylphosphonic acid was obtained in an interesting reaction *via* intermediate formation of an aziridine ring.[143]



The synthesis of 1-aminoalkylphosphonates by Curtius degradation of carboxylic acids, first introduced by Isbell in 1964,[239] has gained some popularity even despite the low overall yields obtained when the intermediate acid azides are prepared *via* hydrazides.[332,333] In more recent procedures the azides are obtained using diphenylphosphoryl azide (DPPA) and the overall yields are considerably improved, as shown below.[334]



The same approach was used in a synthesis of the phosphonic analogue of tryptophan.[335]

The Hofmann degradation of amides to 1-aminoalkylphosphonates was reported but has not met with any interest.[241]

Carboxylic acids are converted to 1-aminoalkylphosphonates without degradation of the carbon chain by a four-step procedure involving the formation of acyl chlorides, their conversion to acylphosphonates, oximation with hydroxylamine, and reduction of oximes.[321] The reduction of oximes is the most troublesome step in this route. It was carried out with diborane, aluminum amalgam, Raney nickel, and, most recently, with zinc in formic acid.[336] Aluminum amalgam and Raney nickel gave nearly the same yields in a synthesis of the phosphonic analogues of tryptophan.[337] The reduction with zinc in formic acid was used in a synthesis of the phosphonic analogue of cysteine.[338] The oximes used as intermediates in the oxime route to 1-aminoalkylphosphonates were reduced in the crude state without closer characterization and are thus rather little known. Only very recently some representatives were obtained in a pure state and thoroughly characterized.[339]

$$ArCH_2COCl \xrightarrow[\text{ether, } 5^\circ]{P(OEt)_3} \underset{\text{1 hr., r.t.}}{\underset{\text{4 hr.}}{ArCH{=}C(OH)P(O)(OEt)_2}} \xrightarrow[\text{EtOH, r.t., 12 hr.}]{\text{pyridine, } NH_2OH}$$

64%

$$ArCH_2\underset{\underset{NOH}{\|}}{C}P(O)(OEt)_2 \xrightarrow[\text{or Al/Hg}]{\text{Raney Ni}} ArCH_2\underset{\underset{NH_2}{|}}{C}HP(O)(OEt)_2$$

68% 70%

$$\xrightarrow[\text{reflux, 48 hr.}]{LiOH,\ H_2O} ArCH_2\underset{\underset{NH_2}{|}}{C}HPO_3H_2 \qquad Ar = 2\text{-indolyl}$$

69%

The synthesis of 1-aminoalkylphosphonates from acylphosphonates by reaction with amines and reducing agents (reductive amination) is severely limited by cleavage of the P-C bond[340,341] by ammonia or amines. Such amination, when successful, gives only low yields of the desired products.[341]

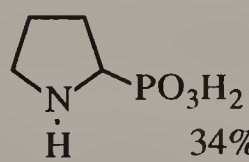
The reduction of *N,N*-dimethylhydrazones of acylphosphonates was reported to give 1-aminoalkylphosphonates, but it does not appear to offer any advantages over the oxime route.[342]

Aminophosphonates were prepared also by reduction of nitroalkylphosphonates, but this approach is not useful because the substrates are rather difficult to obtain .[343] The references to the preparations of nitroalkylphosphonates have been compiled.[344]

6. *N*-Alkylation and *N*-Acylation of Aminoalkylphosphonates

The preparation of simple 1-(*N*-aminoalkyl)phosphonates by alkylation of the amino group is possible using standard chemistry of amines.[248] Intramolecular alkylation was used in a synthesis of the phosphonic analogue of proline.[345]

$$ClCH_2CH_2CH_2\underset{\underset{NH_2}{|}}{C}HPO_3H_2 \xrightarrow[\text{r.t., 1 hr.}]{NaOH,\ H_2O}$$



34%

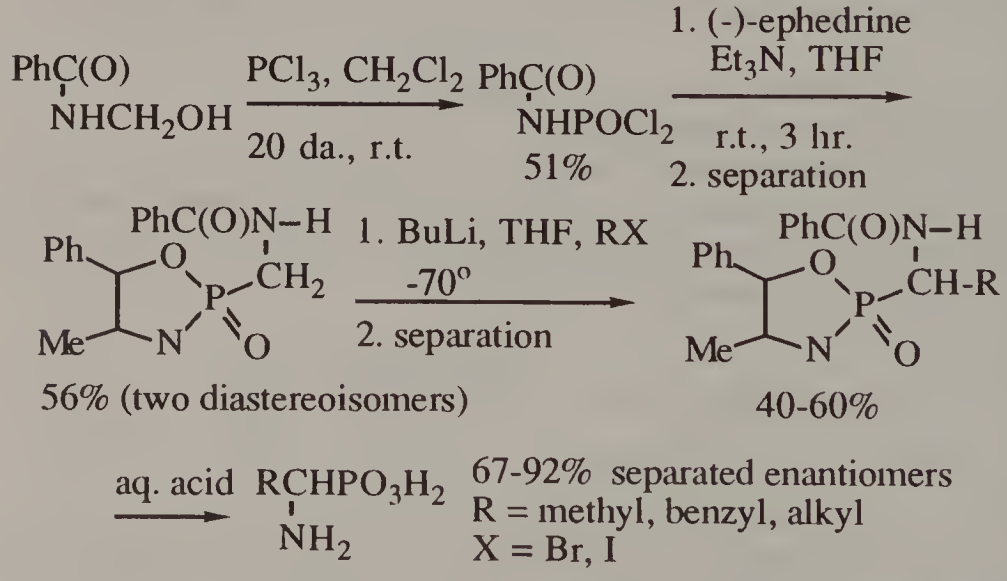
More complex chemistry is involved in the synthesis of the phosphonic analogue of 3-aminonocardinic acid, where the construction of the β-lactam ring requires both acylation and alkylation of the amino group.[346] Another synthesis of

phosphonates containing a β-lactam ring has been described.[347]

N-Acylation of 1-aminoalkylphosphonates is readily accomplished using standard acylating agents and methods.[248] Acylation with dibenzoyl-L-tartaric acid anhydride was used as the key step in the synthesis of both enantiomers of the phosphonic analogue of serine.[348] Acylation with complex acylating agents is a necessary step in the synthesis of phosphonopeptides.[349] The problems encountered there are beyond the scope of this Chapter.

7. Syntheses Involving the Extension of the Carbon Skeleton

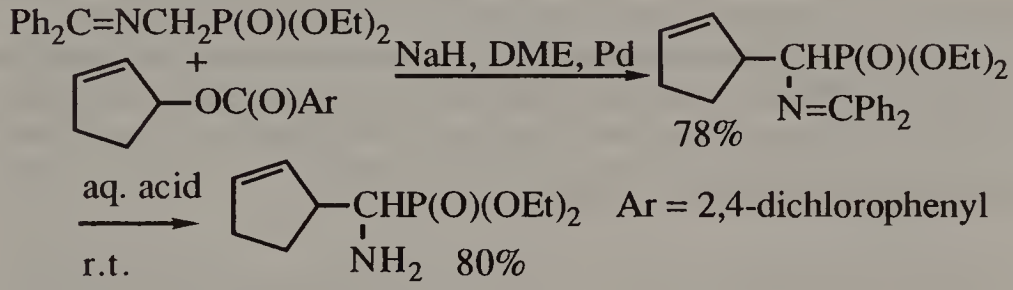
Several interesting syntheses of racemic and optically active 1-aminoalkylphosphonic acids are based upon C-alkylation of carbanions derived from suitably derivatized aminomethylphosphonic acid. Chiral auxiliaries needed for asymmetric syntheses were introduced either by suitable substitution at the nitrogen atom[226,350,351] or by modification of the phosphonate function.[352,353] The latter approach is illustrated with the following asymmetric synthesis of 1-aminoalkylphosphonic acids of high optical purity using (-)ephedrine as the source of chirality.[353] Stereochemical notation is omitted for simplicity.



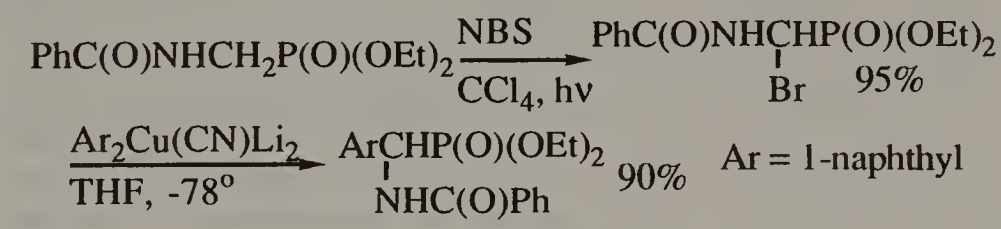
Chiral substitution at the nitrogen atom was accomplished by imine formation from diethyl aminomethylphosphonate and chiral ketones such as (+)-camphor[350] or 2-hydroxypinan-3-one.[352] The carbanions obtained from chiral imines were C-alkylated with

moderate to good asymmetric induction. Alkylation of chiral imines was used also to synthesize optically active 1-aminoalkylphosphinic acids.[226]

Racemic 1-aminoalkylphosphonic acids were prepared by alkylation of imines derived from diethyl aminomethylphosphonate and benzylamine[354] or diphenylmethylamine.[355,356] Good yields of alkylation were achieved under phase transfer conditions.[355] Alkylation of imine carbanions with allylic alkylating agents in the presence of palladium catalysts opens an easy entry to interesting unsaturated aminoalkylphosphonates.[356]

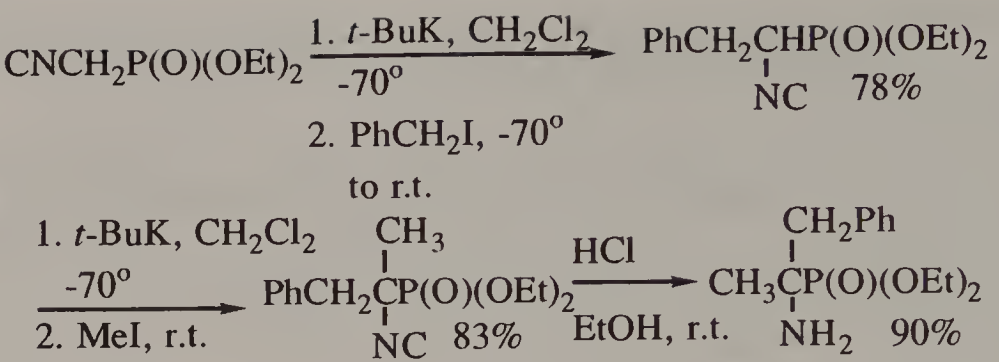


The carbanion route is supplemented with a carbocationic route in which *N*-acylaminomethylphosphonates are brominated and treated with nucleophilic reagents, including enamines, Grignard reagents, and organic cuprates, the latter being most effective.[357,358]

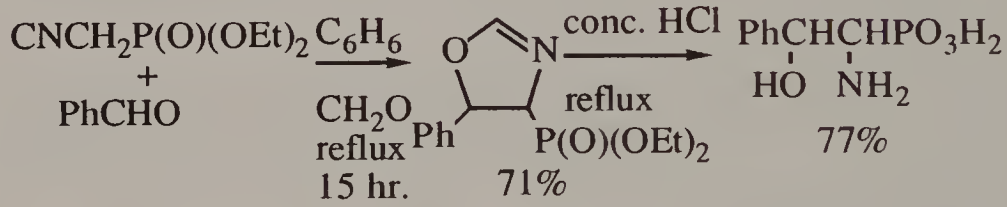


The electrophilic species actually reacting with nucleophiles in these processes are the *N*-acyliminomethylphosphonates formed *in situ* by the nucleophiles acting as bases.[357]

Very useful starting materials for the preparation of 1-aminoalkylphosphonates are the dialkyl isocyanomethylphosphonates developed by Schoelkopf.[256] The isocyano derivatives are readily prepared from *N*-formylamino precursors. They are acidic enough to be C-alkylated and the isocyano group is converted to the amino group by mild acid hydrolysis. Both mono- and dialkylated products are obtained in good yields.[256,354]



The versatility of isocyanoalkylphosphonate synthons is substantially increased by their ability to react with aldehydes and ketones with the formation of oxazolines which are converted by acid hydrolysis to 1-amino-2-hydroxyalkylphosphonic acids. The oxazoline approach was used to prepare the phosphonic analogues of β-substituted serines in racemic forms.[359]



According to recent preliminary reports, the condensation of isocyanomethylphosphonates with aldehydes proceeds with high diastereo- and enantioselectivity in the presence of chiral, ferrocene-based gold(I) catalysts.[360,361] Both enantiomers of *trans*-configured oxazolines were obtained by this method and their hydrolysis afforded pure enantiomers of the phosphonic analogue of β-phenylserine.[361] Similarly, hydrogenolysis of the oxazoline intermediates gave optically active phosphonic analogues of phenylalanine.[360]

Simple optically active 1-aminoalkylphosphonic acids are accessible by asymmetric catalytic hydrogenation of *N*-formyl enamines prepared from aminomethylenebisphosphonic acid by the Wadsworth-Emmons reaction with aldehydes. Considerable asymmetric induction was achieved when the hydrogenation was performed using a rhodium catalyst in the presence of DIOP as the chiral ligand.[362] Synthesis of α-phosphorylated enamines and their C-alkylation are described.[363]

$$\begin{matrix}HCONH_2\\ +\\ PCl_3 + H_3PO_3\end{matrix} \xrightarrow[2.\ H_2O]{1.\ 70^\circ,\ 1\ hr.} H_2NCH(PO_3H_2)_2 \quad 43\% \xrightarrow[DMF,\ 120^\circ,\ 44\ hr.]{HC(OMe)_3,\ H^+}$$

$$HC(O)NH(PO_3Me_2)_2 \quad 67\% \xrightarrow[MeOH,\ r.t.,\ 20\ hr.]{(CH_2O)_n,\ MeONa} H_2C{=}C(NHCHO)P(O)(OMe)_2$$

$$\xrightarrow[DIOP]{H_2,\ Rh} CH_3CH(NHCHO)P(O)(OMe)_2 \quad 99\% \xrightarrow{aq.\ acid} CH_3CH(NH_2)PO_3H_2 \quad 84\%,\ 76\%\ e.e.$$

An extension of the carbon skeleton is included also in the synthesis of the phosphonic analogue (HisP) of histidine from the phosphonic analogue of aspartic acid. In this multi-step synthesis the four-carbon backbone with appropriate functionalities for building the required imidazole ring was constructed from a three-carbon phosphonate using the known reaction of acyl chlorides with diazomethane.[364] The synthesis of HisP marks the completion of efforts aimed at the synthesis of the phosphonic analogues of all protein amino acids encoded in DNA.

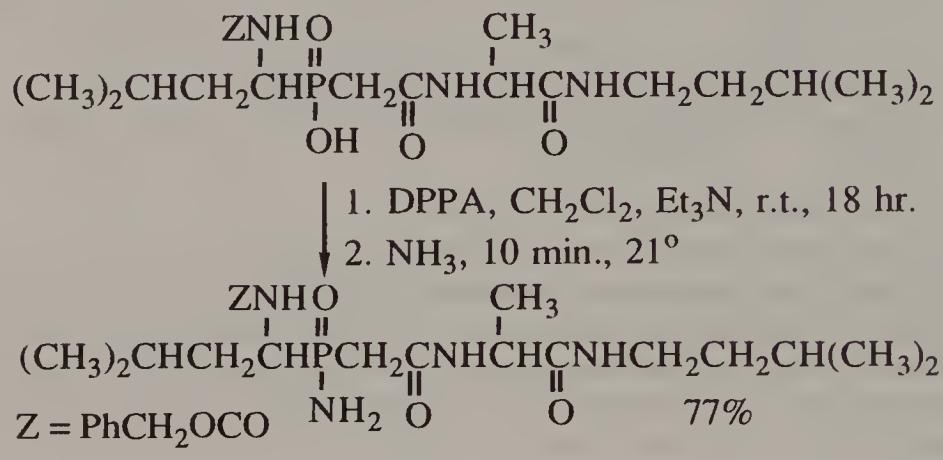
8. Syntheses Involving Transformations of the Phosphonate Function

Derivatization of phosphonates at the phosphorus atom is adequately covered in older, comprehensive reviews.[5,6] In modern chemistry of aminoalkylphosphonates such derivatization appears primarily in connection with syntheses of phosphonopeptides and peptide analogues containing carbon-phosphorus bonds. Some aspects of the chemistry of the phosphonate function emerging in connection with phosphonopeptides were discussed in a recent review.[243] The coverage given in this section is limited to selected examples, the main purpose being to illustrate the most recent trends and developments. The examples do not include the formation and cleavage of esters.

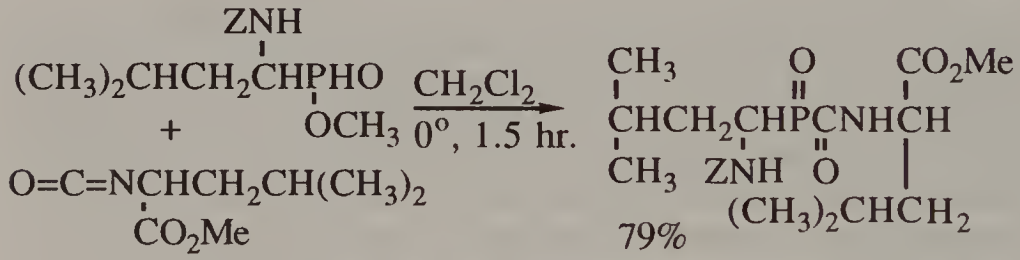
The well known procedures for the preparation of phosphochloridates and phosphofluoridates were adapted by Bartlett to synthesize phosphofluoridate derivatives of 1-aminoalkylphosphonic acids. The analogues of alanine and phenylalanine thus obtained are very potent inactivators of chymotrypsin.[365]

While simple phosphoramidates are readily available by a variety of procedures, the preparation of complex peptide-type structures containing the P-NH_2 function requires milder methods

which could be applied to the intact peptide framework. In an attempt to solve this problem Bartlett, *et al.* used activation with diphenylphosphoryl azide (DPPA) and azido group displacement with ammonia.[366]

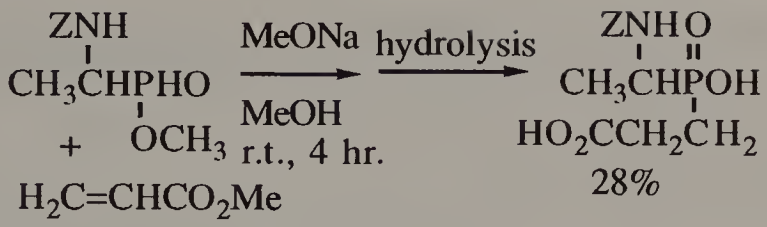


The known synthesis of phosphonoformamides from isocyanates and P(III) reagents was adapted to prepare an unusual peptide analogue containing the carbamoylphosphinic acid moiety. It was prepared by acylation of a silylated phosphonite with the isocyanate derivative of leucine.[367]



Several amino acid and peptide analogues of the dialkylphosphinic acid type are potent inhibitors of peptidases.[3,368,369] They were prepared either by alkylation of the P-H function of aminoalkylphosphinic acids[3,369] or by formation of new P-C bonds to the phosphorus atoms of 1-aminoalkylphosphonates. The latter approach is used in the synthesis of a phosphinic analogue of the amino acid statine.[368]

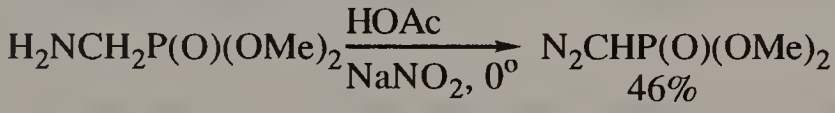
N-Protected 1-aminoalkylphosphinic acids were alkylated by Michael addition to carbon-carbon double bonds, as in the synthesis of a rather unusual analogue of alanylalanine.[369]



B. 1-Diazoalkylphosphonates

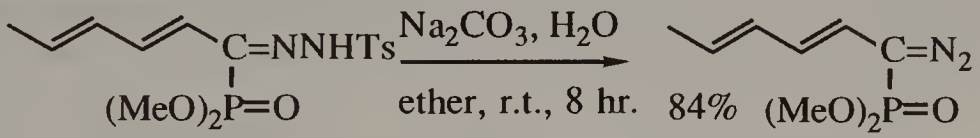
1. Syntheses from Phosphonates by Introduction of the Diazo Group

Dialkyl 1-diazoalkylphosphonates were prepared from aminophosphonates by diazotization, from acylphosphonates by the Bamford-Stevens reaction, or from α-phosphoryl carbanions by reaction with sulfonyl azides. The simplest representative, dimethyl diazomethylphosphonate, was obtained as a distillable liquid from dimethyl aminomethylphosphonate by diazotization.[370]

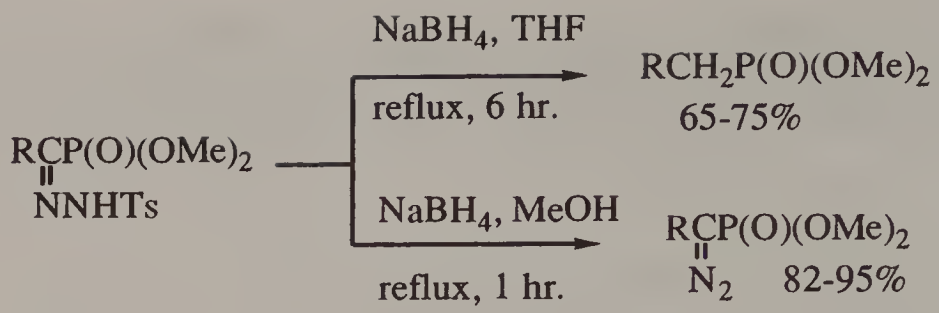


Examples of diazotization of aminophosphonates with propyl nitrite are found in recent Russian literature.[371]

The most frequently used method[372] is based upon the Bamford-Stevens reaction by which *N*-tosyl hydrazones are converted to diazoalkanes by treatment with base. The versatility of this method is shown by the high-yield synthesis of a diazoalkylphosphonate containing a conjugated double bond system.[214]



Sodium borohydride in aprotic solvents reduces α-tosyl hydrazone derivatives to alkylphosphonates with elimination of nitrogen. However, in alcohols the reaction takes a different course and diazoalkylphosphonates are formed in high yields. Diazophosphonates are resistant to reduction with sodium borohydride.[373]



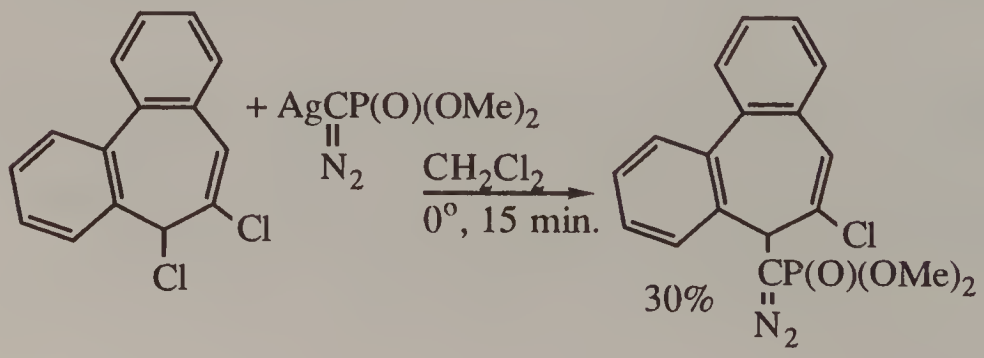
Another frequently used procedure is based on the diazo transfer reaction which occurs when carbanions are treated with sulfonyl azides. Tosyl azide was used most frequently[329,374,375] but there is also an example using *p*-dodecylbenzenesulfonyl-azide.[376]

2. Syntheses by Formation of C-C Bonds

The methods for the synthesis of diazoalkylphosphonates outlined in the previous section are supplemented by electrophilic substitution reactions at the carbon atom bearing the diazo group.

The relatively high acidity of the α-hydrogen makes it possible to prepare C-metallated derivatives which readily react with a wide selection of electrophiles. Even the silver salts of dialkyl diazomethylphosphonates are stable enough for safe handling and were used to prepare derivatives with extended carbon backbones. A thorough discussion of electrophilic diazo alkane substitution is found in the review by Fink and Regitz[377] covering the literature to 1985. Two examples of more recent developments are given here.

The reaction of silver and mercury salts of dialkyl diazomethylphosphonates with resonance-stabilized cations were described by Regitz, *et al.* in a series of papers.[377] A recent contribution deals with the synthesis of derivatives containing a dibenzocycloheptene ring system.[378]



Electrophilic substitution of non-metallated diazoalkylphosphonates occurs in the reaction with tris(dimethylamino)methane.[379]

$$\begin{matrix} N_2CHP(O)(OMe)_2 \\ + \\ CH(NMe_2)_3 \end{matrix} \xrightarrow{\text{r.t., 30 min.}} \underset{N_2}{(Me_2N)_2CHCP(O)(OMe)_2} \quad 100\%$$

3. Syntheses by Transformations of the Phosphonate Function

The range of possible transformations of the phosphonate function is severely limited by the reactivity of the diazo group. Nevertheless, it is possible to convert dialkyl diazoalkylphosphonates to the salts of the corresponding phosphonic acids. The salts are reasonably stable in aqueous solution and were examined (with disappointing results) as possible reagents for photolabeling of biological targets.[375] Sodium 1-diazoalkylphosphonates were prepared from esters by silylation and hydrolysis in basic media.[375]

Quite surprisingly, Regitz and Martin were able to isolate a free diazophosphonic acid in the solid state by chromatography of a *t*-butylammonium salt on silica.[374] The ammonium salt was obtained by treatment of the silyl ester with *t*-butylamine.

VI. Acknowledgments

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VII. Bibliography

1. Rhodes, C.J., Symons, C.R., Scott, C.A., Roduner, E., and Heming, M. (1987). Muonic alkyl radicals with α- or β-phosphorus substituents, *J. Chem. Soc., Chem. Commun.*: 448.
2. Bergstron, D.E., and Shum, P.W. (1988). Synthesis and characterization of new fluorine substituted nonionic dinucleoside phosphonate analogue, *J. Org. Chem.*, *53*: 3953.
3. Allen, M.C., Fuhrer, W., Tuck, B., Wade, R., and Wood,

J.M. (1989). Renin inhibitors. Synthesis of transition-state analogue inhibitors containing phosphorus acid derivatives at the scissile bond, *J. Med. Chem.*, *32*: 1652.
4. Blackburn, G.M. (1981). Phosphonates as analogues of biological phosphates, *Chem. Ind. (London)*: 134.
5. Sasse, K. (1963). Organische Phosphorverbindungen, Teil I, *Methoden der Organischen Chemie*, (E. Mueller, ed.), Georg Thieme Verlag, Stuttgart.
6. Gallenkamp, B., Hofer, W., Krueger, B.-W., Maurer, F., and Pfister, T. (1982). Phosphonsauren und ihre Derivate, Organische Phosphorverbindungen II, *Methoden der Organischen Chemie*, (M. Regitz, ed.), Georg Thieme Verlag, Stuttgart.
7. Elkik, E., and Imbeaux, M. (1989). A convenient synthesis of ethyl (diethoxyphosphoryl)fluoroacetate from ethyl fluoroacetate, *Synthesis*: 861.
8. Burton, D.J., and Flynn, R.M. (1979). A facile synthesis of trifluoromethane- and pentafluorobenzenephosphonates, *Synthesis*: 615.
9. Mahmoud, T., and Shreeve, J.M. (1987). Simple preparation of diethyl trifluoromethanephosphonates, *Synth. Commun.*, *17*: 71.
10. Su, D., Cen, W., Kirchmeier, R.L., and Shreeve, J. (1989). Synthesis of fluorinated phosphonic, sulfonic, and mixed phosphonic/sulfonic acids, *Can. J. Chem.*, *67*: 1795.
11. Burton, D.J., Ishihara, T., and Flynn, R.M. (1982). Difluoromethylene exchange in the preparation of fluorinated bisphosphonates, *J. Fluorine Chem.*, *20*: 121.
12. Dittrich, R., and Haegele, G., (1981). Die Michaelis-Arbuzov Reaktion perhalogenierter Olefine, *Phosphorus Sulfur*, *10*: 127.
13. Kadyrov, A.A., Rokhlin, E.M., and Galakhov, M.V. (1988). Trifluorovinyl phosphonates, *Izv. Akad. Nauk S.S.S.R., Ser. Khim.*: 1885.
14. Blackburn, G.M., and Taylor, G.E. (1988). Syntheses of some fluorine-containing halomethanephosphonate and methylenebisphosphonate esters, *J. Organomet. Chem.*, *348*: 55.
15. Blackburn, G.M., Taylor, G.E., Tattershall, R.H., Thatcher, G.R.J., and McLennan, A. (1987). Phosphonate analogues of biological phosphates, *Proc. 2nd Internatl. Symp. on Phos. Chem. Directed toward Biology*, (K.S. Bruzik and W.J. Stec, eds.), Elsevier Science Publishers,

Amsterdam, pp. 451-464.
16. Blackburn, G.M., and Parratt, M.J. (1986). The synthesis of α-fluoroalkylphosphonates, *J. Chem. Soc., Perkin Trans. I*: 1425.
17. Blackburn, G.M., Brown, D., Martin, S.J., and Parratt, M.J. (1987). Studies on selected transformations of some fluoromethanephosphonates, *J. Chem. Soc., Perkin Trans. I*: 181.
18. Burton, D.J., Pietrzyk, D.J., Ishihara, T., Fonong, T., and Flynn, R.M. (1982). Preparation, stability and acidity of difluoromethylenebisphosphonic acid, *J. Fluorine Chem., 20*: 617.
19. Hutchinson, D.W., and Thornton, D.M. (1988). A simple synthesis of monofluoromethylenebisphosphonic acid, *J. Organomet. Chem., 340*: 93.
20. Obayashi, M., Ito, E., Matsui, K., and Kondo, K. (1982). Diethylphosphinyldifluoromethyllithium, preparation and synthetic application, *Tetrahedron Lett., 23*: 2323.
21. Biller, S.A., Forster, C., Gordon, E.M., Harrity, T., Scott, W.A., and Ciosek, C.P. (1988). Isoprenoid (phosphinylmethyl)phosphonates as inhibitors of squalene synthetase, *J. Med. Chem., 31*: 1869.
22. Coutrot, P., Laurenco, C., Petrova, J., and Savignac, P. (1976). Synthesis of phenyl 1-chloro-1-alken-1-yl sulfides, *Synthesis*: 107.
23. Hall, C.R., Inch, T.D., Peacock, G., Pottage, C., and Williams, N.E. (1984). Chiral mono-, di-, and trichloromethylphosphonates and phosphorothioates: preparation, absolute configuration, and the stereochemical course of their reaction with methoxide, *J. Chem. Soc., Perkin Trans. I*: 669.
24. Coutrot, P., Elgadi, A., and Grison, C. (1989). A facile synthesis of diethyl aziridinylphosphonates and 2-chloroaziridinylphosphonates, *Heterocycles, 28*: 1179.
25. Teulade, M.P., and Savignac, P. (1988). Le *O,O*-diethyltrimethylsilylchloromethylphosphonate α-lithie. I. Preparations et proprietes, *J. Organomet. Chem., 338*: 295.
26. Coutrot, P., Youssefi-Tabrizi, M., and Grison, C. (1986). Diethyl 1-magnesium chloride methanephosphonate, a novel Grignard reagent and its use in organic synthesis, *J. Organomet. Chem., 316*: 13.

27. McKenna, C.E., and Shen, P.D. (1981). Fluorination of methanediphosphonate esters by perchloryl fluoride $FClO_3$, *J. Org. Chem.*, *46*: 4573.
28. McKenna, C.E., and Khawli, L.A. (1986). Synthesis of halogenated phosphonoacetate esters, *J. Org. Chem.*, *51*: 5467.
29. McKenna, C.E., Khawli, L.A., Ahmad, W.-Y., Pham, P., and Bongartz, J.-P. (1988). Syntheses of α-halogenated methanebisphosphonates, *Phosphorus Sulfur*, *37*: 1.
30. Ismailov, V.M., Moskva, V.V., Guseinov, F.I., Zykova, T.V., and Sadykov, I.S. (1986). Synthesis and properties of α-chloro-α-phosphoryl aldehydes, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *56*: 768.
31. Haelters, J.P., Corbel, B., and Sturtz, G. (1988). Synthese d'arylamino-1 ou -3 oxo-2-propylphosphonates, *Phosphorus Sulfur*, *37*: 65.
32. Soroka, M., and Mastalerz, P. (1973). Hofmann degradation and bromination of amides derived from phosphonoacetic acid, *Tetrahedron Lett.*: 5201.
33. Yamamoto, I., Sakai, T., Yamamoto, S. Ohta, K., and Matsuzaki, K. (1985). Synthesis of chlorovinyl phenyl sulfides and sulfones from diethyl chloro-(phenylthio)methanephosphonate, *Synthesis*: 676.
34. Kim, T.H., and Oh, D.Y. (1986). Synthesis of 1-substituted aryl methylthiomethylphosphonates by Friedel-Crafts reaction of aromatic compounds with chloromethylthiomethanephosphonates, *Tetrahedron Lett.*, *27*: 1165.
35. Tue Bi, B., and Devaud, M. (1987) Preparation electrochemique des chlormethyl et dichloromethyl-phosphonates de diethyle, *Tetrahedron Lett.*, *28*: 3799.
36. Hutchinson, D.W., and Semple, G. (1984). The dehalogenation of dihalomethylebisphosphonates, *Phosphorus Sulfur*, *21*: 1.
37. Chambers, R.D., Jaouhari, R., and O'Hagan, D. (1989). The preparation of difluoromethylenephosphonate analogues of glycolytic phosphates. Approaching an isosteric and isoelectronic mimic, *Tetrahedron*, *45*: 5101.
38. Rengaraju, S., and Berlin, K.D. (1972). A case of slow nitrogen inversion due to intramolecular hydrogen bonding, *J. Org. Chem.*, *37*: 3304.
39. Zeifman, Y., Lantseva, L.T., Kadyrov, A.A., and Rokhlin,

E.M. (1984). Halogenation of highly electrophilic fluorine-containing unsaturated compounds, *Izv. Akad. Nauk S.S.S.R., Ser. Khim.*: 1116.

40. Oehler, E., and Zbiral, E. (1984). Synthese, Reaktionen und NMR-Spektren von 2-Brom-3-oxo-1-alkynyl- und 3-Oxo-1-alkynyl-phosphonsaure-dialkylestern, *Monatsch. Chem., 115*: 493.
41. Sturtz, G., and Pondaven-Raphalen, A. (1984). Etude de la reaction de cyclisation des halohydrines-1,2-ethyl phosphonates de diethyle pour l'obtention de l'epoxy-1,2-ethyl phosphonate de diethyle, *Phosphorus Sulfur, 20*: 35.
42. Cabioch, J., Pellerin, B., and Denis, J.-M. (1989). Synthesis of primary α-chlorophosphines by chemoselective reduction of α-chlorophosphonates, *Phosphorus Sulfur, 44*: 27.
43. Gajda, T. (1990). A convenient synthesis of diethyl 1-chloroalkylphosphonates, *Synthesis*: 717.
44. Blackburn, G.M., and Kent, D.E. (1986). Synthesis of α- and γ-fluoroalkylphosphonates, *J. Chem. Soc., Perkin Trans. I*: 913.
45. Seyferth, D., and Marmor, S. (1973). Diethyl lithiodichloromethylphosphonate and tetraethyl lithiochloromethylenebisphosphonate, *J. Organomet. Chem., 59*: 237.
46. Coutrot, P., Laurenco, C., Normant, J.F., Perriot, P., Savignac, P., and Villieras, J. (1977). Synthesis of diethyl 1,1-dichloroalkane and 1-chloroalkanephosphonates, *Synthesis*: 615.
47. Obayashi, M., and Kondo, K. (1982). An improved procedure for the synthesis of 1,1-difluoro-2-hydroxyalkylphosphonates, *Tetrahedron Lett., 23*: 2327.
48. Kim, C.U., Luh, B.Y., Misco, P.F., Bronson, J.J., Hitchcock, M.J.M., Ghazzouli, I., and Martin, J.C. (1990). Acyclic purine phosphonate analogues as antiviral agents, *J. Med. Chem., 33*: 1207.
49. Burton, D.J., and Sprague, L.G. (1989). Allylations of [(diethoxyphosphinyl)difluoromethyl]zinc bromide as a convenient route to 1,1-difluoro-3-alkenephosphonates, *J. Org. Chem., 54*: 613.
50. Burton, D.J., Takei, R., and Shinya, S. (1981). Preparation, stability and synthetic utility of a cadmium stabilized complex of difluoromethylenebisphosphonate, *J. Fluorine*

Chem., *18*: 197.
51. Chambers, R.D., Jaouhari, R., and O'Hagan, D. (1989). Synthesis of difluoromethylenephosphonate derivatives as phosphate mimics, *J. Fluorine Chem.*, *44*: 275.
52. Teulade, M.P., Savignac, P., Aboujade, E.E., and Collignon, N. (1985). Acylation des α-chloromethylphosphonates de dialkyle par voie carbanionique, *J. Organomet. Chem.*, *287*: 145
53. Villieras, J., Perriot, P., and Normant, J.F. (1987). Diethyl 1-chloro-1-lithio-2-oxoalkanephosphonates: Synthesis of α-chloro-α,β-unsaturated ketones, *Synthesis*: 29.
54. Blackburn, G.M., Brown, D., and Martin, S.J. (1985). A novel synthesis of fluorinated phosphonoacetic acids, *J. Chem. Res. (S)*: 92.
55. Burton, D.J., Ishihara, T., and Maruta, M. (1982). A useful zinc reagent for the preparation of 2-oxo-1,1-difluoroalkylphosphonates, *Chem. Lett.*: 755.
56. Burton, D.J., and Sprague, L.G. (1988). Preparation of difluorophosphonoacetic acid and its derivatives, *J. Org. Chem.*, *53*: 1523.
57. Blackburn, G.M., and Parratt, M.J. (1986). Synthesis of α-fluorovinylphosphonates, *J. Chem. Soc., Perkin Trans. I*: 1417.
58. Blackburn, G.M., and Rashid, A. (1989). Enantiospecific syntheses of the methylene and α-fluoromethylenephosphonate analogues of 3-phospho-D-glyceric acid, *J. Chem. Soc., Chem. Commun.*: 40.
59. Blackburn, G.M., and Rashid, A. (1988). Stereoselective syntheses of the methylene- and α-fluoromethylenephosphonate analogues of 2-phospho-D-glyceric acid, *J. Chem. Soc., Chem. Commun.*: 317.
60. Harger, M.J.P., and Wiliams, A. (1986). Reactions of *N*-phenyl-α-halogenophosphonamidates with alkoxide: migration of the anilino group from phosphorus to the α-carbon atom, *J. Chem. Soc., Perkin Trans. I*: 1681.
61. Kato, M., and Yamabe, M. (1981). A new synthetic route to perfluoroalkyl phosphonates involving facile formation of the CF-P linkage, *J. Chem. Soc., Chem. Commun.*: 1173.
62. Farrington, G.K., Kumar, A., and Wedler, F.C. (1989). A

convenient synthesis of diethyl-mercaptomethyl-phosphonate, *Org. Proc. Prep. Int.*, *21*: 390.

63. Milolajczyk, M., Grzejszczak, S., Chefczynska, A., and Zatorski, A. (1979). Addition of elemental sulfur to phosphonate carbanions and its application for synthesis of α-phosphoryl organosulfur compounds, *J. Org. Chem.*, *44*: 2967.
64. Yoneda, S., Kawase, T., and Yoshida, Z. (1978). Syntheses of [1-(alkylthio)]- and (1-mercapto)cycloalkanephosphonic esters by the reactions of cycloalkanethiones with trialkyl phosphites, *J. Org. Chem.*, *43*: 1980.
65. Zimin, M.G., Burilov, A.B., and Pudovik, A.N. (1981). Reaction of silyl phosphites with thioketones, *Zh. Obshch. Khim.*, *51*: 2140.
66. Creary, X., and Mohrsheikh-Mohammedi, M.E. (1986). The nature of cationic intermediates derived from α-thiophosphoryl and α-thiocarbonyl mesylates, *J. Org. Chem.*, *51*: 7.
67. Blumenkopf, T.A. (1986). An efficient preparation of diethyl phenylsulfonylmethylphosphonate, *Synth. Commun.*, *16*: 139.
68. Mikolajczyk, M., Midura, W., Wieczorek, M., and Bujacz, G. (1987). Synthesis and crystal and molecular structure of *O,O*-diphenylphosphorylmethyl phenyl sulfoxide, *Phosphorus Sulfur*, *31*: 19.
69. Corey, E.J., and Shulman, J.I. (1970). A method for the introduction of two carbon appendages at a carbonyl carbon, *J. Am. Chem. Soc.*, *92*: 5522.
70. Bulpin, A., Masson, S., and Sene, A. (1990). Reaction of trialkyl phosphites with phosphonodithioformates: access to substituted methylenebisphosphonates *via* stabilized ylids, *Tetrahedron Lett.*, *31*: 1151.
71. Masson, S., Sene, A., Hutchinson, D.W., and Thornton, D.M. (1988). The reaction between thiophosgene and trialkyl phosphites, *Phosphorus Sulfur*, *40*: 1.
72. Mikolajczyk, M., Popielarczyk, M., and Grzejszczak, S. (1984). Synthese von Sulfidoxed und Sulfonen des mono- und disubstituierten 3,4-Dihydro-2H-thiopyrans, *Z. Chem.*, *24*: 377.
73. Farrington, G.K., Kumar, A., and Wedler, F.C. (1987). Design and synthesis of phosphonate inhibitors of glutamine

synthetase, *J. Med. Chem.*, *30*: 2062.
74. Farrington, G.K., Kumar, A., and Wedler, F.C. (1985). Design and synthesis of new transition-state analogue inhibitors of aspartate transcarbamylase, *J. Med. Chem.*, *28*: 1668.
75. Hakimelahi, G.H., and Ugolini, A. (1982). Addition of elemental sulfur to carbanions and its application for synthesis of isocephams and isopenams, *Tetrahedron Lett.*, *23*: 913.
76. Mikolajczyk, M., Balczewski, P., and Grzejszczak, S. (1980). A facile synthesis of α-phosphoryl sulfides and S,S-acetals of oxomethanephosphonates, *Synthesis*: 127.
77. Mikolajczyk, M., and Balczewski, P. (1989). Synthesis and reactivity of diethyl (methylthio)(trimethylsilyl)methylphosphonate, *Synthesis*: 101.
78. Gorzynski-Smith, J., Finck, M.S., Kontoleon, B.D., Trecoske, M.A., Giordano, L.A., and Renzulli, L.A. (1983). A convenient synthesis of dimethyl [(alkylthio)methyl]phosphonates and dimethyl [(arylthio)methyl]phosphonates, *J. Org. Chem.*, *48*: 1110.
79. Flitsch, W., Rosche, J., and Lubisch, W. (1987). Synthesewege zu 1-substituierten Butadienylphosphonaten, *Ann.*: 661.
80. Mikolajczyk, M., Kielbasinski, P., and Grzejszczak, S. (1983). A new synthesis of α-alkylthioketones, *Synthesis*: 332.
81. Blackburn, G.M., and Maciej, T.W. (1985). Trihalogenomethylsulfenylation of tetraisopropyl methylenebis phosphonates, *J. Chem. Soc., Perkin Trans. I*: 1935.
82. Gajda, T. (1988). A facile synthesis of diethyl 1-(phenylthio)alkylphosphonates, *Synthesis*: 327.
83. Inokawa, S., and Yamamoto, H. (1983). A new synthetic approach to α,β-unsaturated phosphonates, *Phosphorus Sulfur*, *16*: 79.
84. Corey, E.J., and Shulman, J.I. (1970). The application of lithium reagents from (1-methylthio)alkylphosphonate esters to the synthesis of ketones, *J. Org. Chem.*, *35*: 777.
85. Mikolajczyk, M., Grzejszczak, S., and Lyzwa, P. (1982). Conversion of 1,3- into 1,4-dicarbonyl compounds by means of α-phosphoryl sulfides. Total synthesis of dihydrojasmone and methylenomycin B, *Tetrahedron Lett.*, *23*:

2237.
86. Koizumi, T., Tanaka, N., Iwata, M., and Yoshii, E. (1982). A convenient synthesis of diethyl 1-alkenephosphonates, *Synthesis*: 917.
87. Martin, S.F., and Garrison, P.J. (1982). Synthesis and some reactions of diethyl 1-methylthio-1-(*Z*),3-butadiene-phosphonate, *Synthesis*: 394.
88. Gross, H., and Keitel, I. (1982). Heterosubstituierte Olefine durch Horner Reaktion mit α-substituierten Phosphonaten, *Z. Chem.*, *22*: 117.
89. Venugopalan, B., Hamlet, A.B., and Durst, T. (1981). A short synthesis of the Δ^1-carbopenem ring system, *Tetrahedron Lett.*, *22*: 191.
90. Ishibashi, H., Sato, T., Irie, M., Ito, M., and Ikeda, M. (1987). Carbon-carbon bond forming reactions with α-phosphoryl-α-thio carbocations, *J. Chem. Soc., Perkin Trans. I*: 1095.
91. Kim, T.H., Kim, D.Y., and Oh, D.Y. (1987). Reaction of Pummerer reaction intermediate with aromatic compounds: a novel synthesis of 1-(1-substituted-aryl)methylthiomethane-phosphonates, *Synth. Commun.*, *17*: 755.
92. Stamos, J.K. (1986). Arylation of α-phosphoryl sulfides *via* their Pummerer rearrangement intermediates generated from the corresponding sulfoxides, *Tetrahedron Lett.*, *27*: 6261.
93. Mikolajczyk, M. (1989). α-Phosphonate carbanions: from simple reactions to the synthesis of cyclopentenones and cyclopentanones, *Rev. Heteroatom Chem., Vol. 2*, (S. Oae, ed.), MYU, Tokyo, pp. 19-39.
94. Mikolajczyk, M., Grzejszczak, S., and Korbacz, K. (1981). Addition of elemental selenium to phosphonate carbanions - a key step in the synthesis of vinylphosphonates, *Tetrahedron Lett.*, *22*: 3097.
95. Prasad, K., Kneussel, P., Schulz, G., and Stuetz, P. (1982). A new method of carbon extension at C-4 of azetidinones, *Tetrahedron Lett.*, *23*: 1247.
96. Ishikawa, K., Akiba, K., and Inamoto, N. (1976). Synthesis of 1,4-benzodithiafulvenes *via* Wittig reaction, *Tetrahedron Lett.*: 3695.
97. Akiba, K., Ishikawa, K., and Inamoto, N. (1978).

Synthesis of 1,4-dithiafluvenes and 1,4-dithiafulvalenes by carbonyl olefination using 2-dimethoxyphosphinyl-1,3-benzodithiols, *Bull. Chem. Soc. Jpn.*, *51*: 2674.

98. Mlotkowska, B., Gross, H., Costisella, B., Mikolajczyk, M., Grzejszczak, S., and Zatorski, A. (1977). Synthese offenkettiger und cyclischer S,S-acetale von Formylphosphonsaureestern, *J. prakt. Chem.*, *319*: 17.
99. Mikolajczyk, M., Balczewski, P., Wroblewski, K., Karolak-Wojcciechowska, J., Miller, A., Wieczorek, M.W., Antipin, M.Y., and Struchkov, Y.T. (1984). Axial preference of 2-dimethoxyphosphoryl substituent in 1,3,5-trithiane, *Tetrahedron*, *40*: 4885.
100. Mikolajczyk, M., Graczyk, P., Wieczorek, M.W., and Bujacz, G. (1988). A solution and solid state conformation of 2-phosphoryl substituents in 1,3-oxathianes, *Tetrahedron Lett.*, *29*: 6801.
101. Gross, H., Keitel, I., Costisella, B., Mikolajczyk, M., and Midura, W. (1983). Zur Synthese von Bis-Alkylmercapto-methanphosphonsauredialkylestern, *Phosphorus Sulfur*, *16*: 257.
102. Comins, D.L., Jacobine, A.F., Marshall, J., and Turnbull, M.M. (1978). Phosphonate ester preparation from active methylene compounds and phosphorochloridate esters, *Synthesis*: 309.
103. Akhmetkhametova, F.M., Rolnik, L.E., and Proskurina, M.W. (1987). The reaction of ethyl trithioorthoformate with diisopropyl phosphonate, *Zh. Obshch. Khim.*, *57*: 1918.
104. Kim, T.H., and Oh, D.Y. (1985). New synthetic method of O,S-thioacetals of formylphosphonates, *Tetrahedron Lett.*, *26*: 3479.
105. Costisella, B., Keitel, I. (1987). Phosphonoformaldehyd-O,S-acetale bzw. Phosphonoameisensaure-orthoester durch anodische Methoxylierung, *Synthesis*: 44.
106. Mikolajczyk, M., Zatorki, A., Grzejszczak, S., Costisella, B., and Midura, W. (1978). Pummerer rearrangement of α-phosphoryl sulfoxides and asymmetric induction in the transfer of chirality from sulfur to carbon, *J. Org. Chem.*, *43*: 2518.
107. Costisella, B., and Keitel, I. (1988). Synthese und Reaktionen von 1-Acetoxy-1-methylthiomethanephosphoryl Verbindungen, *Phosphorus Sulfur*, *40*: 161.
108. Kim, T.H., and Oh, D.Y. (1988) Synthesis of S,S-thioacet-

als of formylphosphonate from chloro(arylthio)methanephosphonate, *Synth. Commun.*, *18*: 1611.

109. Bulpin, A., Masson, S., and Sene, A. (1989). The use of phosphonodithioformates for the synthesis of ketene dithioacetals, *Tetrahedron Lett.*, *30*: 3415.
110. Mikolajczyk, M., Midura, W., Miller, A., and Wieczorek, M. (1987). Synthesis of α-phosphorylethyl *p*-tolyl sulfoxide and asymmetric induction on the α-carbon atom, *Tetrahedron*, *43*: 2967.
111. Mikolajczyk, M., and Zatorski, A. (1973). α-Phosphoryl sulfoxides, *Synthesis*: 669.
112. Drabowicz, J., Midura, W., and Mikolajczyk, M. (1979). A convenient procedure for oxidation of sulfides to sulfoxides by bromine/aqueous potassium hydrogen carbonate reagent in a two phase system, *Synthesis*: 39.
113. Posner, G.H., and Brunelle, D.J. (1972). α,β-Ethylenic sulfones from sulfonomethylphosphonate carbanions and aldehydes and ketones, *J. Org. Chem.*, *37*: 3547.
114. Shahah, I., and Almog, J. (1969). Horner-Wittig synthesis of α,β-unsaturated sulfides and sulfones, *Synthesis*: 170.
115. Shahah, I., and Almog, J. (1970). Horner-Wittig synthesis of unsaturated sulfides and sulfones. II, *Synthesis*: 145.
116. Mikolajczyk, M., Popielarczyk, M., and Grzajszczak, S. (1981). Synthesis of distyryl sulfides, sulfoxides, and sulfones by Horner-Wittig reaction in two-phase system, *Phosphorus Sulfur*, *10*: 369.
117. Su, D., Guo, C.-Y., Willet, R.D., Scott, B. Kirchmeier, R.L., and Shreeve, J.M. (1990). Synthesis of *trans*-1,2-difluoroethenediylbis(phosphonic acid) and other unsaturated phosphonic acids, *J. Am. Chem. Soc.*, *112*: 3152.
118. Burton, D.J., Modak, A.S., Guneratne, R., Su, D., Cen, W., Kirchmeier, R.L., and Shreeve, J.M. (1989) Synthesis of (sulfodifluoromethyl)phosphonic acid, *J. Am. Chem. Soc.*, *111*: 1773.
119. Milolajczyk, M., Midura, W., Grzejszczak, S., Zatorski, A., and Chefczynska, A. (1978). Dimethylphosphorylmethyl *p*-tolyl sulfoxide. Resolution, stereospecific synthesis and the Horner-Wittig reaction, *J. Org. Chem.*, *43*: 473.
120. Solladie, G., and Moine, G. (1984). Application of chiral sulfoxides in asymmetric synthesis: the enantiospecific syn-

thesis of the chroman ring of α-tocopherol (vitamin E), *J. Am. Chem. Soc.*, *106*: 6097.
121. Hoffmann, R.W., Goldmann, S., Gerlach, R., and Maak, N. (1980). Stereochemie der [2,3] sigmatropen Umlagerung von (1-Cycloalkenylmethyl)-sulfoxiden, *Ber.*, *113*: 845.
122. Mikolajczyk, M. Midura, W., and Kajtar, M. (1988). α-Phosphoryl sulfoxides. Chirooptical properties of α-phosphoryl sulfoxides, *Phosphorus Sulfur*, *36*: 79.
123. Hofmann, R.W., and Maak, N. (1976). Allylalkohole aus α,β-ungesaettigten Sulfoxiden, *Tetrahedron Lett.*: 2237.
124. Minami, T., Yamanouchi, T., Takenaka, S., and Hirao, I. (1983). Synthesis of butadienylphosphonates containing electronegative substituents and their synthetic applications to functionalized cyclopentenylphosphonates, *Tetrahedron Lett.*, *24*: 767.
125. Comasseto, J.V., and Petragnani, N. (1978). The reaction of selenophosphonates with carbonyl compounds, *J. Organomet. Chem.*, *152*: 295.
126. Kleschick, W.A., and Heathcock, C.H. (1978). Synthesis and chemistry of ethyl 2-diethylphosphonoacrylate, *J. Org. Chem.*, *43*: 1256.
127. Engel, R. (1987). Phosphorus addition at sp^2 carbon, *Org. React.*, *36*: 175.
128. Zimin, M.G., Cherkasov, R.A., and Pudovik, A.N. (1986). New data on the addition of P-H compounds to multiple bonds, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *56*: 859.
129. Mikroyannidis, J.A. (1987). Hydroxy and/or carboxy substituted phosphonic and bisphosphonic acids usable as corrosion and scale inhibitors, *Phosphorus Sulfur*, *32*: 113.
130. Kanaan, M., and Burgada, R. (1988). α-Diceto diphosphonates et hydroxymethylene tetraphosphonates synthese, structure et hydrolyse, *Phosphorus Sulfur*, *37*: 217.
131. Mikroyannidis, J.A., Tsolis, A.K., and Gourghiotis, J. (1982). Synthesis and chemical properties of substituted 2-hydroxy-2-phosphonylethanals and 1,2-dihydroxy-1,2-bisphosphonylethanes, *Phosphorus Sulfur*, *13*: 279.
132. Phillion, D.P., and Andrew, S.S. (1986). Synthesis and reactivity of diethyl phosphonomethyltriflate, *Tetrahedron Lett.*, *27*: 1477.
133. Texier-Boullet, F., and Foucauld, A. (1982). A convenient

synthesis of dialkyl 1-hydroxyalkanephosphonates using KF or CsF without solvents, *Synthesis*: 165.

134. Texier-Boullet, F., and Foucauld, A. (1982). Synthesis of 1-hydroxyalkanephosphonic esters on alumina, *Synthesis*: 916.
135. Villemin, D., and Racha, R. (1986). Activation anionique du phosphite de diethyle par le fluoride de potassium depose sur alumine, synthese de phosphonates functionalizes, *Tetrahedron Lett.*, *27*: 1789.
136. Zhdanov, Y.A., Glebova, E.I., Kistian, G.K., and Uzlova, L.A. (1984). The use of potassium fluoride in the synthesis of sugar derived α-hydroxyphosphonates, *Zh. Obshch. Khim.*, *54*: 1205.
137. Mikroyannidis, J.A. (1984). New synthesis of substituted 1,2-dihydroxy-1,2-bisphosphonylethanes, *Phosphorus Sulfur*, *20*: 323.
138. Baraldi, P.G., Guarneri, M., Moroder, F., Pollini, G.P., and Simoni, D. (1982). Synthesis of 1-phthalimidoalkane-phosphonates, *Synthesis*: 653.
139. Kamber, M., and Just, G. (1985). α-Phosphonolactones. The use of allyl esters as easily removable phosphonate protecting groups, *Can. J. Chem.*, *63*: 823.
140. Sasaki, M., Kato, T., Yamamoto, S., and Mukai, K. (1984). Antifungal activity of (hydroxy)pyridin-3-yl (methyl)phenylphosphonates and related compounds, *J. Pesticide Sci.*, *9*: 717.
141. Tatsuoka, T., Imao, K., and Suzuki, K. (1986). Synthesis of 2-3'-anhydro-1'-deoxy-1'-phosphono-1-β-D-fructofuranosyl uracil, *Heterocycles*, *24*: 617.
142. Hammerschmidt, F. (1988). Hydroxylierung von deuteriert-en (2-Aminoethyl)phosphonsaure zu (2-Amino-1-hydroxy-ethyl)phosphonsaure in *Acanthamoeba castellanii*, *Ann.*: 537.
143. Hammerschmidt, F., and Voellenkle, H. (1989). Absolute Konfiguration der (2-Amino-1-hydroxyethyl)phosphonsaure aus *Acanthamoeba castellanii*, *Ann.*: 577.
144. Nguyen, L.M., Niesor, E., and Bentzen, C.L. (1987). *gem*-Diphosphonate and *gem*-phosphonate-phosphate compounds with specific high density lipoprotein inducing activity, *J. Med. Chem.*, *30*: 1426.
145. El Manouni, D., Leroux, Y., and Burgada, R. (1989). Syn-

these d'α-cetophosphonates et d'esters d'hydroxymethylenediphosphonates, *Phosphorus Sulfur*, *42*: 73.
146. Pudovik, A.N., and Zimin, M.G. (1980). Addition reactions of partially esterified phosphorus acids. Rearrangements of α-hydroxyalkyl phosphorus esters and their α-mercapto and α-amino analogues, *Pure Appl. Chem.*, *52*: 989.
147. Hammerschmidt, F., and Voellenkle, H. (1986). Zur Stereochemie der Phosphat-Phosphonate Umlagerung, *Ann.*: 2053.
148. Jacques, J., Leclercq, M., and Brienne, M.-J. (1981). La formation de sels augmente-T-elle la frequence des dedoublements spontanes?, *Tetrahedron*, *37*: 1727.
149. Hoffmann, M. (1990). Optically active 1-hydroxy-3-methylbutanephosphonic acid, *J. prakt. Chem.*, *332*: 251.
150. Wynberg, H., and Smaardijk, A.A. (1983). Asymmetric catalysis in carbon-phosphorus bond formation, *Tetrahedron Lett.*, *24*: 5899.
151. Smaardijk, A.A., Noorda, S., van Bolhuis, F., and Wynberg, H. (1985). The absolute configuration of α-hydroxyphosphonates, *Tetrahedron Lett.*, *26*: 493.
152. Girotra, N.N., and Wendler, N.L. (1969). Syntheses and transformations in the phosphonomycin series, *Tetrahedron Lett.*: 4647.
153. Sasaki, M. (1986). Optical resolution of 1-hydroxyethylphosphinic acid and its esters, *Agric. Biol. Chem.*, *50*: 741.
154. Wozniak, L., and Chojnowski, J. (1989). Silyl esters of phosphorus-common intermediates in synthesis, *Tetrahedron*, *45*: 2465.
155. Walker, D.M., McDonald, J.F., Franz, J.E., and Logush, E.W. (1990). Design and synthesis of γ-oxygenated phosphinothricins as inhibitors of glutamine synthetase, *J. Chem. Soc., Perkin Trans. I*: 659.
156. Majewski, P. (1987). A new method for the preparation of bis(1-hydroxyalkyl)phosphinic acids, *Synthesis*: 555.
157. Hanaya, T., and Yamamoto, H. (1989). Synthesis and structural analysis of 4-deoxy-4-(hydroxyphosphinyl and phenylphosphinyl)-D-ribofuranoses, *Bull. Chem. Soc. Jpn.*, *62*: 2320.
158. Wroblewski, A.E. (1986). Synthesis of enantiomeric dimethyl (1,2,3,4-tetrahydroxybutyl)phosphonates, *Ann.*: 1854.

159. Thiem, J., and Guenther, M. (1984). Abramov-Reaktion von Kohlenhydratderivaten mit freien anomeren Zentren, *Phosphorus Sulfur*, *20*: 67.
160. Creary, X., Geiger, C.C., and Hilton, K. (1983). Mesylate derivatives of α-hydroxyphosphonates. Formation of carbocations adjacent to the diethyl phosphonate group, *J. Am. Chem. Soc.*, *105*: 2851.
161. Penz, G., and Zbiral, E. (1982). Zur Synthese von (±)-*cis*-1,2-Epoxy-3-oxoalkyl-phosphonsaureestern-Phosphonomycinanaloga, *Monatsh. Chem.*, *113*: 1169.
162. Karaman, R., Goldblum, A., Breuer, E., and Leader, H. (1989). Acylphosphonic acids and methyl hydrogen acylphosphonates: physical and chemical properties and theoretical calculations, *J. Chem. Soc., Perkin Trans. I*: 765.
163. Lalinde, N., Tropp, B.E., and Engel, R. (1983). Isosteres of natural phosphates. 10. Synthesis of analogues related to glycerol 3-phosphate, *Tetrahedron*, *39*: 2369.
164. Yamashita, M., Kojima, M., Yoshida, H., Ogata, T., and Inokawa, S. (1980). New synthesis and hydroboration of vinylphosphonates, *Bull. Chem. Soc. Jpn.*, *53*: 1625.
165. Penz, G., and Zbiral, E. (1985). Synthese der (3-Oxo-2-tosyloxy-1-alkenyl)phosphonsauredialkylester - Synthone zur Gewinnung von (Heteromethyl)-phosphonsaureestern und 2-substituierten 3-Oxophosphonsaureestern, *Ber.*, *118*: 4131.
166. Pondaven-Raphalen, A., and Sturtz, G. (1987). Etude de la reaction de dihydroxylation de phosphonates α,β-, β,γ-, et γ,δ- ethyleniques a l'aide d'hydroperoxydes catalysee par le tetroxyde d'osmium: specificite d'action de l'hydroperoxyde de tertiobutyle, *Phosphorus Sulfur*, *29*: 329.
167. Oehler, E., Kang, H.-S., and Zbiral, E. (1988). (2,3-Epoxy-4-oxoalkyl)phosphonsaureester als Synthone fuer Thiazole, *Ber.*, *121*: 533.
168. Chakravarty, P.K., Greenlee, W.J., Parsons, W.H., Patchett, A.A., Combs, P., Roth, A., Bush, R.D., and Mellin, T.N. (1989). (3-Amino-2-oxoalkyl)phosphonic acids and their analogues as novel inhibitors of D-alanine ligase, *J. Med. Chem.*, *32*: 1886.
169. Waszkuc, T., Janecki, T., and Bodalski, R. (1984). A convenient synthesis of α-hydroxyaldehydes and hydroxy-

methylketones, *Synthesis*: 1025.
170. Vidal, Y., Clin, B., Cassaigne, A., and Neuzil, E. (1982). Derives d'addition de la fosfomycine: l'acide hydroxy-1-amino-2-propyl phosphonique, *Bull. Soc. Pharm. Bordeaux*, *121*: 3.
171. Hammerschmidt, F., Schneider, E., and Zbiral, E. (1980). Ein allgemeiner Zugang zu 1,2-propadienylphosphonaten, *Ber.*, *113*: 3891.
172. Koenigskramer, R., and Zimmer, H. (1980). Benzoins *via* an acyl anion equivalent. Novel one-pot preparation of benzo- [b]furans *via* benzoins using hydriodic acid, *J. Org. Chem.*, *45*: 3994.
173. Evans, D.A., Takacs, J.M., and Hurst, K.M. (1979). Phosphonamide stabilized allylic carbanions. New homoenolate anion equivalents, *J. Am. Chem. Soc.*, *101*: 371.
174. Sekine, M., Nakajima, M., Kume, A., Hashizume, A., and Hata, T. (1982). Versatile utility of α-(trimethylsiloxy)alkylphosphonates as key intermediates for transformation of aldehydes into several carbonyl derivatives, *Bull. Chem. Soc. Jpn.*, *55*: 224.
175. Sekine, M., Nakajima, M., and Hata, T. (1982). A new type of P-C and C-C bond cleavage reaction in α-trimethylsiloxy-β-oxophosphonates, *Bull. Chem. Soc. Jpn.*, *54*: 218.
176. Richtarski, G., Soroka, M., Mastalerz, P., and Starzemska, H. (1975). Deamination and rearrangement of 1-hydroxy-1-phenyl-2-aminoethylphosphonic acid, *Pol. J. Chem.*, *49*: 2001.
177. Petrov, K.A., Chauzov, V.A., and Agafonov, S.V. (1982). α-Alkoxyalkyl and related phosphorus compounds, *Russ. Chem. Rev., Engl. Transl.*, *51*: 234.
178. De Clercq, E., Holy, A., Rosenberg, I., Sakuma, T., Balzarini, J., and Maugdal, P.C. (1986). A novel selective broad-spectrum anti-DNA virus agent, *Nature*, *323*: 464.
179. Holy, A. (1987). Phosphonomethyl analogues of nucleotides and their derivatives, *Nucleos. Nucleot.*, *6*: 147.
180. Wilson, J.R.H. (1986). Synthesis of diethyl alkoxymethylphosphonates *via* Lewis acid promoted regiospecific cleavage of alkoxy-4-chlorophenoxymethanes, *J. Chem. Soc., Perkin Trans. I*: 1065.
181. Epstein, W.W., and Garrosian, M. (1988). High yield

synthesis of α-alkoxyphosphonium salts and α-alkoxyphosphonates, *Phosphorus Sulfur*, *35*: 349.
182. Schaumann, E., and Grabley, F.F. (1977). Darstellung und Eigenschaften von α-Alkoxyalkylphosphonsaureestern, *Ann.*: 88.
183. Holy, A., Rosenberg, I., and Dvorakova, H. (1989). Synthesis of *N*-(2-phosphonylmethoxyethyl) derivatives of heterocyclic bases, *Coll. Czech. Chem. Commun.*, *54*: 2190.
184. Burkhouse, D., and Zimmer, H. (1984). Novel synthesis of 1-alkoxy-1-arylmethanephosphonic acid esters, *Synthesis*: 330.
185. Kim, D.Y., and Oh, D.Y. (1986). A facile synthesis of diethyl 1-alkoxymethanephosphonates, *Synth. Commun.*, *16*: 859.
186. Meuwly, R., and Vasella, A. (1986). Synthesis of 1,2-*cis*-configurated glycosylphosphonates, *Helv. Chim. Acta*, *69*: 25.
187. Dessignes, A., and Vasella, A. (1988). Synthesis of a non-isosteric, isopolar monophosphonate analogue of β-D-fructose 2,6-bisphosphonate, *Carbohydr. Res.*, *174*: 47.
188. Vaghefi, M.M., Bernacki, R.J., Dailey, N.K., Wilson, B.E., and Robins, R.K. (1987). Synthesis of glucopyranosylphosphonate analogues of certain natural nucleoside diphosphate sugars as potential inhibitors of glucosyl transferases, *J. Med. Chem.*, *30*: 1383.
189. Briner, K., and Vasella, A. (1987). Glycosylphosphonates of 2-amino-2-deoxyaldoses, *Helv. Chim. Acta*, *70*: 1341.
190. Holy, A., and Rosenberg, I. (1982). Preparation of 5'-*O*-phosphonomethyl analogues of nucleoside-5'-phosphates, 5'-diphosphates and 5'-triphosphates, *Coll. Czech. Chem. Commun.*, *47*: 3447.
191. Bronson, J.J., Ghazzouli, I., Hitchcock, M.J., Webb, R.R., and Martin, J.C. (1989). Synthesis and antiviral activity of the nucleotide analogue (*S*)-1-[3-hydroxy-2-(phosphonylmethoxy)propyl]cytosine, *J. Med. Chem.*, *32*: 1457.
192. Holy, A., and Rosenberg, I. (1987). Synthesis of 9-(2-phosphonylmethyloxymethyl) adenine and related compounds, *Coll. Czech. Chem. Commun.*, *52*: 2801.
193. Rosenberg, I., and Holy, A. (1987). Synthesis of potential prodrugs and metabolites of 9-(*S*)-(3-hydroxy-2-phosphon-

ylmethoxypropyl)adenine, *Coll. Czech. Chem. Commun.*, *52*: 2792.
194. Holy, A., and Rosenberg, I. (1987). Synthesis of isomeric and enantiomeric *O*-phosphonylmethyl derivatives of 9-(2,3-dihydroxypropyl)adenine, *Coll. Czech. Chem. Commun.*, *52*: 2775.
195. Rosenberg, I., Holy, A., and Masojidkova, M. (1988). Phosphonylmethoxyalkyl and phosphonoalkyl derivatives of adenine, *Coll. Czech. Chem. Commun.*, *53*: 2753.
196. Alberg, D.G., and Bartlett, P.A. (1989). Potent inhibition of 5-enolpyruvylshikimate-3-phosphate synthase by a reaction intermediate analogue, *J. Am. Chem. Soc.*, *111*: 2337.
197. Kluge, A.F., and Cloudsdale, J.S. (1979). Phosphonate reagents for the synthesis of enol ethers and one-carbon homologation to aldehydes, *J. Org. Chem.*, *44*: 4847.
198. Binder, J., and Zbiral, E. (1984). Diethyl (trimethylsilyl-ethoxymethyl)phosphonat - ein neuartiges Reagens fuer variable Aufbaustrategien von α-Hydroxycarbonylverbindungen und Vinylphosphonaten, *Tetrahedron Lett.*, *25*: 4213.
199. Binder, J., and Zbiral, E. (1986). A new procedure for homologation of carbonyl compounds to α-hydroxy carboxylic esters by means of diethyl-(trimethylsilylethoxymethyl)-phosphonate, *Tetrahedron Lett.*, *27*: 5829.
200. Springs, B., and Haake, P. (1976). A one-step synthesis of epoxyphosphonates, *J. Org. Chem.*, *41*: 1165.
201. Texier-Boullet, F., and Foucauld, A. (1980). Reactions en millieu heterogene liquide-solide: reactions de Wittig-Horner et addition du phosphite de diethyle sur les composes carbonyles en presence de KF, 2 H_2O, *Tetrahedron Lett.*, *21*: 2161.
202. Redmore, D. (1971). Heterocyclic systems bearing phosphorus substituents. Synthesis and chemistry, *Chem. Rev.*, *71*: 315.
203. Inokawa, S., Kawata, Y., Yamamoto, K., Kawamoto, H., Yamamoto, H., Takagi, K., and Yamashita, M. (1981). Synthesis of 5(*R*)- or 5(*S*)-5,6-anhydro-1,2-*O*-isopropylidene-5-*C*-phosphinyl-α-D-xylohexofuranose derivatives, *Carbohydr. Res.*, *88*: 341.
204. Shen, Y., Liao, Q., and Qiu, W. (1990). A novel synthesis

of α-fluoroalkylvinyl- or α-fluoroepoxyalkyl-phosphonates, *J. Chem. Soc., Perkin Trans. I*: 695.

205. Oehler, E., El-Badawi, M., and Zbiral, E. (1985). (1,2-Epoxy-3-oxoalkyl)phosphonsaureester als Synthone fuer heterocyclische Carbonylverbindungen, *Ber.*, *118*: 4099.
206. Sturtz, G., and Pondaven-Raphalen, A. (1983). Epoxidation catalytique de phosphonates α,β- et β,γ-ethyleniques a l'aide d'hydroperoxides, *Bull. Soc. Chim. Fr. II*: 125.
207. Mertel, H.E., and Meriwether, H.T. (1982). Synthesis of tritium-labeled fosfomycin, *J. Labelled Comp. Radiopharm, XIX*: 405.
208. Sobolev, V.G., and Ionin, B.I. (1985). Stereospecific epoxidation of 1-alkenephosphonates, *J. Gen. Chem. U.S.S.R., Engl. Transl., 55*: 1455.
209. Giordano, C., and Castaldi, G. (1989). First asymmetric synthesis of enantiomerically pure (1*R*,2*S*)-(-)-(1,2-epoxypropyl)phosphonic acid (fosfomycin), *J. Org. Chem., 54*: 1470.
210. Coutrot, P., and Savignac, P. (1978). A one-step synthesis of diethyl 1,2-epoxyalkanephosphonates, *Synthesis*: 34.
211. Perriot, P., Villieras, J., and Normant, J.F. (1978). Diethyl 1-chloro-1-lithioalkanephosphonates. A general synthesis of diethyl 1,2-epoxyalkanephosphonates and 1-alkoxycarbonyl-1-chloroalkanephosphonates, *Synthesis*: 33.
212. Zhdanov, Y.A., Uzlova, L.A., and Glebova, Z.I. (1980). Esters of α-ketophosphonic acids - synthesis, structure and reactions, *Usp. Khim., 49*: 1730.
213. Zygmunt, J., Kafarski, P., and Mastalerz, P. (1978). Preparation of oxoalkanephosphonic acids, *Synthesis*: 609.
214. Theis, W., and Regitz, M. (1985). Synthesis and reactions of α-diazophosphonates with a conjugated 1,3-diene unit, *Tetrahedron, 41*: 2625.
215. Tam, R.C., Mattocks, K.L., and Tishler, M. (1981). Enol-keto tautomerism of α-ketophosphonates, *Proc. Natl. Acad. Sci. U.S.A., 78*: 3301.
216. Liorber, B.G., Tarzivolova, T.A., Pavlov, V.A., Zykova, T.V., Kisilev, V.V., Tumasheva, N.A., Sliskii, A.Y., and Shagvaleev, T.S. (1987). Phosphorylated β-dicarbonyl compounds, *J. Gen. Chem. U.S.S.R., Engl. Transl., 57*:

465.
217. Szpala, A., Tebby, J.C., and Griffiths, D.V. (1981). Reaction of phosphites with unsaturated acid chlorides: synthesis and reactions of dimethyl but-2-enoyl-phosphonates, *J. Chem. Soc., Perkin Trans. I*: 1363.
218. Britelli, D.R. (1985). A study of the reaction of 2-haloacyl halides with trialkyl phosphites. Synthesis of (2-substituted acyl)phosphonates, *J. Org. Chem., 50*: 1845.
219. Ishihara, T., Maekawa, T., Yamasaki, Y., and Ando, T. (1987). Reaction of F-alkanoic acid chlorides with trialkyl phosphites, *J. Fluorine Chem., 34*: 323.
220. Vasella, A., and Voeffray, R. (1982). Asymmetric synthesis of α-aminophosphonic acids by cycloaddition of *N*-glycosyl-*C*-dialkoxyphosphonyl nitrones, *Helv. Chim. Acta, 65*: 1953.
221. Moskva, V.V., and Mavrin, V.Y. (1987). *O,O*-diethyl formylphosphonate, *Zh. Obshch. Khim. S.S.S.R., 57*: 2793.
222. Talanian, R.V., Brown, N.C., McKenna, C.E., Ye, T.-G., Levy, J.N., and Wright, G.E. (1989). Carbonyldiphosphonate, a selective inhibitor of mammalian DNA polymerase, *Biochemistry, 28*: 8270.
223. Zhdanov, Y.A., Uzlova, L.A., Glebova, Z.I., and Morozova, G.M. (1987). Application of the dimethyl sulfoxide-acetic anhydride system to the oxidation of α-hydroxyphosphonates derived from sugars, *Zh. Obshch. Khim., S.S.S.R., 57*: 1896.
224. Fujii, M., Ozaki, K., Sekine, M., and Hata, T. (1987). A new method for stereospecific and stereoselective generation of deoxyribonucleoside phosphorothioates *via* the acylphosphonate intermediates, *Tetrahedron, 43*: 3395.
225. Dingwall, J.G., Ehrenfreund, J., and Hall, R.G. (1989). Diethoxymethylphosphonites and phosphinates. Intermediates for the synthesis of α-, β-, and γ-aminoalkylphosphonous acids, *Tetrahedron, 45*: 3787.
226. McCleary, P.P., and Tuck, B. (1989). Synthesis of 1-aminoalkylphosphinic acids. Part 2. An alkylation approach, *J. Chem. Soc., Perkin Trans. I*: 1319.
227. Malenko, D.M., and Gololobov, Y.G. (1981). New synthesis of phosphorylated formals, *Zh. Obshch. Khim. S.S.S.R., 51*: 1432.

228. Livantsov, M.V., Proskurnina, M.V., Prischenko, A.A., and Lutsenko, I.F. (1984). Synthesis and properties of phosphorylated formals, *J. Gen. Chem. U.S.S.R., Engl. Transl., 54*: 2237.
229. Nesterov, L.W., and Aleksandrova, N.A. (1985). Arbuzov reaction of dialkyl trialkylsilyl phosphites with ortho esters of carboxylic acids - a new heterolytic chain process in organophosphorus chemistry, *Zh. Obshch. Khim. S.S.S.R., 55*: 223.
230. Livantsov, M.V., Prishchcenko, A.A., and Lutsenko, I.F. (1985). The reaction of hypophosphorous acid with trialkyl formates, *J. Gen. Chem. U.S.S.R., Engl. Transl., 55*: 2195.
231. Ovchinnikov, V.V., Cherezev, S.V., Cherkasov, R.A., and Pudovik, A.N. (1985). The reactivity of cyclic and acyclic P-H compounds in reactions of electrophilic addition to ketene acetals and enamines, *J. Gen. Chem. U.S.S.R., Engl. Transl., 55*: 1109.
232. Sekine, M., Mori, H., and Hata, T. (1982). Protection of phosphonate function by means of ethoxycarbonyl group. a new method for generation of reactive silyl phosphite intermediates of, *Bull. Chem. Soc. Jpn., 55: 239*.
233. Vaghefi, M.M., McKernan, P.A., and Robins, R.K. (1986). Synthesis and antiviral activity of certain nucleoside 5'-phosphonoformate derivatives, *J. Med. Chem., 29*: 1389.
234. Lambert, R.W., Martin, J.A., Thomas, G.J., Duncan, I.B., Hall, M.J., and Heimer, E.P. (1989). Synthesis and antiviral activity of phosphonoacetic and phosphonoformic acid esters of 5-bromo-2'-deoxyuridine and related pyrimidine nucleosides and acylnucleosides, *J. Med. Chem., 32*: 367.
235. Molin, H., Noren, O., and Claesson, A. (1989). Studies of the synthesis of sugar phosphonates related to 3-deoxy-D-manno-2-octulosonic acid (KDO), *Carbohydr. Res., 194*: 209.
236. Iyer, R.P., Phillips, L.R., Biddle, J.A., Thakker, D.R., Egan, W., Aoki, S., and Mitsuya, H. (1989). Studies on acyloalkyl acylphosphonates as potential prodrugs of the antiviral trisodium phosphonoformate (Foscarnet sodium), *Tetrahedron Lett., 30*: 7141.
237. Prishchenko, A.A., Livantsov, M.V, Boganova, N.V., and Lutsenko, I.F. (1988). Synthesis of trialkoxymethylphosphonates, *Zh. Obshch. Khim. S.S.S.R., 58*: 2168.

238. Petrov, K.A., Chauzov, V.A., and Erokhina, T.S. (1974). Aminoalkyl phosphorus compounds, *Russ. Chem. Rev., Engl. Transl., 43*: 984.
239. Redmore, D. (1976). The chemistry of P-C-N systems, *Topics in Phosphorus Chemistry, Vol. 8*, (Griffith, E.J., and Grayson, M., eds.), J. Wiley and Sons, Inc., p.515.
240. Maier, L. (1983). Advances in the chemistry of aminophosphinic acids, *Phosphorus Sulfur, 14*: 295.
241. Kukhar, V.P., and Solodenko, V.A. (1987). Phosphorus analogues of aminocarboxylic acids, *Russ. Chem. Rev., Engl. Transl., 56*: 859.
242. Dhawan, B., and Redmore, D. (1987). Optically active 1-aminoalkylphosphonic acids, *Phosphorus Sulfur, 32*: 119.
243. Kafarski, P., Lejczak, B., and Mastalerz, P. (1984). Phosphonopeptides - Synthesis and biological activity, *Beitraege zur Wirkstofforschung, Vol 25*, (Oehme, P., Loewe, H., Gores, E., and Axt, J., eds.).
244. Engelmann, M., and Pikl, J. (1942). Phosphonic acids derived from organic acylamidomethyl compounds, *U.S. Patent 2,304,156.*
245. Soroka, M. (1989). Comments on the synthesis of aminomethylphosphonic acid, *Synthesis*: 547.
246. Pulwer, M.J., and Balthazor, T.M. (1986). A convenient synthesis of aminomethylphosphonic acid, *Synth. Commun., 16*: 733.
247. Tyka, R., and Haegele, G. (1984). A convenient synthesis of *N*-alkylaminomethanephosphonic and *N*-alkylaminomethanephosphinic acids, *Synthesis*: 218.
248. Tyka, R., Haegele, G., and Peters, J. (1988). *N*-Alkylaminomethyl-*P*-ethyl and *t*-butylphosphinic acid, *Synth. Commun., 18*: 425.
249. Wojtowicz, H., and Mastalerz, P. (1987). 1-Aminoalkyl-(chloromethyl)phosphinic acids and their *N*-tosyl derivatives, *Synthesis*: 477.
250. Kober, R., and Steglich, W. (1983). Untersuchen zur Reaktion von Acylaminobrommalonestern und Acylaminobromessigestern mit Trialkylphosphiten - eine einfache Synthese von 2-Amino-2-(diethoxyphosphoryl)essigsaure-ethylester, *Ann.*: 599.
251. Schmidt, U., Lieberknecht, A., and Wild, J. (1984). Synthesis of dehydroamino acids and amino acids from *N*-acyl-2-(dialkoxyphosphinyl)glycine esters, *Synthesis*: 53.

252. Vo Quang, Y., Carniato, D., Vo Quang, L., and Le Goffic, F. (1985). A highly efficient synthesis of 1-amino-2-chloroethanephosphonates, *Synthesis*: 62.
253. Vo Quang, Y., Oique, S., Carniato, D., Vo Quang, L., and Le Goffic, F. (1988). A new and convenient synthesis of alkyl 1-amino-2-chloroethylphosphinates, *Synth. Commun.*, *18*: 1091.
254. Osapay, G., Szilagyi, I., and Seres, J. (1987). Conversion of amino acids and dipeptides into their phosphonic analogues, *Tetrahedron*, *43*: 2977.
255. Flynn, G.A., Bight, D.W., Bohme, E.H.W., and Metcalf, B.W. (1985). The synthesis of fluorinated aminophosphonic acid inhibitors of alanine racemase, *Tetrahedron Lett.*, *26*: 285.
256. Rachon, J., Schoellkopf, U., and Wintel, T. (1981). 1-Aminoalkylphosphonsauren durch Alkylieren von α-metalliertem Isocyanmethylphosphonsaure-diethylester, *Ann.*: 709.
257. Satoh, H., and Tsuji, T. (1984). 1-Phosphacephalosporin. I. Synthesis of racemic 7-substituted-1-phosphadethia-3-cephem-1-oxides, *Tetrahedron Lett.*, *25*: 1733.
258. Satoh, H., and Tsuji, T. (1984) 1-Phosphacephalosporin. II. Synthesis of optically active 7-substituted-1-phosphadethia-3-cephem-1-oxides, *Tetrahedron Lett.*, *25*: 1737.
259. Campbell, M.M., Carruthers, N.I., and Mickel, S.J. (1982). Aminophosphonic and aminophosphinic analogues of aspartic acid, *Tetrahedron*, *38*: 2513.
260. Shono, T., Matsumura, Y., and Tsubata, K. (1981). A new carbon-phosphorus bond forming reaction and synthesis of aminoalkylphosphonic acid derivatives, *Tetrahedron Lett.*, *22*: 3249.
261. Ku, B., and Oh, D.Y. (1988). Facile synthesis of α-phosphorylated α-amino acids, *Tetrahedron Lett.*, *29*: 4465.
262. Seebach, D., Charczuk, R., Gerber, C., and Renaud, P. (1989). Elektrochemische Decarboxylierung von L-Threonin- und Oligopeptid - Derivaten unter Bildung von *N*-Acyl-*N,O*-acetalen: Herstellung von Oligopeptiden mit Carboxamid- oder Phosphonat-*C*-Terminus, *Helv. Chim. Acta*, *72*: 401.
263. Burkhouse, D.W., and Zimmer, H. (1988). New synthetic methodology for the preparation of substituted 1-aryl-1-pyridylaminomethanephosphonic acid esters, *Synth. Commun.*,

18: 1437.
264. Tyka, R., and Haegele, G. (1989). Synthesis of aminobenzylphosphonous acids *via* direct amidoalkylation of hypophosphorous acid, *Phosphorus Sulfur*, *44*: 103.
265. Wieczorek, J.S., and Gancarz, R. (1976). Aminophosphonic acid derivatives of fluorene, *Pol. J. Chem.*, *50*: 2171.
266. Martinov, I.V., Aksinenko, A.Y., Chekhlov, A.N., and Sokolov, W.W. (1989). The reaction of hexafluoroacetoneimine with P-H acids, *Zh. Obshch. Khim. S.S.S.R.*, *59*: 809.
267. Gancarz, R., and Wieczorek, J.S. (1977). A useful method for the preparation of 1-aminoalkanephosphonic acids, *Synthesis*: 625.
268. Kudzin, Z.H., and Majchrzak, M.W. (1989). 1-Aminoalkanephosphonic acids. Addition of diethyl phosphite to *N*-diisobutylaluminio-aldimines, *J. Organomet. Chem.*, *376*: 245.
269. Petrillo, E.W., and Spitzmiller, E.R. (1979). Synthesis of 2-phosphonopyrrolidine and its substitution for proline as an inhibitor of angiotensin-converting enzyme, *Tetrahedron Lett.*: 4929.
270. Issleib, K., and Moegelin, W. (1986). *N*-(Phosphinomethyl)aminosauren und *N*-Bis(Phosphinomethyl)aminosauren bzw. deren Ester, *Synth. React. Inorg. Met.-Org. Chem.*, *16*: 645.
271. Issleib, K., Balszuweit, A., Mueller, K., and Moegelin, W. (1980). *N*-Alkyl-aminomethanphosphonsaure-dialkylester *via* Hexahydro-s-triazine, *Z. anorg. allg. Chem.*, *469*: 109.
272. Solodenko, V.A., and Kukhar', V.P. (1987). Synthesis of α-phosphonopiperidine, *Zh. Obshch. Khim. S.S.S.R.*, *57*: 2392.
273. Barton, D.H.R., Motherwell, W.B., and Zard, S. (1982). A simple construction of the corticosteroid side chain from 17-keto steroids, *Nouveau J. Chim.*, *6*: 295.
274. Redmore, D. (1978). Chemistry of phosphorous acid: new routes to phosphonic acids and phosphate esters, *J. Org. Chem.*, *43*: 992.
275. Smith, S.J., Zimmer, H., Fluck, E., and Fischer, P. (1988). Substituent effects on the ^{31}P, ^{13}C, and ^{1}H NMR chemical shifts of substituted diphenyl 1-phenylamino-1-phenylmethanephosphonates and their anions, *Phosphorus Sulfur*, *35*: 106.

276. Hoppe, I., Schoellkopf, U., Nieger, M., and Egert, E. (1985). Asymmetric addition of a chiral cyclic phosphite to a cyclic imine - synthesis of phosphonic acid analogues of D- and L-penicillamine, *Angew. Chem., Int. Ed. Engl.*, *24*: 1067.
277. Drauz, K., Koban, H.C., Martens, J., and Schwarze, W. (1985). Phosphonic and phosphinic analogues of penicillamine, *Ann.*: 448.
278. Tyka, R. (1970). Novel synthesis of α-aminophosphonic acids, *Tetrahedron Lett.*: 677.
279. Hakimelahi, G.H., and Just, G. (1980). Two simple methods for the synthesis of trialkyl α-aminophosphonoacetates. Trifluoromethanesulfonyl azide as an azide transfer agent, *Synth. Commun.*, *10*: 429.
280. Lukszo, J., Kowalik, J., and Mastalerz, P. (1978). Advantages of using di(*p*-methylbenzyl) hydrogen phosphite in syntheses of aminophosphonates from aldimines, *Chem. Lett.*: 1103.
281. Soroka, M., and Zygmunt, J. (1988). Tritylamine (triphenylmethylamine) in organic synthesis. I. The synthesis of *N*-triphenylmethyl)alkylamines, 1-(triphenylmethylamino)alkylphosphonic esters and 1-aminoalkylphosphonic acids and esters, *Synthesis*: 370.
282. Tarusova, I.B., Novikova, E.S., Prishchenko, A.A., Yakovleva, G.M., and Khomutov, R.M. (1982). Synthesis of diphosphate analogues based on the esters of methylenediphosphonic acid, *Izv. Akad. Nauk S.S.S.R.*: 402.
283. Issleib, K., Doepfer, K.-P., and Balszuweit, A. (1983). Aminodiphosphonsauren und Diaminodiphosphonsauren - Synthese und Transaminierungsverhalten, *Phosphorus Sulfur*, *14*: 171.
284. Assche, I.V. (1990). Diaminopimelic acid as lead in drug design, Ph.D. Thesis, Universiteit Antverpen.
285. Baylis, E.K., Campbell, C.D., and Dingwall, J.G. (1984). 1-Aminoalkylphosphonous acids. Part I. Isosteres of the protein amino acids, *J. Chem. Soc., Perkin Trans. I*: 2845.
286. Cates, L.A., Lee, V.-S., Lehmann, J., Coyle, J.T., and Ferkany, J.W. (1984). Excitatory amino acid receptor interactions of a novel α-phosphinic acid analogue of α-methylaspartic acid, *J. Pharm. Sci.*, *73*: 1550.
287. Grobelny, D. (1987). A new synthetic route to 1-aminoalkyl-

phosphonous acids, *Synthesis*: 942.
288. Varaprasad, I.V.S., and Jaiswal, D.K. (1982). A facile synthesis of *O,O*-dialkyl-α-(*p*-toluenesulfonamido)benzylphosphonates, *Indian J. Chem.*, *21B*: 525.
289. Kotynski, A., and Stec, W.J. (1978). Synthesis of enantiomers of 1-amino-2-phenylethylphosphonic acid, *J. Chem. Res. (S)*: 41.
290. Tronchet, J.M.J., Winter-Mihaly, E., Rupp, J., Barbalat-Rey, F., and Geoffroy, M. (1985). α-Deoxy-α-hydroxyamino sugar phosphonates and the corresponding nitroxide free radicals, *Carbohydr. Res.*, *136*: 375.
291. Huber, R., and Vasella, A. (1990). The kinetic anomeric effect. Additions of nucleophiles and of dipolarophiles to *N*-glycosylnitrones and to *N*-pseudoglycosylnitrones, *Tetrahedron*, *46*: 33.
292. Huber, R., Knierzinger, A., Obrecht, J.-P., and Vasella, A. (1985). Nucleophilic additions to *N*-glycosylnitrones. Asymmetric synthesis of α-aminophosphonic acids, *Helv. Chim. Acta*, *68*: 1730.
293. Huber, R., and Vasella, A. (1987). Nucleophilic additions to *N*-glycosylnitrones. Asymmetric synthesis of *N*-hydroxy-α-aminophosphonic and α-aminophosphonic acids, *Helv. Chim. Acta*, *70*: 1461.
294. Bernet, B., Krawczyk, E., and Vasella, A. (1985). Diastereoseletivity in the reaction of *N*-glycosylnitrones: 1,3-dipolar cycloaddition and addition of the phosphite anion, *Helv. Chim. Acta*, *68*: 2299.
295. Levin, I.A., Baleeva, T.G., Gosman, I.P., and Goldfarb, E.I. (1985). Homolytic reactions of organophosphorus compounds. Synthesis, stability and homolysis of arylazo- and arylazoalkylphosphonates, *Zh. Obshch. Khim. S.S.S.R.*, *55*: 1290.
296. Diel, P., and Maier, L. (1988). Herstellung, Eigenschaften und biologische Wirkung von Hydrazinomethylphosphon- und Phosphinsauren und Derivaten, *Phosphorus Sulfur*, *36*: 85.
297. Diel, P., and Maier, L. (1988). Herstellung, Eigenschaften und biologische Wirkung von *N*-Aminoglyphosate und Azaglyphosate, *Phosphorus Sulfur*, *39*: 159.
298. Nifantev, E.E., Zyk, N.V., and Koroteev, M.P. (1975).

The reaction of phosphorous acid diesters with azines, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *45*: 1424.

299. Rachon, J., and Wasielewski, C. (1976). Synthesis of α-aminophosphonic and α-hydrazinophosphonic acids from aliphatic aldazines, *Pol. J. Chem.*, *50*: 477.
300. Osipova, M.P., Lukin, P.M., and Kukhtin, V.A. (1982). α-Hydroxylaminophosphonates, *Zh. Obshch. Khim. S.S.S.R.*, *52*: 449.
301. Elhaddadi, M., Jacquier, R., Petrus, F., and Petrus, C. (1989). A new and convenient synthesis of 1-benzylaminoalkylphosphonic acids from oximes, *Phosphorus Sulfur*, *45*: 161.
302. Gruszecka, E., Soroka, M., and Mastalerz, P. (1979). Phosphonic analogues of α-methylaspartic and α-methylglutamic acids, *Pol. J. Chem.*, *53*: 2327.
303. Delgado, R., Siegfried, L.C., and Kaden, T.A. (1990). Protonation studies and complexation properties of tetraazamacrocyclic methylenephosphonates with earth-alkali ions, *Helv. Chim. Acta*, *73*: 140.
304. Redmore, D., and Dhawan, B. (1983). Novel unsymmetrical *N,N*-bis(methylene)bisphosphonic acids of α,ω-diamines, *Phosphorus Sulfur*, *16*: 233.
305. Maier, L., and Diel, P.J. (1989). Some reactions of *O*-ethyl-2-chloroethylphosphonite, *Phosphorus Sulfur*, *45*: 165.
306. Dhawan, B., and Redmore, B. (1989). Preparation of bis-(methylphosphinic acids) from primary amines, *J. Chem. Res. (S)*: 34.
307. Kapura, A.A., and Shermergorn, I.M. (1989). Aminomethylation of hypophosphorous acid with higher primary amines and formaldehyde, *Zh. Obshch. Khim. S.S.S.R.*, *59*: 1283.
308. Charandabi, M.R.M.D., Ettel, M.L., Kaushik, M.P., Huffman, J.H., and Morse, K.W. (1989). Characterization and properties of some dialkyl 1-(*N,N*-dialkylamino)alkylphosphonates, *Phosphorus Sulfur*, *44*: 223.
309. Kametani, T., Suzuki, Y., Kigasawa, K., Hiiragi, M., Wakisaka, K., Sugi, H., Tanigawa, K., Fukawa, K., Irino, O., Saita, O., and Yamabe, S. (1982). Synthesis and biological studies on phosphonopeptides having alkyl-, phenyl and heterocyclic substituents, *Heterocycles*, *18*: 295.
310. Kotovich, B.P. (1987). On the reaction of dialkyl phosphon-

ates with ketones and secondary amines, *Zh. Obshch. Khim. S.S.S.R.*, *57*: 1416.
311. Dzhembaev, B.Z., Abiurov, B.D., Zaporozhskaya, N.I., and Mindaev, B.U. (1989). On the reaction of ethylenediamine and dimethyl phosphonate with ketones derived from piperidine, *Zh. Obshch. Khim. S.S.S.R.*, *59*: 77.
312. Birum, G.H. (1974). Urylenediphosphonates. A general method for the synthesis of α-ureidophosphonates and related structures, *J. Org. Chem.*, *39*: 209.
313. Huber, J.W., and Middlebrooks, M. (1977). Synthesis of aminoalkylphosphonic acids from ureidoalkanephosphonates, *Synthesis*: 883.
314. Tam, C.C., Mattocks, K.L., and Tischler, M. (1982). Synthesis of phosphomethionine and related compounds, *Synthesis*: 188.
315. Oshikawa, T., and Yamashita, M. (1989). Preparations of optically active 1-aminoalkylphosphonic acids from chiral carbamates and chiral ureas, *Bull. Chem. Soc. Jpn.*, *62*: 3177.
316. Huber, J.W., and Gilmore, W.F. (1979). Optically active α-aminophosphonic acids from ureidophosphonates, *Tetrahedron Lett.*: 3049.
317. Oleksyszyn, J., Tyka, R., and Mastalerz, P. (1977). Guanidinoalkylphosphonic acids, *Synthesis*: 571.
318. Oleksyszyn, J., Tyka, R., and Mastalerz, P. (1978). Direct synthesis of 1-aminoalkylphosphonic and -phosphinic acids from phosphorus trichloride or dichlorophosphines, *Synthesis*: 479.
319. Oleksyszyn, J., Gruszecka, E., Kafarski, P., and Mastalerz, P. (1982). New phosphonic analogues of aspartic and glutamic acid by aminoalkylation of P(III) chlorides, *Monatsh. Chem.*, *113*: 59.
320. Sosnovsky, G., Lukszo, J., Gravela, E., and Zuretti, M.F. (1985). Phosphonic and phosphinic analogues of ornithine, *J. Med. Chem.*, *28*: 1350.
321. Diel, P., and Maier, L. (1988). Herstellung und Eigenschaften von α-amino-ω-carboxyphosphon- und phosphinsauren, *Phosphorus Sulfur*, *29*: 201.
322. Yuan, C., and Wang, G. (1990). A convenient synthesis of alkyl hydrogen α-benzyloxycarbonylaminobenzylphosphon-

ates, *Synthesis*: 256.
323. Oleksyszyn, J., Subotkowska, L., and Mastalerz, P. (1979). Diphenyl 1-aminoalkylphosphonates, *Synthesis*: 985.
324. Vo Quang, Y., Carniato, D., Vo Quang, L., Lacoste, A.-M., Neuzil, E., and Le Goffic, F. (1986). (1-Amino-2-propenyl)phosphonic acid, an inhibitor of alanine racemase and D-alanine:D-alanine ligase, *J. Med. Chem.*, *29*: 579.
325. Yuan, C., and Qi, Y. (1986). A facile synthesis of α-amino-substituted benzylphosphonic and -phosphinic acids by use of thiophosphoramide, *Synthesis*: 821.
326. Yuan, C., Wang, G., and Chen, S. (1990). A facile and direct route to dialkyl 1-(benzyloxycarbonylamino)alkylphosphonates, *Synthesis*: 522.
327. Soroka, M. (1990). A revised mechanism of the reaction of phosphorus trichloride, amides and aldehydes or ketones in acetic acid (Oleksyszyn reaction), *Ann.*: 331.
328. Colvin, E.W., Kirby, G.W., and Wilson, A.C. (1982). *O*-(Diphenylphosphinyl)hydroxylamine: a new reagent for electrophilic *C*-amination, *Tetrahedron Lett.*, *23*: 3835.
329. Shiraki, C., Saito, H., Takahashi, K., Urakawa, C., and Hirata, T. (1988). Preparation of amino(diethoxyphosphoryl)acetic esters. Catalytic hydrogenation of diazo compounds to amines, *Synthesis*: 399.
330. Cameron, D.G., Hudson, H.R., Ojo, I.A.O., and Pianka, M. (1988). *N*-(ω-Guanidinoalkyl)aminoalkanephosphonic acids and their aminophosphonic precursors, *Phosphorus Sulfur*, *40*: 183.
331. Zygmunt, J., and Mastalerz, P. (1981). Synthesis of 1-amino-2-hydroxyethanephosphonic acid, the phosphonic analogue of serine, *Pol. J. Chem.*, *55*: 1981.
332. Gross, H., Beisert, S., and Costisella, B. (1981). Derivatives of pyrrolomethanephosphonic acid and *N*-vinylpyrroles, *J. prakt. Chem.*, *323*: 877.
333. Okada, Y., Iguchi, S., Mimura, M., and Yagyu, M. (1980). Synthesis of *N*-L- and D-alanyl-1-aminoethylphosphonic acid, *Chem. Pharm. Bull.*, *28*: 1320.
334. Erion, M.D., and Walsh, C.T. (1987). 1-Aminocyclopropanephosphonate: time-dependent inactivation of 1-aminocyclopropanecarboxylate deaminase, *Biochemistry*, *26*: 3417.
335. Chen, S.F., Kumar, S.D., and Tischler, M. (1983). The

synthesis of D,L-phosphonotryptophan, *Tetrahedron Lett.*, *24*: 5461.
336. Kowalik, J., Kupczyk-Subotkowska, L., and Mastalerz, P. (1981). Preparation of dialkyl 1-aminoalkylphosphonates by reduction of dialkyl 1-hydroxyiminoalkylphosphonates with zinc in formic acid, *Synthesis*: 57.
337. Subotkowski, W., Kowalik, J., Tyka, R., and Mastalerz, P. (1981). The phosphonic analogues of tryptophan, *Pol. J. Chem.*, *55*: 853.
338. Zygmunt, J., and Mastalerz, P. (1981). 1-Amino-2-mercaptoethanephosphonic acid, the phosphonic analogue of cysteine, *Pol. J. Chem.*, *55*: 713.
339. Gibson, D., and Karaman, R. (1989). Metal complexes of α-hydroxyiminophosphonic acid derivatives, *Inorg. Chem.*, *28*: 1928.
340. Soroka, M., and Mastalerz, P. (1974). On the cleavage of P-C bond in 1-oxophosphonates, *Zh. Obshch. Khim. S.S.S.R.*, *44*: 463.
341. Flynn, G.A., and Giroux, E.L. (1986). The synthesis of an aminophosphonic acid converting enzyme inhibitor, *Tetrahedron Lett.*, *27*: 1757.
342. Kudzin, Z.H., and Stec, W. (1980). Synthesis of *O,O*-dialkyl 1-aminoalkylphosphonates, *Synthesis*: 1028.
343. Russell, G., Ros, F., Hershberger, J., and Tashtoush, H. (1982). Participation of dialkyl phosphites and thiophosphites in aliphatic $S_{RN}1$ reactions, *J. Org. Chem.*, *47*: 1480.
344. Kandil, A.A., Porter T.M., and Slessor, K.N. (1987). One-step synthesis of stabilized phosphonates, *Synthesis*: 411.
345. Subotkowska, W., Tyka, R., and Mastalerz, P. (1980). Phosphonic analogue of proline, *Pol. J. Chem.*, *54*: 503.
346. Anderson, D.W., Campbell, M.M., Malik, M., Prashad, M., and Wightman, R.W. (1990). Phosphonopeptides and 3-aminophosphononocardinic acid, *Tetrahedron Lett.*, *31*: 1759.
347. Shiozaki, M., and Masuko, H. (1987). A synthesis of optically active 4-diethoxyphosphinyl-3-(1-hydroxyethyl)-2-azetidinone, *Bull. Chem. Soc. Jpn.*, *60*: 645.
348. Lejczak, B., Kafarski, P., Soroka, M., and Mastalerz, P. (1984). Synthesis of the phosphonic analogue of serine, *Synthesis*: 577.

349. Kafarski, P., and Lejczak, B. (1989). Mixed carboxylic-carbonic anhydride method in phosphonopeptide synthesis, *Tetrahedron*, *45*: 7387.
350. Schoellkopf, U., and Schuetze, R. (1987). Asymmetrische Synthese von (*S*)-(1-Aminoalkyl)phosphonsaure-diethylestern unter Verwendung von (+)-Campher als chiralem Hilfreagens, *Ann.*: 45.
351. Jacquier, R., Ouazzani, F., Roumestand, M.-L., and Viallefont, P. (1988). Synthesis of enantiomerically pure aminophosphonic acids, *Phosphorus Sulfur*, *36*: 73.
352. Bartlett, P.A., and McLaren, K.L. (1987). Diastereoselectivity in the alkylation of chiral 2-aminomethyl-1,3,2-dioxaphosphorinane 2-oxides, *Phosphorus Sulfur*, *33*: 1.
353. Sting, M., and Steglich, W. (1990). Synthese optisch activer 1-aminoalkylphosphonsauren der (*S*) und (*R*)-Reihe mit Hilfe von (-) Ephedrin als Auxiliar, *Synthesis*: 132.
354. Diel, P.J., and Maier, L. (1984). Herstellung und Eigenschaften von *N*-Phosphonomethylglycin Derivaten, *Phosphorus Sulfur*, *20*: 313.
355. Genet, J.P., Uziel, J., Touzin, A.M., and Juge, S. (1990). Synthesis of diethyl (1-aminoalkyl)phosphonates under solid-liquid phase transfer catalysis conditions, *Synthesis*: 41.
356. Genet, J.P., Uziel, J., and Juge, S. (1988). Synthesis of α-aminophosphonic acids by Pd(0) alkylation of diethyl aminomethylphosphonate Schiff bases, *Tetrahedron Lett.*, *29*: 4559.
357. Schrader, T., Kober, R., and Steglich, W. (1986). Syntheses von 1-Aminophosphonsaure-derivaten ueber Acyliminophosphonsaure-Ester, *Synthesis*: 372.
358. Schrader, T., and Steglich, W. (1989). Synthese von α-Aminophosphonsauren und α-Aminophosphinsauren ausgehend von den entsprechenden *N*-Acylimino-Derivaten, *Synthesis*: 97.
359. Schoellkopf, U., and Wintel, T. (1984). Synthesis of 1-amino-2-hydroxyalkanephosphonic acids (phosphonic analogues of serine) *via* diethyl 2-oxazoline-4-phosphonates, *Synthesis*: 1033.
360. Sawamura, M., Ito, Y., and Hayashi, T. (1989). Asymmetric synthesis of (1-aminoalkyl)phosphinic acids *via* asymmetric aldol reaction of (isocyanomethyl)phosphonates, catalyzed by a chiral ferrocenylphosphine-gold(I) complex,

Tetrahedron Lett., *30*: 2247.
361. Togni, A., and Pastor, S.D. (1989). Enantioselective synthesis of β-hydroxy-α-aminophosphonic acid precursors, *Tetrahedron Lett.*, *30*: 1071.
362. Schoellkopf, U., Hoppe, I., and Thiele, A. (1985). Enantioselective synthesis of L-(1-aminoethyl)phosphonic acid by asymmetric catalytic hydrogenation, *Ann.*: 555.
363. Ahlbrecht, H., and Farnung, W. (1984). Erzeugung und Reaktivitaet von 1-(Diethoxyphosphoryl)-1-(dimethylamino)-allyl-Anionen, *Ber.*, *117*: 1.
364. Merrett, J.D., Spurden, W.C., Thomas, W.A., Tong, B.P., and Whitcombe, I.W.A. (1988). The synthesis and rotational isomerism of 1-amino-2-imidazol-4-ylethylphosphonic acid (phosphonohistidine, HisP) and 1-amino-2-imidazol-2-ylethylphosphonic acid (phosphonoisohistidine, isoHisP), *J. Chem. Soc., Perkin Trans. I*: 61.
365. Bartlett, P.A., and Lamden, L.A. (1986). Inhibition of chymotrypsin by phosphonate and phosphonamidate peptide analogues, *Bioorg. Chem.*, *14*: 356.
366. Bartlett, P.A., and Acher, F. (1986). Synthesis of phosphonamides and phosphinamides related to pepstatin, *Bull. Soc. Chim. Fr.*: 771.
367. Giannounis, P.P., and Bartlett, P.A. (1987). Phosphorus amino acid analogues as inhibitors of leucine aminopeptidase, *J. Med. Chem.*, *30*: 1603.
368. Bartlett, P.A., and Kezer, W.B. (1984). Phosphinic acid dipeptide analogues: Potent, slow-binding inhibitors of aspartic peptidases, *J. Am. Chem. Soc.*, *106*: 4282.
369. Parsons, W.H., Patchett, A.A., Bull, H.G., Schoen, W.R., Taub, D., Davidson, J., Combs, P.L., Springer, J.P., Gadebusch, H., Weissberger, B., Valiant, M.E., Mellin, T.N., and Busch, R.D. (1988). Phosphinic acid inhibitors of D-alanyl-D-alanine ligase, *J. Med. Chem.*, *31*: 1772.
370. Seyferth, D., Marmor, R.S., and Hilbert, P. (1971). Some reactions of dimethylphosphono-substituted diazoalkanes, *J. Org. Chem.*, *36*: 1379.
371. Khokhlov, P.S., Mikityuk, A.D., Kashemirov, B.A., and Kukalenko, S.S. (1985). Synthesis of α-diazo-α-phosphorylacetamides, *Zh. Obshch.Khim. S.S.S.R.*, *55*: 2254.
372. Regitz, M., and Maas, G. (1986). *Diazo compounds*, Academic Press, Inc., New York.

373. Rosini, G., Baccolini, G., and Cacchi, S. (1975). Reactions of 1-oxoalkanephosphonate tosylhydrazones with sodium borohydride: A new synthesis of dimethyl alkanephosphonates and dimethyl 1-diazoalkanephosphonates, *Synthesis*: 44.
374. Regitz, M., and Martin, R. (1985). *tert*-Butylammoniumsalze von α-Diazophosphin- und α-diazophosphosauren, *Tetrahedron*, *41*: 819.
375. Bartlett, P.A., Carruthers, N.I., Winter, B.M., and Long, K.P. (1982). α-Diazophosphonic acids as potential photoaffinity labeling reagents: Synthesis, stability and photochemistry, *J. Org. Chem.*, *47*: 1284.
376. Andrus, A., Christensen, B.G., and Heck, J.W. (1984). Synthesis of 3-methylphosphonylthienamycin and related 3-phosphonyl carbapenems, *Tetrahedron Lett.*, *25*: 595.
377. Fink, J., and Regitz, M. (1985). Electrophilic diazoalkane substitution, *Synthesis*: 569.
378. Arenz, S., Boehsar, M., and Regitz, M. (1986). Dibenzo [a,c]cyclooctene und Dibenzo[a,c]heptafulvene aus 5-(Diazomethyl)-5-H-dibenzo[a,c]cycloheptenen, *Ber.*, *119*: 1755.
379. Regitz, M., and Schoder, W. (1985). Amino- und Iminomethylierung von Diazomethyl Verbindungen, *Synthesis*: 178.
380. Soroka, M., and Mastalerz, P. (1976). The synthesis of phosphonic and phosphinic analogues of aspartic acid and asparagine, *Pol. J. Chem.*, *50*: 661.

CHAPTER 8

SOME ASPECTS OF H-PHOSPHONATE CHEMISTRY

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I. Introduction

Chemical synthesis of phosphorus-containing natural products *via* H-phosphonate intermediates has in the last few years begun to emerge as an alternative methodology to the well established phosphite and phosphate approaches. While the latter one deals with phosphorus(V) compounds (oxidation state +5), the phosphite and H-phosphonate methodologies utilize phosphorus(III) compounds (oxidation state +3).

The parent compound for the phosphorus(III) derivatives (oxidation state +3) is phosphonic acid (phosphorous acid, H_3PO_3). It is a dibasic acid ($pK_1 = 1.5$ and $pK_2 = 6.8$),[1] slightly stronger than phosphoric acid ($pK_1 = 2.1$, $pK_2 = 7.1$, and $pK_3 \sim 12$). A characteristic feature of phosphonic acid is that it may exist in two tautomeric forms, the phosphite and the phosphonate forms, with the latter being the predominant one. The important structural elements of the phosphonate form, *i.e.* presence of the P-H bond, lack of a lone electron pair on phosphorus, and a tetracoordinated tetrahedral structure, are preserved in simple salts of phosphonic acids as well as in its mono- and diesters. Since triesters of phosphorous acid (phosphite triesters) and other tricoordinated derivatives (*e.g.* phosphoramidites) lack these characteristic features (no P-H bonds, a lone pair of electrons on the phosphorus atom, pyramidal structures), they are usually treated as a separate class of compounds, and they will not be discussed in this review.

The structure of phosphonic acid and its esters (phosphonate *vs.* phosphite form, see Fig. 1) was a rather controversial issue in the early days of phosphorus chemistry. Nowadays, the following lines of evidence are commonly accepted as indicative of the phosphonate structure [(1a), (2a), (3a)][2] of these compounds: (i) a phosphonic acid is dibasic and forms two series of salts; (ii) IR spectra of H-phosphonate diesters show absorptions at 2380-2450

cm^{-1} (ν_{P-H}) and 1260-1300 cm^{-1} ($\nu_{P=O}$) and no absorption characteristic for the P-O-H bonds; (iii) tetrahedral structure of some phosphonate anions in the solid state, as judged from X-ray analysis; (iv) ^{1}H and ^{31}P NMR spectra in solution show splitting patterns of signals characteristic for hydrogen directly bound to phosphorus ($^{1}J_{PH}$ = 490-760 Hz), and ^{31}P chemical shift values fall in the region characteristic for tetracoordinated species (10 to 0 ppm, relative to phosphoric acid).

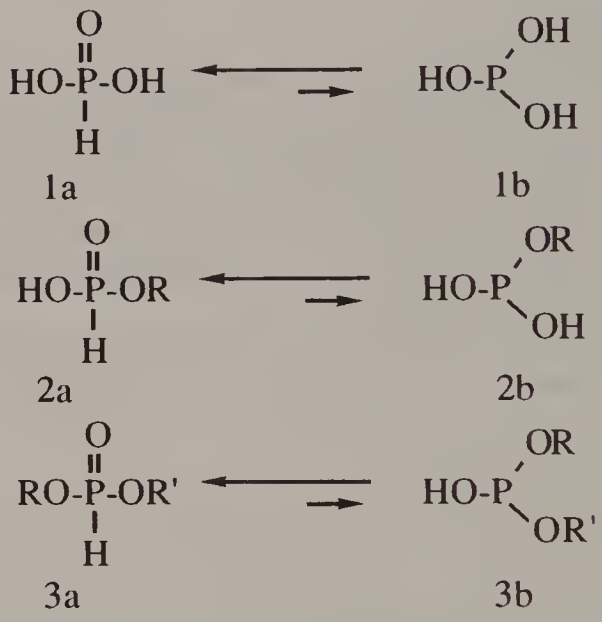


Figure 1 - Equilibria of phosphonic acid and its esters

Even though a true equilibrium apparently exists between the phosphite and phosphonate forms (as one may infer from various chemical reactions[3] and from kinetic studies[4]) the amount of the former one is believed to be below level of any spectroscopic methods used. However, from some thermodynamic data it was possible to calculate the equilibrium constants for the tautomerization.[1] They were found to be ~10^{10}, 10^{9}, and 10^{7} in favour of the phosphonate form for phosphonic acid, ethyl H-phosphonate, and diethyl H-phosphonate respectively.[1] Values of pK_a for dissociation of the P-H bonds have also been calculated from thermodynamic data.[1] For diethyl H-phosphonate, monoethyl H-phosphonate, and for phosphonic acid the estimated values are ~13, 26, and 38 respectively.

Though H-phosphonate esters have been known for a rather long time and also used occasionally in natural product chemistry,[5,6] it is only recently that their chemical properties have begun to be appreciated[7] and explored.[8-12] Most of current chemical applications of H-phosphonate derivatives make use of the favourable phosphite-phosphonate equilibrium. Due to the preponderance of the phosphonate form, the H-phosphonate monoesters are stable and resistant to oxidation in solution, but upon activation with various condensing agents, they become at least as reactive as tricoordinated phosphorus(III) derivatives. The H-phosphonate diesters, also due to their existence in the phosphonate form, are stable, neutral compounds, subject to purification on silica gel. Although they are more resistant toward oxidation than phosphite triesters, it is possible to convert them under mild conditions into phosphate esters or into various phosphate analogues containing P-N, P-S, and P-Se bonds.

In this review chemical properties and synthetic methods for the preparation of H-phosphonate monoesters, diesters, and their thio analogues will be discussed. The main emphasis has been put on H-phosphonate esters derived from natural products (nucleosides, sugars, lipids), and only occasionally will we refer to simple alkyl esters of phosphonic acid.

Since the nomenclature of phosphonic acid derivatives can be confusing, some comments seem appropriate. In older literature chemical names did not make any distinction between the phosphite and phosphonate forms. For example, names like dialkyl phosphite and dialkyl phosphonate, as well as phosphorous acid and phosphonic acid have been used interchangably. Since H_3PO_3 and its mono- and diesters do exist in the phosphonate forms, they should correctly be called phosphonic acid and phosphonate esters, respectively. For the sake of clarity and to avoid confusion with compounds containing P-C bonds, it is in our opinion advisable to add also the prefix H- to the name "phosphonate", to emphasize the presence of a P-H bond. Thus, we will refer throughout this review to the mono- and diesters of phosphonic acid as the H-phosphonate mono- and H-phosphonate diesters. The name "phosphite" will be reserved for the tricoordinated species derived from the phosphite form of phosphonic acid (*e.g.* triethyl phosphite).

II. Synthesis of H-Phosphonate Monoesters

Alkyl H-phosphonate monoesters can conveniently be prepared by ammonolysis of the corresponding diesters. The

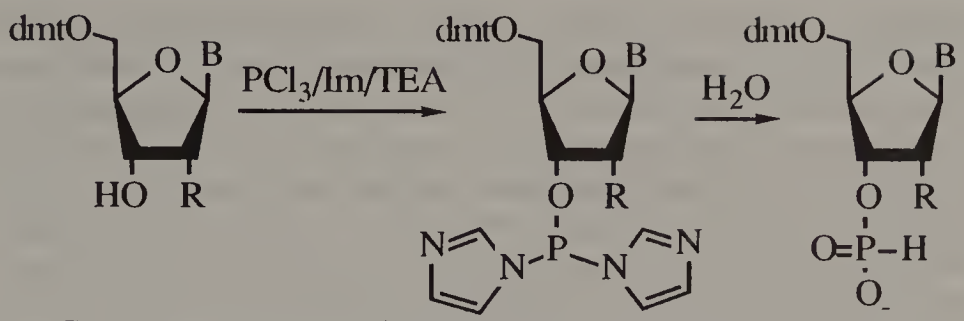
reaction is fast and affords alkyl, benzyl, and phenyl H-phosphonate monoesters as crystalline materials in high yield.[13] Alkaline[14] (NaOH) or acidic[15] (H_2SO_4) hydrolysis seems to be less suitable for that purpose. Some symmetrical diesters (simple alkyl and benzyl) also undergo fast dealkylation to produce the monoesters. As dealkylating reagents, triethylamine,[15] thiourea,[16] or sodium iodide[17] are used. Though H-phosphonate monoesters are also formed in the reaction of phosphorus chloride with alcohols, followed by hydrolysis, the yields are usually low.[18]

The growing interest in hydrogenphosphonates as useful intermediates in the synthesis of phosphorus-containing compounds caused a high demand for a reliable and economical method for the preparation of H-phosphonate monoesters derived from natural products. Several methods have been reported in the literature for that purpose. They can be divided into four major groups: (i) esterification of phosphonic acid in the presence of various condensing agents;[19-22] (ii) reactions of phosphorus trichloride with alcohols;[6,23] (iii) transesterification of trialkyl or triaryl phosphites with appropriate hydroxylic components;[24] (iv) reactions of tris(dimethylamino)phosphine with alcohols.[25]

Most of these methods, unfortunately, suffer from variable yields and incompatibility with common protecting groups used in natural product chemistry. In some instances the H-phosphonate monoesters have also been treated as intermediates on the way to phosphate esters, and thus, they have not been isolated.

An efficient and rather general method, applicable for the preparation of H-phosphonate monoesters derived from natural products, is shown in Fig. 2. It is based on the PCl_3/imidazole/triethylamine[8] reagent system, and gives consistently high yields (75-90%) of the protected deoxy- and ribonucleoside 3'-H-phosphonates,[9,36] glycosyl H-phosphonates,[26] and glycero-3-H-phosphonates.[27]

A similar reagent system, in which imidazole has been replaced by 1,2,4-triazole, was also reported[12] for the preparation of deoxynucleoside 3'-H-phosphonates. Although the reagents give comparable yields of H-phosphonate monoesters, there is, in principle, higher risk of formation of the symmetrical H-phosphonate diesters with the triazole containing reagent, due to its slightly higher reactivity.



R = H and B = thymine, cytosine, adenine, guanine
R = O-TBDMS and B = uracil, cytosine, adenine, guanine

Figure 2 - Formation of H-phosphonate monoesters

Efficient methods for the synthesis of H-phosphonate monoesters has been reported by van Boom, *et al.*[28] They make use of monofunctional phosphitylating reagents, bis(*N*,*N*-di-iso-propylamino)chlorophosphine (4) and 2-chloro-5,6-benzo-1,3,2-dioxaphosphorin-4-one (5) (salicylchlorophosphite).[29] The former reagent seems to be of less general use since acidolysis is required as a final reaction step. Such conditions may be incompatible with some acid-labile protecting groups used in natural product syntheses. Salicylchlorophosphite (5), a crystalline, stable and easily prepared reagent,[29] reacts with alcohols[30] to produce a phosphite intermediate which can be converted into an H-phosphonate monoester *via* hydrolysis. Though yields reported for simple aliphatic alcohols were rather low,[30] the reagent proved to be very efficient for the phosphitylation of nucleosides.[28] The only possible inconvenience is that some nucleoside H-phosphonate monoesters produced in such a way require painstaking chromatography to separate them from hydrolysis products of the reagent.

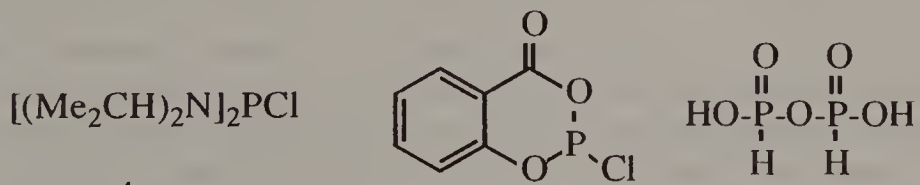


Figure 3 - Phosphitylating reagents

The most straightforward method, *i.e.* condensation of phosphonic acid with appropriate alcohols in the presence of arene

sulfonyl derivatives[22] has been hampered by concomitant formation of H-phosphonate diesters[31] and oxidation of H-phosphonate monoesters.[32] However, using a limited amount of a condensing agent [*e.g.* pivaloyl chloride (7) or 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide (8), Fig. 4] it is possible to convert phosphonic acid into its H-pyrophosphonate (6),[33] which may in turn act as a phosphonylating agent. The procedure is experimentally simple and reliable, and affords deoxynucleoside 3'-H-phosphonates in high yield (86-92%).[33] The only precaution which should be taken is not to exceed the 1:0.5 ratio of phosphonic acid to a condensing agent, otherwise symmetrical H-phosphonate diesters may be formed. Since (6) reacts rather slowly with sterically hindered hydroxyl functions, *e.g.* the 3'-OH group in 2'-*O*-protected ribonucleosides,[33] some regioselectivity can be achieved, in principle, with this reagent.

H-Phosphonate monoesters can also be prepared in good yield *via* transesterification of reactive H-phosphonate diesters, *e.g.* bis(1,1,1,3,3,3-hexafluoro-2-propyl)-H-phosphonate,[34] or bis-(2,2,2-trifluoroethyl)-H-phosphonate,[35] followed by hydrolysis. Applications of the latter reagent have been documented on several examples,[35] *e.g.* preparation of benzyl, phenyl, galactopyranosyl, cholesteryl, and deoxynucleoside H-phosphonates. The authors observed some incompatibilities of the reagent with 2,2,2-tribromoethoxycarbonyl and 2,4-dinitrophenylsulfenyl groups, and with the isopropylidene group involving the anomeric carbon of sugars. Since treatment with ammonium hydroxide is required as the last reaction step, the method may be less suitable for compounds containing rather sensitive, base-labile groups.

Among other synthetic methods available for the preparation of H-phosphonate monoesters one may mention a phosphitylation of nucleosides with 2-cyanoethylphosphorodiamidite, followed by β-elimination of the 2-cyanoethyl group from the appropriate H-phosphonate diesters,[7] anionic debenzylation of nucleoside benzyl H-phosphonates,[5] and oxidative phosphonylation with phosphinic acid in the presence of mesitylenedisulfonyl chloride.[31]

III. Synthesis of H-Phosphonate Diesters

A. Synthetic Methods

Diesters of phosphonic acid are important synthetic intermediates for the preparation of various natural products and their

analogues containing phosphodiester linkages, *e.g.* oligonucleotides,[9,12,36] nucleopeptides,[37] sugar phosphates,[26,38] and phospholipids.[27]

H-Phosphonate diesters can be obtained in a number of ways, *e.g.* (i) reaction of phosphonic acid and an alcohol with azeotropic removal of the water formed;[39] (ii) reaction of phosphorus chloride with 3 equivalents of an alcohol without a base;[40] (iii) reaction of phosphorus chloride with 2 equivalents of an alcohol and a base, followed by hydrolysis;[41] (iv) from phosphorochloridite esters[42] *via* their hydrolysis; (v) from phosphite triesters *via* hydrolysis[43] or acidolysis.[44] Unfortunately, all of these methods afford symmetrical diesters and thus seem to be of less synthetic value in natural product synthesis. The only exception is probably a reaction of phosphorus chloride with 1 equivalent of a higher alcohol and 2 equivalents of methanol.[45] Under such conditions the asymmetric (methyl alkyl) H-phosphonate diesters are formed in good yields, apparently *via* a phosphite triester intermediate, which undergoes demethylation during the course of the reaction.

Transesterification of diethyl H-phosphonate,[46] or reactive H-phosphonate diesters, *e.g.* bis(1,1,1,3,3,3-hexafluoro-2-propyl)-H-phosphonate,[34] or bis(2,2,2-trifluoroethyl)-H-phosphonate[35] with alcohols usually produces asymmetric diesters in good yields. Unfortunately, since only one alkyl group in the starting H-phosphonate diester can be replaced during the transesterification, the produced asymmetric diesters are most suitable as intermediates in the preparation of H-phosphonate monoesters (*vide supra*). Both alkyl groups in simple H-phosphonate diesters can be replaced during transesterification only under special circumstances, *e.g.* when cyclic H-phosphonate diesters are formed.[46]

The only method of preparative value for the synthesis of H-phosphonate diesters derived from natural products is a condensation of H-phosphonate monoesters with the appropriate hydroxylic components in the presence of a coupling agent. This method originates from pioneering work of Todd, *et al.*[47] on the mixed anhydrides of H-phosphonate monoesters. While exploring various approaches to oligonucleotide synthesis, the authors found, *inter alia* that the mixed anhydrides derived from nucleoside H-phosphonates and diphenyl chlorophosphate react with other nucleosides to form dinucleoside H-phosphonate diesters.[5]

Unfortunately, because of only a moderate yield of condensations (which was apparently due to the unsuitable reaction conditions used) and lack of an efficient oxidation method, the authors did not appreciate the potential significance of H-phosphonates as synthetic intermediates, and these studies were abandoned.

In 1984, when H-phosphonate chemistry began to be investigated again for the purpose of oligonucleotide synthesis, three important features of H-phosphonate esters became apparent.[7,8] First, nucleoside H-phosphonate monoesters undergo rapid condensation with a nucleosidic component in the presence of a condensing agent to produce the corresponding diesters. The rate of condensation is usually comparable to that observed for the nucleoside phosphoramidites. Second, the products of condensation (*i.e.* H-phosphonate diesters) are resistant to further activation by the condensing agent, and thus no phosphite triesters are formed. Third, the yield of H-phosphonate diesters is substantially lower when the condensation is carried out with so-called "preactivation", *i.e.* when a nucleosidic component is added to the mixture of H-phosphonate monoester that has been preactivated with a condensing agent.

To ensure fast and efficient coupling to H-phosphonate diesters, condensations are usually carried out in pyridine or in a mixture of solvents containing pyridine.[7-9,11,12] Most of the investigated coupling reagents, *e.g.* arenesulfonyl derivatives[7,8] [*e.g.* (9)], acyl chlorides[9,11] [*e.g.* (7)], chlorophosphates[7-9,48] [*e.g.* (8), (10), (11)], proved to be very reactive and efficient in promoting the condensations under such conditions.

When equimolar amounts of an H-phosphonate monoester and a hydroxylic component are condensed in the presence of 2-3 equivalents of a coupling agent, the appropriate H-phosphonate diester is usually produced in high yield without noticable formation of side products.[7,9] The diesters can either be isolated[49,50] (silica gel or silanized silica gel chromatography) or converted *in situ* into phosphate derivatives or their analogues *via* oxidation.[51,52] Though condensations can be carried out in neutral solvents in the presence of triethylamine,[10,48] these reactions are always substantially faster in the presence of pyridine or other nucleophilic catalysts.

Synthetic procedures which make use of condensing reagents for the formation of an ester linkage often suffer from competitive reactions of coupling reagents with a hydroxylic component. This usually results in formation of undesired products, *i.e.* sulfonyl-

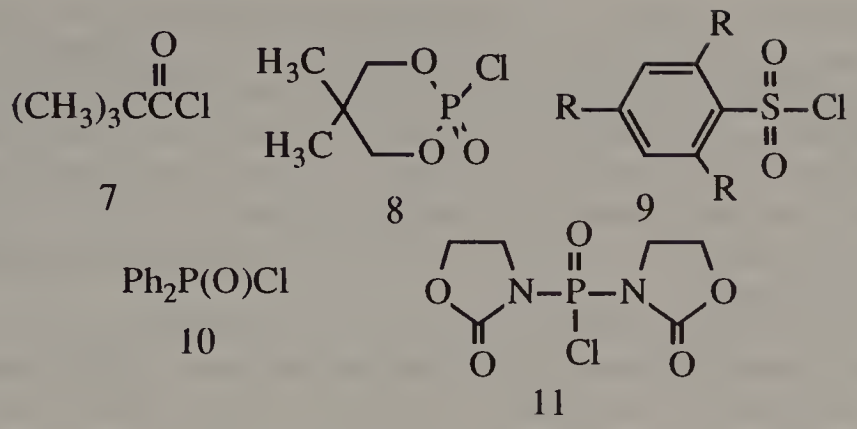


Figure 4 - Condensing agents

ated, phosphorylated, or acylated derivatives of an alcohol, depending on the kind of condensing agent used. This problem can be practically neglected[53] in the case of H-phosphonate diester synthesis due to the high rate of the condensations. Some other possible side reactions which may occur during the H-phosphonate diester formation will be discussed later in the text.

B. Mechanistic Aspects of H-Phosphonate Diester Formation

Condensation of H-phosphonate monoesters with a hydroxylic component in the presence of a condensing agent is a multistep reaction which apparently involves formation of reactive H-phosphonate or phosphite intermediates, followed by their reactions with a hydroxylic component. From a synthetic point of view it is important to know what kind of intermediates are responsible for fast and clean formation of H-phosphonate diesters during the condensation reactions, and what are the most suitable conditions for their generation.

Investigations of the coupling reactions using ^{31}P NMR spectroscopy[10,32,54,55] have indicated that the first reaction step (the activation) is apparently rate-limiting for all studied condensing agents,[10,32,55] and thus no reactive intermediates could be detected during the course of condensation.

In this situation most efforts have been put into investigation

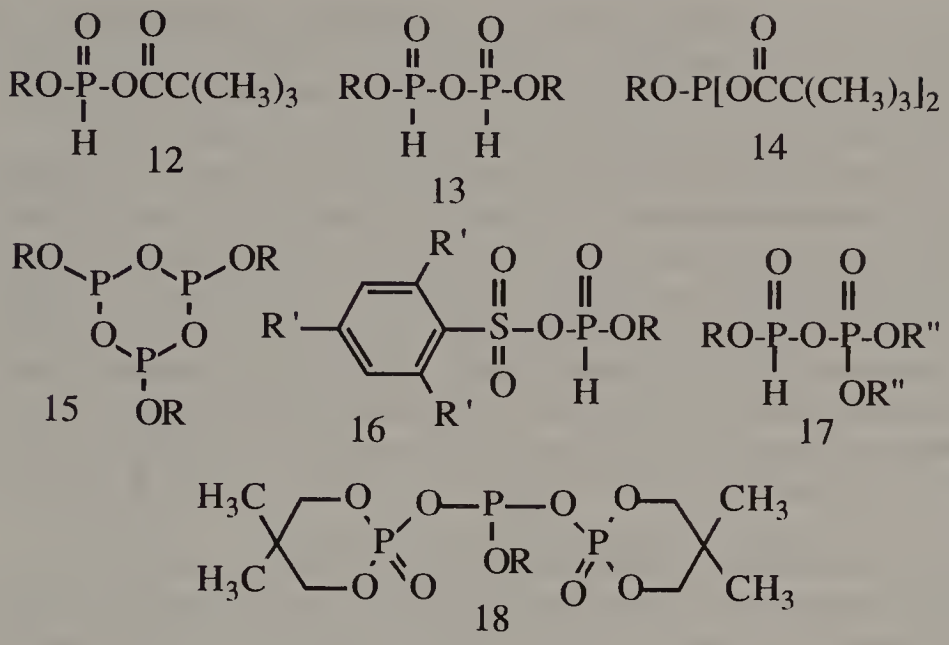
of activation pathways of H-phosphonate monoesters with different condensing agents [(7)-(11)].[10,32,54,55] Although several intermediates can be formed, it is usually possible to produce them as single species under the appropriate reaction conditions, and to investigate their chemical reactivity. From these investigations useful information concerning the most probable chemical nature of the intermediates involved in the H-phosphonate diester synthesis can be inferred.

When the activation is carried out in a stepwise manner by adding limited amounts of a condensing agent to a solution of an H-phosphonate monoester in pyridine, formation of various intermediates can be detected using ^{31}P NMR spectroscopy. Pivaloyl chloride [PV-Cl (7)] reacts with H-phosphonate monoesters in pyridine affording three intermediates:[10] the mixed acylphosphonic anhydride (12), the corresponding H-pyrophosphonate (13), and the bisacyl phosphite (14). The first two intermediates are formed with a limited amount of PV-Cl (0.5-1 equivalent), and the third one (14), when 3 or more equivalents of the condensing agent are used. When allowed to react with an alcohol, these intermediates afford the corresponding H-phosphonate diester, a mixture of H-phosphonate diester and monoester, and a phosphite triester, respectively. The mixed-anhydride (12) and the H-pyrophosphonate (13) react at comparable rates with alcohols,[10] while the bisacyl phosphite (13) is somewhat less reactive. From these studies one may infer that (12) and (13) are most likely to be intermediates involved in the formation of H-phosphonate diesters.

Since phosphite triesters are not formed during the condensations, it is not likely that the species (14) is involved as an intermediate

Recently, a remarkable effect of quinoline on the activation of H-phosphonate monoesters has been reported.[56] It was found that in acetonitrile containing ~20% of quinoline, the activation reaction with pivaloyl chloride affords almost exclusively the mixed-anhydride (12), even with an excess of the condensing agent. This may be of great value in the synthesis of H-phosphonate diesters.

The activation of H-phosphonate monoesters with arene sulfonic acid derivatives[32,55] (9) is a more complicated reaction due to concomitant oxidation of H-phosphonate esters (*vide infra*). However, when the activation is carried out with a limited amount of the condensing agent (9) (R = methyl or isopropyl, X = Cl or an azole), two intermediates, namely the H-pyrophosphonate (13) and the trimetaphosphite (15) can be detected in the ^{31}P NMR spectra



R = protected nucleosid-3'-yl or ethyl
R' = H, methyl, or isopropyl
R" = ethyl or phenyl

Figure 5 - Possible intermediates in the formation of H-phosphonate diesters

during initial stages of the reaction.[10,32,55] The same kind of intermediates have also been detected when diphenyl chlorophosphate[55] (10), or bis(2-oxo-3-oxazolidinyl)phosphinic chloride[55] (11) was used as a condensing agent. With chlorophosphates (10) and (11) as coupling agents it is possible to generate (15) as a single species and to investigate its chemical reactivity. It was found[55] that the trimetaphosphite (15) reacts with alcohols affording mixtures of phosphite triesters, H-phosphonate di- and monoesters, or mainly phosphite triesters and H-phosphonate diesters if a condensing agent is present. Since during condensation only H-phosphonate diesters are formed, it is not likely that (15) is

involved as an actual intermediate. The H-pyrophosphonate (13) and/or the corresponding H-phosphono-sulfonic (16) or H-phosphono-phosphoric (17) mixed-anhydrides instead seem to be likely candidates.

Less reactive chlorophosphates, *e.g.* 2-chloro-5,5-dimethyl-1',3,2-dioxaphosphorinane 2-oxide[48] (8), afford during activation of H-phosphonate monoesters in pyridine mainly intermediates of type (18)[57] (as detected by ^{31}P NMR spectroscopy). These, however, react with alcohols to produce phosphite triesters. Thus, in this case again, it seems feasible that H-phosphonate diester formation takes place *via* the corresponding H-phosphono-phosphoric mixed-anhydride of type (17), or *via* the H-pyrophosphonate (13), although none of these intermediates can be detected by ^{31}P NMR spectroscopy during the condensation.

In conclusion, even though the H-pyrophosphonate (13) is a rather reactive species and can, in principle, be produced during the condensation reactions involving all investigated coupling agents, it is not likely that H-phosphonate diesters are formed exclusively *via* this intermediate. Probably (13) is a major intermediate when arene sulfonyl derivatives (9) and diphenyl chlorophosphate (10) are used as condensing agents. However, in the case of other coupling agents [(7), (8), and (11)], the mixed anhydrides of type (12) and (17) may contribute more substantially than (13) to the formation of H-phosphonate diesters. On the other hand, since there is no obvious explanation for the high reactivity of (12), (13), or (17), it is possible that some other highly reactive di- and tricoordinated phosphorus species[58] (not detectable by ^{31}P NMR spectroscopy) are generated from those anhydrides and act as phosphonylating agents during the condensation.

It may also be suggested that clean formation of H-phosphonate diesters from the corresponding monoesters is due to the fact that the rate-limiting step in condensations is activation of the H-phosphonate monoesters (at least in pyridine). Thanks to this, probably only monoactivated species derived from H-phosphonate monoesters [*e.g.* intermediates (12), (13), (17), or others] can be formed during the condensation, since they are apparently trapped by an hydroxylic component to produce the H-phosphonate diesters well before they could undergo further activation. However, if H-phosphonate monoesters are preactivated[8,10,32,54,55] with condensing agents, other intermediates can be produced [*e.g.* (14), (15), and (18)], which upon reaction with alcohols afford a mixture of phosphite triesters and H-phosphonate esters.

IV. Reactions of H-Phosphonate Esters

A. General Chemical Properties

Simple alkyl H-phosphonate monoesters are usually stable liquids, resistant to air oxidation and to hydrolysis by air moisture. Some salts of the monoesters (especially ammonium salts) are crystalline materials while other (*e.g.* triethylammonium or pyridinium salts) are usually oils, gums, or syrups. Dialkyl H-phosphonates are liquids resistant to air oxidation, but they slowly hydrolyze in the presence of air moisture to the monoesters. H-Phosphonate esters derived from natural products (nucleosides, lipids, amino acids) are usually more stable than simple alkyl esters, and they can be stored as solids without noticable decomposition.

Both H-phosphonate mono- and diesters form alkali metal salts but under different reaction conditions. In aqueous sodium hydroxide the monoesters are converted into monosodium salts,[14] while the diesters undergo only hydrolysis. Sodium salts of H-phosphonate diesters can, however, be obtained under anhydrous conditions by treatment with sodium,[59] sodium hydride,[60] or sodium alcoholates.[61] In contradistinction to H-phosphonate monoesters, salts derived from H-phosphonate diesters exist predominantly in the phosphite form.[3] Chemical properties together with spectroscopic evidence seem to indicate that the metal-oxygen bond in such salts has covalent rather than ionic character.[3]

The stability of alkyl H-phosphonate esters toward aqueous acids and bases has also been investigated, but mainly on the occasion of their preparation (*vide supra*). In general, H-phosphonate monoesters undergo hydrolysis to phosphonic acid faster in acidic than in basic medium.[19,62] The opposite is true for H-phosphonate diesters, which hydrolyze much faster to the monoesters under basic conditions[13,15] than in the presence of acids. Hydrolysis of H-phosphonate esters is highly dependent on steric factors. This makes H-phosphonates derived from natural products much more stable than simple alkyl esters. It is possible to purify them on silica gel columns, as well as to remove some protecting groups in these compounds under acidic[9,10] and anhydrous basic conditions.[7] Under aqueous basic conditions H-phosphonate diesters, both alkyl and natural product derivatives, undergo rather fast and unspecific hydrolysis to a mixture of the corresponding H-phosphonate monoesters.

In contradistinction to phosphate triesters, which undergo both P-O and C-O bond cleavage during acidic hydrolysis,[63] the H-phosphonate diesters hydrolyze both in alkali and in acids with exclusive fission of the P-O bond.[63] This was proved by a complete retention of configuration of an optically active alcohol produced by hydrolysis of the corresponding H-phosphonate esters.[63] It is also interesting to compare some available kinetic data concerning rates of hydrolysis of simple alkyl esters of phosphorous acids. These data have recently been assembled and interpreted by Westheimer, *et al.*[64] Even though the conclusions about possible mechanisms involved still contain uncertainties, general tendencies concerning the hydrolytic stability of such esters[64] are rather clear. The rate of alkaline hydrolysis of dimethyl H-phosphonate is ~10^4 faster than of trimethyl phosphite, and it also exceeds those of dimethyl methylphosphonate (C-phosphonate) and trimethyl phosphate by factors of about 10^5 and 10^6, respectively. These large differences almost certainly arise from the presence of the ionizable hydrogen at the phosphorus center in dimethyl H-phosphonate, but a detailed mechanism which can account for these is not obvious. A plausible reaction pathway, involving a spontaneous rearrangement of the anion of dimethyl H-phosphonate into the products *via* metaphosphite as an intermediate,[64] would require the rate of hydrolysis to be strictly proportional to the alkali concentration. However, the hydrolysis of H-phosphonate diesters is known to be both general-base and general-acid catalyzed,[65] and this might rather suggest that the abstraction of the proton from an H-phosphonate diester is the rate-limiting step. Unfortunately, such an assumption is in disagreement with findings that the rate of hydrogen-deuterium exchange and the rate of oxidation with iodine (*vide infra*) exceed that of hydrolysis by a factor of at least 10^3. A mechanism which is compatible with the available kinetic data was suggested by Westheimer, *et al.*[64] and it is shown in Fig. 6.

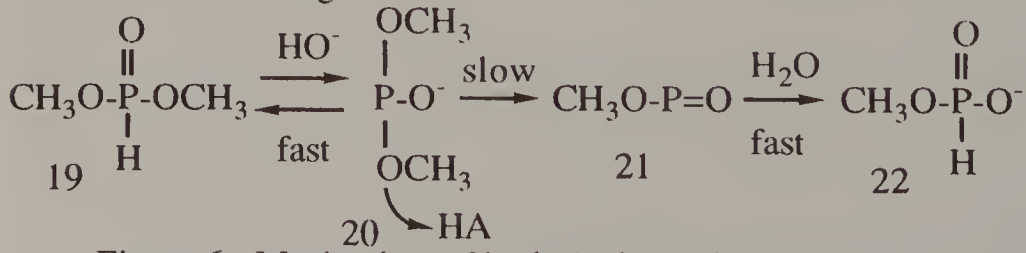


Figure 6 - Mechanism of hydrolysis of dimethyl H-phosphonate

It assumes formation of the metaphosphite (21) from the phosphite form (20) in the rate-limiting step, which is general-acid catalyzed.

H-Phosphonate diesters also undergo several other reactions of a general character. They include the Michaelis-Becker reaction,[66,67] addition to double bonds (C=C,[68] C=O,[69,70] C=N,[71] C=S,[72] N=O[73]), transesterification,[74] dealkylation,[74] chlorination,[75] fluorination,[76] and others.[77]

The most important reactions of H-phosphonate esters from a synthetic point of view, *i.e.* oxidation and reactions with acyl chlorides and other condensing agents, are treated separately below.

B. Oxidation

Oxidation of H-phosphonate mono- and H-phosphonate diesters is a most important reaction from the point of view of synthetic applications. The versatility of H-phosphonate intermediates stems from the fact that by changing oxidation conditions they can be converted into phosphate esters or into various phosphate analogues. However, since H-phosphonate esters are usually more resistant toward oxidation than phosphite triesters, efficient but mild procedures, compatible with sometimes fragile natural product derivatives, had to be developed for that purpose.

In the early days of phosphorus chemistry H-phosphonate monoesters were mainly used as starting material for the preparation of phosphate monoesters. The most efficient oxidation procedures for that purpose involved potassium permanganate,[78] bromine in pyridine,[79] and hexachloroacetone[80] as oxidizing agents. With the exception of potassium permanganate, in all other instances, formation of substantial amounts of the corresponding pyrophosphates was usually observed. Attempts have also been made to produce phosphodiester derivatives directly from H-phosphonate monoesters by oxidizing the latter ones in the presence of alcohols. Although oxidative couplings of nucleoside H-phosphonate monoesters with hydroxylic components with the help of bromine[79] failed to produce significant amounts of phosphate diesters, simple alkyl H-phosphonate monoesters afforded under such conditions the expected diesters (yield ~60%). Better results in oxidative coupling of nucleoside H-phosphonate monoesters were obtained by using arene sulfonic acid derivatives together with 2,2'-dipyridyl disulfide (yields 60-80%).[25]

The efficiency of oxidation of H-phosphonate monoesters

can be enhanced substantially by converting these esters into trivalent phosphorus silyl esters[81] prior to oxidation (Fig. 7).[82] Silyl phosphites of type (23), due to the presence of a lone pair of electrons on the trivalent phosphorus atom, are more reactive toward electrophiles and oxidizing agents than H-phosphonate esters. This feature of silyl phosphites has been exploited in nucleotide chemistry for the conversion of nucleoside 5'-H-phosphonates into nucleoside 5'-phosphates[21,83] (25), nucleoside *S*-phenyl phosphorothioates[82] (24), and into nucleoside 5'-phosphophosphorothioates[21] (26) (Fig. 7). In these transformations dimethyl sulfoxide,[83] 2,2'-dipyridyl disulfide,[21] diphenyl disulfide,[82] and elemental sulfur[21] were used as oxidizing agents.

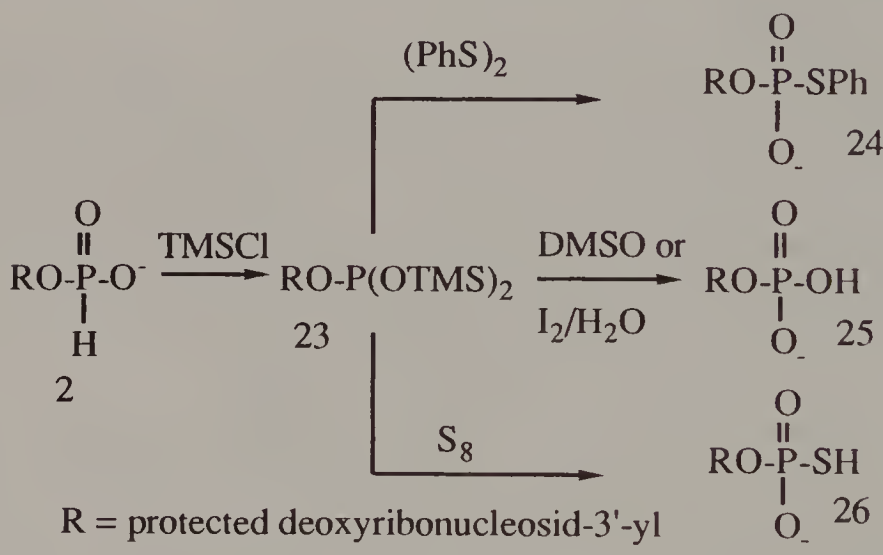
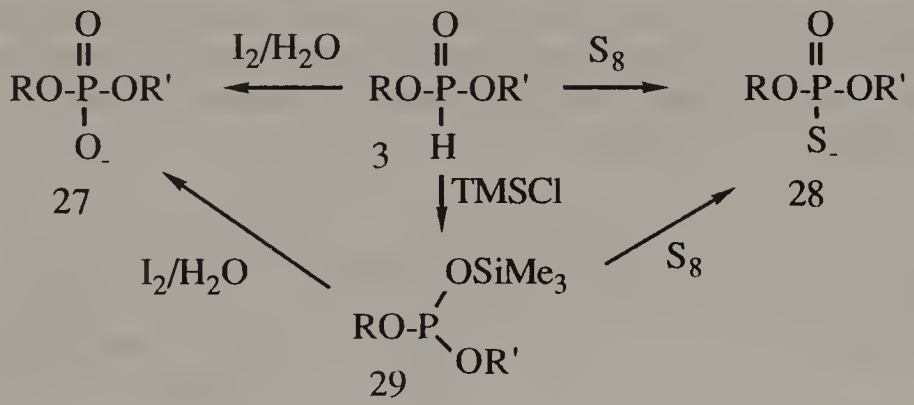


Figure 7 - Oxidation of H-phosphonates through silyl phosphites

It was recently reported that silyl phosphites can also be oxidized under aqueous conditions using iodine in aqueous pyridine.[51] Smooth conversion of nucleoside 3'-disilyl esters (23) (R = protected nucleoside) into the corresponding phosphate monoesters (25) seems to indicate that the oxidation is faster than hydrolysis of the silyl esters, or that isomerization of the *in situ* formed nucleoside phosphite into the rather unreactive H-phosphonate form is slower than the oxidation.[51]

Several oxidizing reagents have been investigated for the purpose of phosphodiester synthesis starting from H-phosphonate diesters. Most mild oxidizing reagents, such as benzoyl

peroxide,[78] perbenzoic acid,[78] active manganese dioxide,[78] iodobenzene diacetate,[51] or tetrabutylammonium periodate[51] proved to be rather unreactive toward H-phosphonate diesters. Other reagents, previously used for the oxidation of H-phosphonate monoesters, produced stable phosphotriester intermediates[51] which were difficult to convert into the desired phosphate diesters. However, it was found that H-phosphonate diesters can be converted into phosphodiesters rapidly and under mild conditions using iodine in aqueous pyridine.[51,52] A tertiary base, or a basic solvent (*e.g.* pyridine) seems to be an indispensable component of the reaction mixture, else the oxidation is slow.[51]



R = protected nucleosid-3'-yl
R' = protected nucleosid-5'-yl

Figure 8 - Oxidations of H-phosphonate diesters

It was also found that water has to be present during the oxidation of H-phosphonate diesters with iodine in order to avoid formation of the corresponding pyrophosphates, and to prevent dealkylation of the phosphodiesters.[51] In similarity to the oxidation of H-phosphonate monoesters, the presilylation in this case was found to be compatible with aqueous oxidation conditions (Fig. 8).[51] Various phosphate analogues can be produced from H-phosphonate diesters by changing the oxidation conditions, as will be discussed later in the text.

For oxidative coupling of H-phosphonate diesters, chlorinating reagents such as *N*-chlorosuccinimide[84] and carbon tetrachloride[85] were found to be most useful. The former reagent efficiently converts H-phosphonate diesters into chlorophosphates,[84] which then can be transformed into the corresponding

triesters upon reaction with alcohols, or into the phosphodiesters upon hydrolysis. Applications of carbon tetrachloride will be discussed later in the context of phosphate analogue synthesis.

Other chemical[86-88] and stereochemical[89,150,151] aspects of H-phosphonate diester oxidation, and reactions of silyl phosphites with various electrophiles[50,90] have also been investigated.

Together with the oxidation of H-phosphonate esters, the deuterium exchange of the phosphorus-bound hydrogen in phosphonic acid[91] and its mono- and diesters[92] have been studied. This exchange occurs rather fast in the case of H-phosphonate diesters, and the reaction is both base[93] and acid[94] catalyzed. Kinetic studies have also shown that the exchange reaction follows the same rate law[93,94] as found for the oxidation of H-phosphonate diesters with iodine,[95] with the phosphite species (3b) being the most likely intermediate in both reactions (Fig. 9).

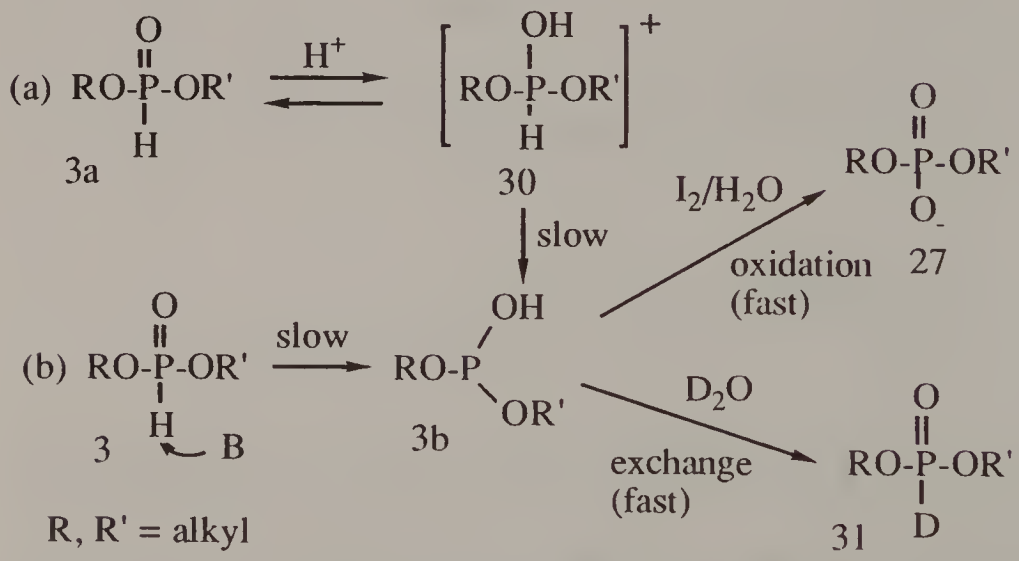


Figure 9 - Oxidation of and hydrogen-deuterium exchange in H-phosphonate diesters

In the acid catalyzed oxidation[94] (or exchange) (Fig. 9a) the first step is apparently a reversible protonation of the phosphoryl group of (3a), which is followed by cleavage of the P-H bond in the intermediate (30) to produce the phosphite (3b). Formation of the latter is assumed to be the rate-limiting step in both oxidation and the exchange reaction.[94] In agreement with this, a kinetic

isotope effect (k_H/k_D) of 4 was found for the acid catalyzed oxidation of normal and deuterated substrates.[94]

In the base catalyzed oxidation[93] of H-phosphonate diesters by iodine, the first step apparently is the removal of the phosphorus-bound hydrogen in (3a) by a base, with formation of the phosphite species (3b) (Fig. 9b). The phosphite form is very reactive, and its formation is assumed to be the rate-limiting step.[93] However, in contradistinction to the acid catalyzed oxidation, in this case (acetate anion acting as a base) no isotope effect was observed for deuterated substrates.[93] This was rationalized by assuming a triangular transition state, similar to the so-called hydride shifts for which usually very small isotope effects are observed.[96] Though compatible with experimental data, this interpretation is rather speculative. More recent studies[97] have shown that a pronounced isotope effect (k_H/k_D ~1.6 to 2.8) is observed with stronger bases, *e.g.* phosphate and carbonate dianions, and as expected, it increases with increasing base strength. Unfortunately, for the hydroxide catalyzed reaction, exceedingly variable data were obtained.[97] It is assumed that due to a possible exchange of deuterium during the course of the reation the observed isotope effect may be rather low[97] (the maximum effect was calculated to be ~5.6).

C. Reactions with Acyl Chlorides

Phosphonic acid[98] and its mono-[10,99] and diesters[48,53,100] react with acyl chlorides or with some reactive carboxylic acid anhydrides to form three types of acyl-containing products: acyl phosphites [*e.g.* (35) in Fig. 10], acyl H-phosphonates [*e.g.* (33) in Fig. 10], and acylphosphonates [*e.g.* (36) in Fig. 11]. Formation of the P-O and P-C derivatives in these reactions is probably due to the fact that H-phosphonates are ambident nucleophiles and can attack electrophilic centres (*e.g.* the carbonyl function of an acyl chloride) either with oxygen [formation of (33) or (35)] or with phosphorus [formation of (36) or (38)]. If reactive acyl chlorides are used, acylphosphonates usually undergo further transformations which involve nucleophilic attack of the phosphorus on the carbonyl centre of the acylphosphonate. For acylphosphonate diesters this leads to the formation of diphosphonate derivatives[101] having two P-C bonds, or to rather complicated mixtures of condensates, as for example in the reaction of phosphonic acid with acetic anhydride.[102] In general, acyl

phosphites and acyl H-phosphonates are very susceptible to hydrolysis, while acylphosphonates (P-C bond) are rather stable compounds.

More interesting from a practical point of view are reactions of H-phosphonate derivatives with moderately reactive acyl chlorides (*e.g.* pivaloyl chloride) since these are used as condensing agents for the formation of H-phosphonate diesters. Under such reaction conditions it is possible to observe using ^{31}P NMR spectroscopy[10,99,100] formation of distinct acyl phosphite or acyl H-phosphonate intermediates, which are subsequently converted into acylphosphonates.

Studies on the activation pathway of phosphonic acid[98] with pivaloyl chloride have shown that, depending on the amount of a condensing reagent used, three intermediates were potentially formed, namely the pyrophosphonate (32), the phosphono-acyl mixed anhydride (acyl H-phosphonate) (33), and the triacyl phosphite (35) (Fig. 10).

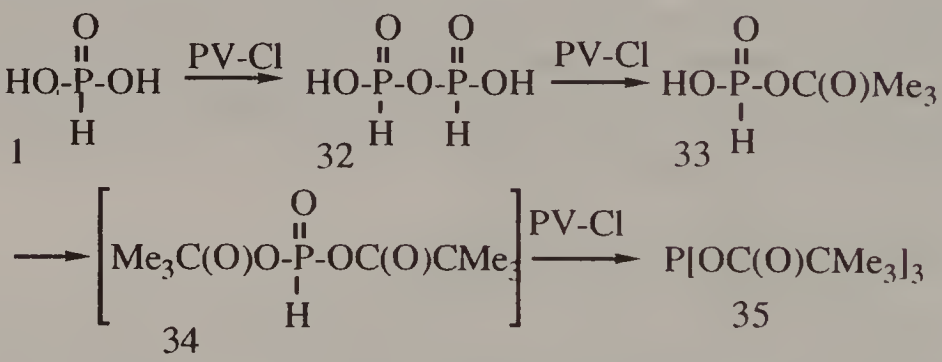


Figure 10 - Reaction of phosphonic acid with PV-Cl

The latter compound is most likely formed *via* the bisacyl H-phosphonate (34), but this intermediate was not detected, probably because it is immediately converted into the triacyl phosphite. Some chemical properties of acyl H-phosphonates, acyl phosphites, and acylphosphonates will be discussed later in the text.

H-Phosphonate monoesters react with limited amounts of pivaloyl chloride[10] in pyridine affording a mixture of the mixed anhydride (12) and bisacyl phosphite (14). With an excess of acyl chloride only (14) is formed initially. Upon prolonged reaction, slow (usually after overnight) formation of the acylphosphonate (36) is observed (Fig. 11).[99] Since this reaction is considerably

slower than those which lead to (12) and (14), it seems[99] likely that (36) is formed from bisacyl phosphite (14) *via* an Arbuzov type reaction.

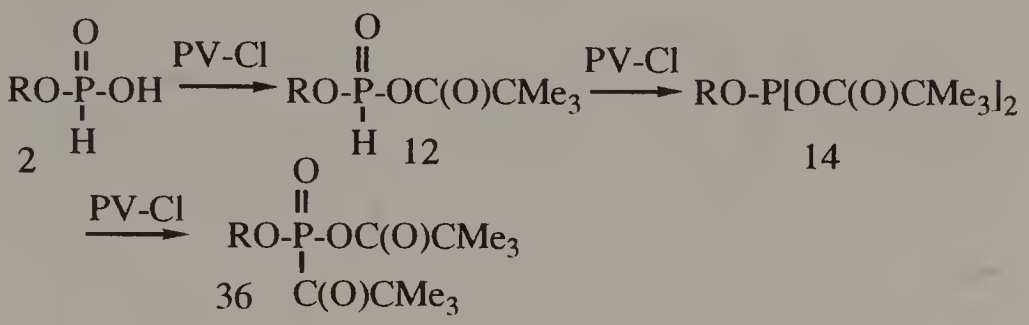
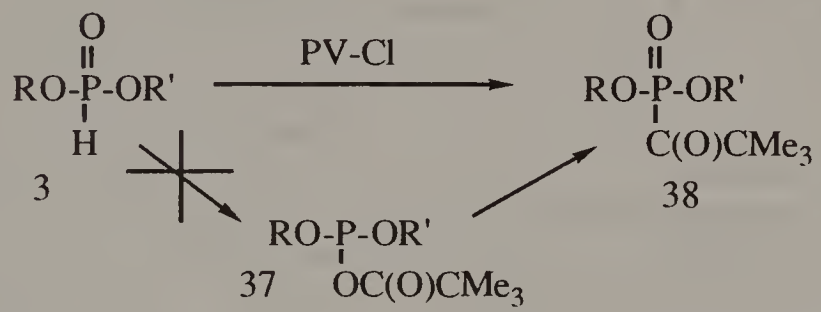


Figure 11 - Reaction of H-phosphonate monoesters with PV-Cl

Diesters of phosphonic acid react even slower with an excess of pivaloyl chloride to produce the acylphosphonates[100] of type (38) (Fig. 12).



R = protected deoxyribonucleosid-3'-yl or ethyl
R' = protected deoxyribonucleosid-5'-yl or ethyl

Figure 12 - Formation of acylphosphonates from H-phosphonate diesters

Activation of H-phosphonate diesters by acyl chlorides, *i.e.* formation of monoacyl phosphites of type (37) usually does not occur.[10] However, if one of the substituents in H-phosphonate diesters has a sufficiently strong electron-withdrawing character, such compounds may be formed.[103]

Sterically hindered aromatic acyl chlorides (*e.g.* mesitoyl chloride) react with H-phosphonate mono-[57] and diesters[104] in

pyridine in a different way than aliphatic acid chlorides, affording products which have been tentatively identified as 1-mesitoyl-1,4-(1,2)-dihydropyridine-4(2)phosphonates, (39) and (40) (Fig. 13).

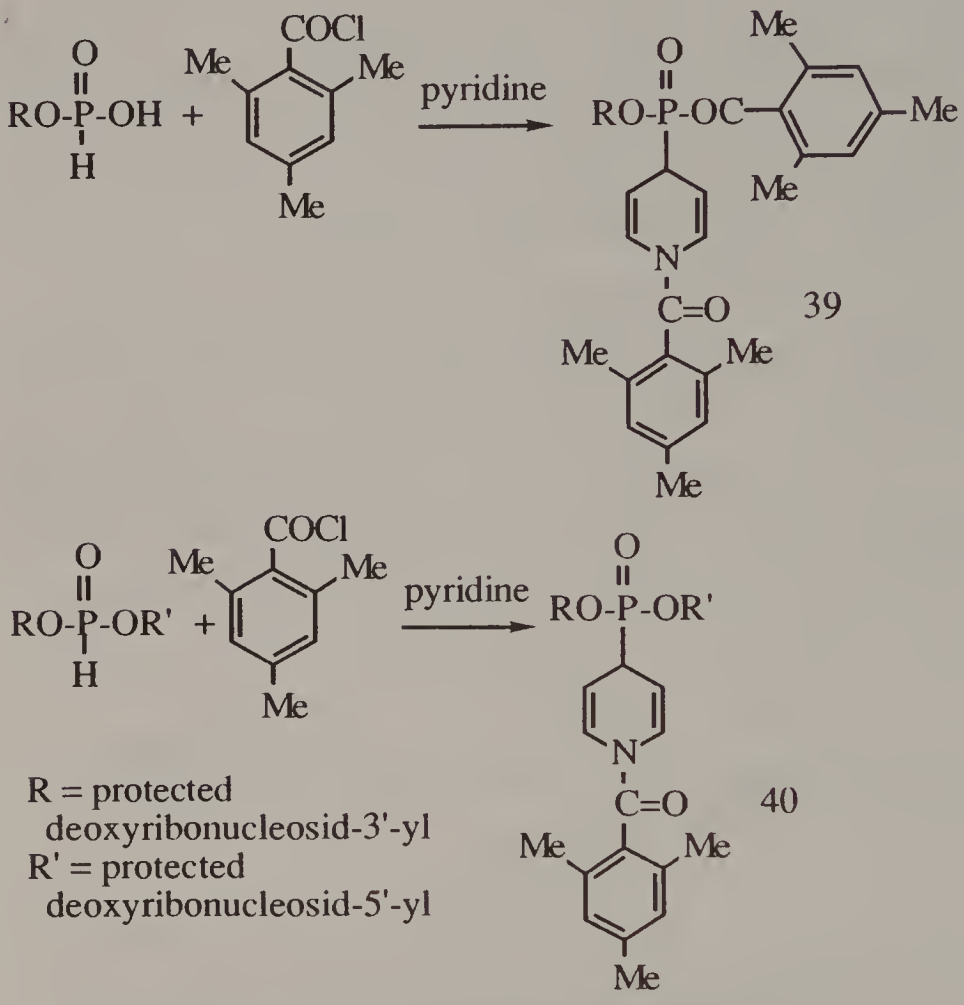


Figure 13 - Reaction of mesitoyl chloride with H-phosphonate mono- and diesters

Acyl groups linked to the H-phosphonate or phosphite moiety make the phosphorus atom in these compounds more electrophilic, which facilitates nucleophilic substitution at this centre.[105] This feature has been exploited in H-phosphonate[10] and phosphite[106,145] ester syntheses. The synthetic utility of acyl H-phosphonates differs, depending on the degree of esterification of phosphonic acid. The acyl H-phosphonate (12)[10] derived from H-phosphonate monoesters (see H-phosphonate diester synthesis) afford in the reaction with alcohols exclusively the corresponding

diesters, while the mixed H-phosphono-acyl anhydride[98] of type (33) reacts in a more complex way. Though (33) is a monofunctional phosphonylating agent, it produces predominantly the symmetric H-phosphonate diesters, or a mixture of H-phosphonate mono- and H-phosphonate diesters,[98] depending on stoichiometry of the reagents. Only with a large excess of simple aliphatic alcohols does (33) afford H-phosphonate monoesters[98] as a major product. Acyl phosphites [*e.g.* (12), (14), (35)] are good phosphitylating agents and they are readily accessible by reaction of phosphonic acid and its monoesters with acyl chlorides.[10,98] Monoacyl phosphites of type (37) cannot be obtained from the corresponding H-phosphonate diesters.[10] However, they can be prepared from bisacyl phosphites (14) upon reaction with alcohols.[145] Yields of phosphite triesters produced from acyl phosphites can be enhanced if an acyl chloride is present during the phosphitylation.[98,145] This is apparently connected with capture of carboxylic anions, produced during the phosphitylation, by an acyl chloride which prevents deacylation of acyl phosphites[98,147] (14), (35), or (37) by these anionic species.

Acylphosphonates were demonstrated to be useful synthetic intermediates.[108-111] Nucleophiles attack these compounds mainly at the carbonyl centre of an acyl group,[109,112] in contradistinction to acyl phosphites (or acyl H-phosphonates) that preferentially undergo reactions at the phosphorus center.[10,116] Dialkyl acylphosphonates act as efficient acylating agents toward primary and secondary amines.[112] Since H-phosphonate diesters are generated from acylphosphonates during reaction with amines, the acyl group in these compounds can also be viewed as a protecting group for the H-phosphonate function. This feature has been exploited in a synthesis of dinucleoside H-phosphonates starting from nucleoside acylphosphonates[108,109] (Fig. 14a). The latter compounds (41) can be activated by a condensing agent and coupled with a nucleosidic component to produce dinucleoside acylphosphonates (42). Upon treatment with *n*-butylamine, (42) afforded the H-phosphonate diesters (43).

Another type of reaction is shown in Fig. 14b. Reductive removal of the trichloroethyl group from 2,2,2-trichloroethoxycarbonylphosphonate diesters (44) with zinc powder produces carboxylphosphonates (45) which can be converted into the silyl phosphites of type (46) by successive silylation[110,111] (Fig. 14). The reaction proceeds without isomerization, as proved by

formation of only one isomer upon subsequent sulfurization of the silyl derivatives (46) prepared from each of the individual diastereoisomers of dinucleoside acylphosphonate (44).[111]

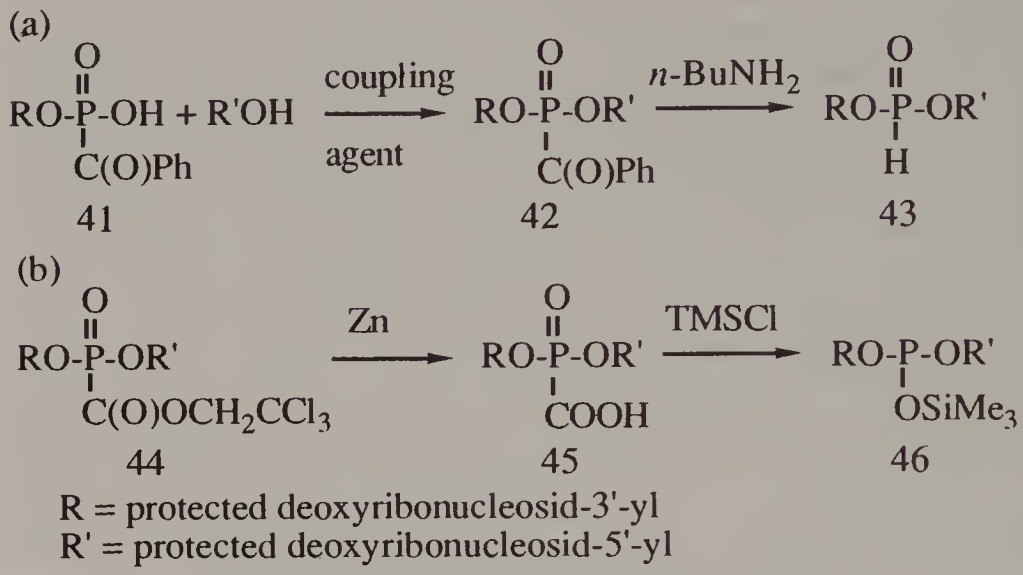
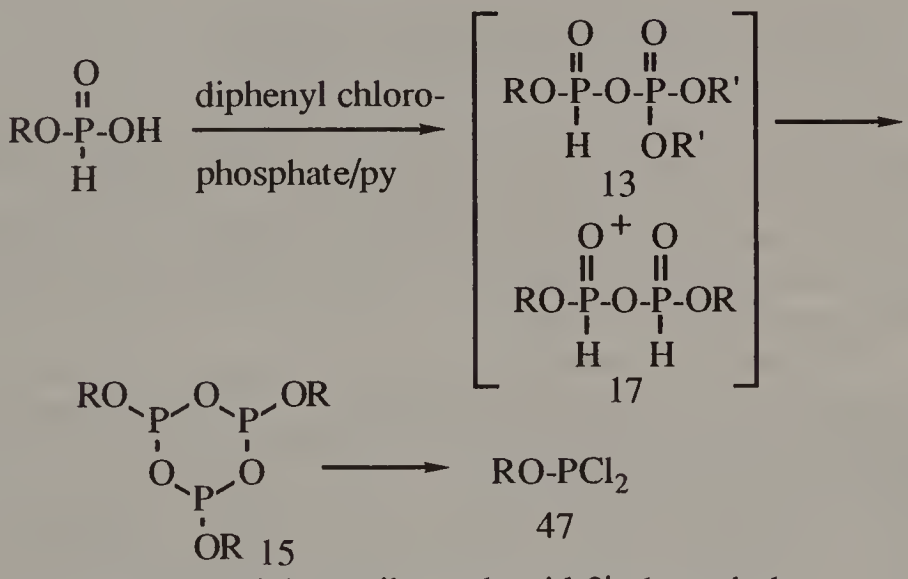


Figure 14 - Some reactions of acylphosphonates

D. Reactions with Other Condensing Agents (Chlorophosphates, Arenesulfonic Acid Derivatives)

H-Phosphonate monoesters react with dialkyl[113] and diaryl[47] chlorophosphates in neutral solvents in the presence of tertiary amines to form the corresponding H-phosphono-phosphoric anhydrides (17) (Fig. 5). This type of mixed anhydride has been of considerable synthetic interest since they react with O-nucleophiles preferentially at the H-phosphonate centre[47] to produce H-phosphonate diesters. In most instances the identity of mixed anhydrides has been proved indirectly[5,47] by their conversion into the expected products. Only simple alkyl derivatives of type (17) have been isolated (yields ~50%).[113] However, it is not certain if they were the only products of the reaction. The formation of (17) is most likely accompanied by a concomitant reaction of (17) with the H-phosphonate monoester[5] which leads to the H-pyrophosphonate (13). The extent of the latter reaction depends on the nature of chlorophosphate and the reaction conditions. ^{31}P NMR studies have shown that reaction of equimolar amounts of ethyl H-phosphonate and diphenyl chlorophosphate in acetonitrile in the presence of two equivalents of

pyridine preferentially produces the corresponding H-pyrophosphonate (13).[10] In neat pyridine, or in acetonitrile/pyridine (1/1, v/v) mixture, the mixed anhydrides (17) and the pyrophosphonates (13) cannot be detected in the reaction mixture by ^{31}P NMR since they apparently undergo rapidly further activation.[55] The chemical nature of products formed in such reactions depends on reactivity and excess of the chlorophosphate used.[104] With diphenyl chlorophosphate (10), compounds (13) and (17) are converted into the trimetaphosphite (15) (Fig. 5)[55] which reacts further to the dichlorophosphite (47) (Fig. 15).[104] Dialkyl chlorophosphates [*e.g.* (8)] seem to react differently with H-phosphonate monoesters.[57] Though the initial activation stage is likely to be similar to that with diphenyl chlorophosphate, the predominant product in this case is the mixed anhydride[57] of type (18). The trimetaphosphite (15) is formed only in small quantities alongside (18) under such reaction conditions.



R = protected deoxyribonucleosid-3'-yl or ethyl
R' = phenyl

Figure 15 - Reaction of H-phosphonate monoesters with diphenyl chlorophosphate

H-Phosphonate diesters, being uncharged compounds, are rather unreactive toward dialkyl and diaryl chlorophosphates. Even during prolonged treatment in pyridine with excess of chlorophosphate, no reaction can be detected as judged from ^{31}P NMR

spectra.[53] However, sodium salts of H-phosphonate diesters, which under anhydrous conditions exist exclusively in the phosphite form (48),[114] react readily with diethyl chlorophosphate to produce tetraalkyl hypophosphates (49) and tetraalkyl esters of the phosphorous-phosphoric mixed anhydrides of type (50) (Fig. 16).[115]

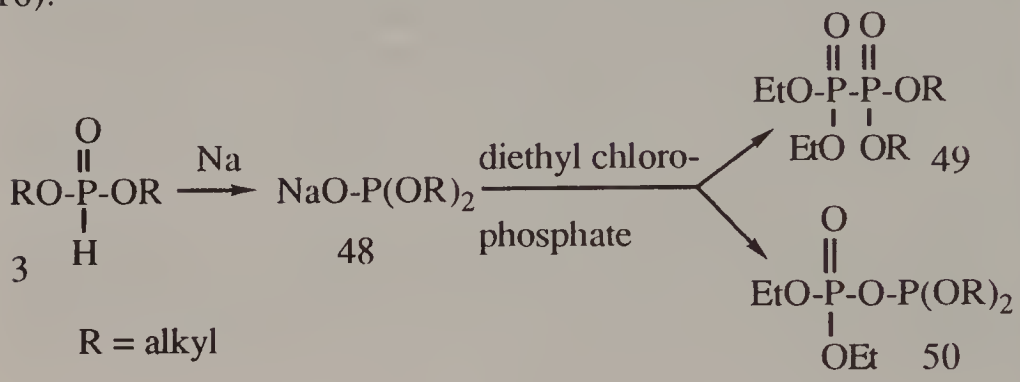
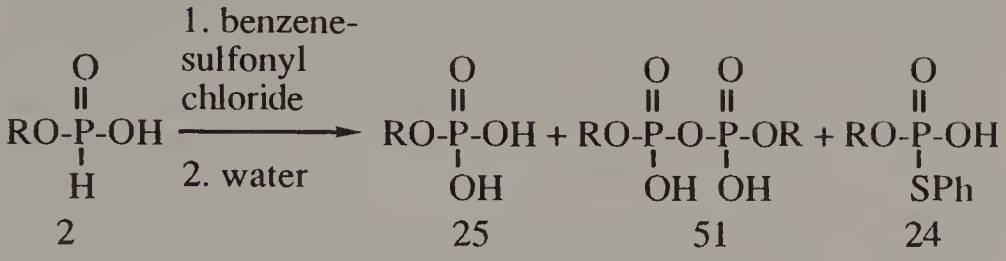


Figure 16 - Reaction of H-phosphonate diesters as the sodium salt with diethyl chlorophosphate

This is apparently due to the ambident character of (48) which may be attacked by electrophiles at the phosphorus centre [formation of hypophosphate (49)], or at the oxygen [formation of the mixed anhydride (50)]. Since compounds (49) are usually major products of the reactions,[115,116] it seems that attack on the phosphorus centre is favoured.

Reaction of arenesulfonic acid derivatives with H-phosphonate esters has recently been investigated.[7,8,25] It was found that similarly with chlorophosphates, arenesulfonyl chlorides activate H-phosphonate monoesters, and thus may act as condensing agents. Though the H-phosphono-sulfonic mixed anhydride (16) (Fig. 5) is probably the first reactive intermediate formed in such reactions, its presence was not detected by ^{31}P NMR spectroscopy during the course of the reaction.[7,8,32] This is probably due to high reactivity of such anhydrides which are rapidly converted in pyridine into the H-pyrophosphonate (13) and then into the trimetaphosphite (15).[32] In contradistinction to the reaction with chlorophosphates,[55] the latter intermediate subsequently undergoes rather complicated transformations of redox character in which arenesulfonyl derivatives act as oxidizing agents.[32] Final products of such a reaction[32] (after hydrolysis) are the phosphate monoester (25), the symmetric pyrophosphate (52), and the *S*-aryl phosphorothioate

diester (24) (Fig. 17).



R = protected deoxyribonucleosid-3'-yl or ethyl

Figure 17 - Reaction of H-phosphonate monoesters with arenesulfonyl chlorides

In pyridine, H-phosphonate diesters undergo slow oxidation (several hours) with arenesulfonyl derivatives.[53] The reaction is substantially faster (few minutes) in the presence of triethylamine[53] or nucleophilic catalysts, *e.g. N*-methylimidazole.[53] However, since a mixture of phosphate and phosphorothioate esters (2:1) are formed during the oxidation, arenesulfonyl derivatives seem to be of little synthetic value as oxidizing agents.

V. Synthesis of Some Biologically Important Phosphodiesters and Their Analogues *via* H-phosphonate Intermediates

A. Synthesis of Oligonucleotides

Machine-assisted solid phase synthesis of oligonucleotides is an area in which H-phosphonate chemistry is gaining considerable interest as an alternative to the well established phosphoramidite and phosphate procedures. The most important features of the synthesis of oligonucleotides *via* the H-phosphonate approach are simplicity, versatility, and effectiveness. Nucleoside 3'-H-phosphonates,[9,12,28,31,33-35,117] which serve as starting material for the synthesis, are stable compounds, resistant to air oxidation, and easy to prepare and purify. When activated with various condensing agents, however, they become very reactive and couple efficiently with appropriate hydroxylic components to form H-phosphonate diesters. Due to the stability of the P-H bonds in H-phosphonate diesters, the products of condensations are resistant to further activation, and thus no protecting group is required at the phosphorus centre. On the other hand, since H-phosphonate

diesters are more susceptible to oxidation than the monoesters,[51,52] they can be converted under mild conditions into the corresponding phosphodiesters, or, by changing oxidation conditions, also to various oligonucleotide analogues.

During the last few years several reports appeared in the literature concerning syntheses of oligodeoxyribo-[9,11,12,54,118-124,129-133] and oligoribonucleotides[36,124-128,134] *via* H-phosphonate intermediates. All of them make use of a simple synthetic cycle which includes two chemical steps: (i) deprotection of the terminal 5'-OH function in a solid-phase bound oligonucleotide, and (ii) condensation of this with a nucleoside 3'-H-phosphonate in the presence of a condensing agent. In a final cycle H-phosphonate functions in an oligonucleotide are converted into phosphodiester linkages (oxidation), which is followed by splitting the oligomer from the support and its deprotection by standard methods.

The condensation is carried out in pyridine or in a mixture of acetonitrile and pyridine, and it usually goes to completion in 1-2 min. Although several condensing agents proved to be useful in the solution synthesis of dinucleoside H-phosphonate diesters,[7,8,48,49] mainly pivaloyl chloride or 1-adamantanecarbonyl chloride is used for the purpose of solid phase synthesis of oligonucleotides. In a machine-assisted synthesis, solutions of nucleoside H-phosphonates and pivaloyl chloride are delivered to a solid phase support in alternating mode in form of short segments[9] to avoid double activation of the nucleotidic component [formation of compounds of type (14)].[10] Yields are usually high (97.0-99.5%), but they are notably dependent on technical aspects connected with the solvent delivery system of the particular machine (for each type of machine reaction conditions have to be thoroughly optimized). However, some recent alterations in the method are likely to change that.[56,103]

Since H-phosphonate functions in oligonucleotides are stable during all chemical steps in a synthetic cycle, oxidation can be carried out when the assembly of an oligonucleotide chain is completed. This is usually done with an aqueous solution of iodine in pyridine,[9,36] or with iodine in the presence of another base (triethylamine, *N*-methylimidazole).[11,12] Since H-phosphonate diesters become more susceptible to oxidation when converted into silyl derivatives, the oxidation procedure may also include a presilylation step (*e.g.* treatment with trimethylsilyl chloride) if required. In order to produce uniformly modified oligonucleotides

containing phosphoramidate or phosphorothioate linkages this cycle can be changed accordingly (*vide infra*).

Attempted solid phase synthesis of oligonucleotides using diphenyl chlorophosphate (10) or arenesulfonic acid derivatives (9) gave rather low yields of oligonucleotides with the desired chain length.[9] However, it was reported[129] that in a syringe synthesis mesitylenesulfonyl 3-nitro-1,2,4-triazole gave better results than pivaloyl chloride. Also, syntheses with another condensing agent, 1,3-dimethyl-2-chloroimidazolium chloride, have been reported to give satisfactory results.[130-132] There is probably still much to be explored concerning optimal reaction conditions and condensing agents for the formation of H-phosphonate diesters.

Although a capping step during oligonucleotide synthesis *via* H-phosphonate intermediates seemes to be superfluous,[9,11] some recent studies have shown that its incorporation into a synthetic protocol may improve the overall performance of the method.[133] Since the standard capping procedure (acylation with acetic anhydride in the presence of a nucleophilic catalyst more powerful than pyridine) is not compatible with H-phosphonate chemistry (P-acylation)[53] phosphonylation with isopropyl H-phosphonate in the presence of 1-adamantanecarbonyl chloride was chosen for that purpose.[133] It was also found that 1-adamantanecarbonyl chloride offered some advantages (in terms of stability) as a condensing agent over pivaloyl chloride.[133]

Another important modification introduced into the H-phosphonate method of oligonucleotides seemed to be the replacement of pyridine by quinoline as a solvent during the condensation step.[56] Since under such reaction conditions H-phosphonate monoesters afford as an intermediate almost exclusively the mixed-anhydride (12), these may alleviate some possible problems connected with double activation of the nucleotidic substrate [formation of intermediates of type (14)].

Studies have also been carried out to investigate possible side-reactions[53] which may occur during oligonucleotide synthesis *via* H-phosphonate intermediates. These have shown that the rate of H-phosphonate diester formation with various condensing agents[(7)-(11)] is high enough to ensure clean and practically quantitative formation of dinucleoside H-phosphonates.[53] However, a clear distinction should be made between the "solution" and "solid phase" synthesis of oligonucleotides. In the former one equimolar amounts of nucleotidic and nucleosidic materials are used together with 2-3 equivalents of coupling agents. Under such

conditions the reaction can be quenched long before any side-products can be detected. On the other hand, in solid phase synthesis, when 10-20 molar excess of a nucleotidic component and 50-100 molar excess of a condensing agent are used, the subsequent reactions of H-phosphonate diesters with condensing agents can probably not be completely excluded. For these reasons arenesulfonic acid derivatives may be unsuitable as condensing agents because they cause oxidation of H-phosphonate diesters with a concomitant formation of phosphorothioates. Pivaloyl chloride, which is commonly used both in solution and in solid phase synthesis of oligonucleotides, should be considered as a safe and efficient reagent, in light of these studies. The reaction of guanine residues with the reagent is slow and produces modifications (acylation) which, however, are reversed during the final deprotection.[53] Alternatively, protection of the heteroaromatic lactam system in guanine should eliminate this source of side-reactions. Although no detectable amounts of acylphosphonates (reaction at the P-H centre) are observed when H-phosphonate diesters are exposed to a treatment with pivaloyl chloride (30 min, 3-5 equivalents), it is difficult to estimate the extent of this reaction during solid phase synthesis of oligonucleotides. In principle, this kind of potential modification can be reversed by treatment of oligonucleotides with a primary amine[111] before the oxidation cycle, but more studies are still needed to examine this problem. In any case, even if the P-acylation may occur to a small extent during oligonucleotide synthesis involving acyl chlorides as coupling agents, it is not likely that this will lead to modification of internucleotidic linkages in synthetic oligonucleotides produced by this method. During the final deprotection with aqueous ammonia, oligonucleotidic chains will be cleaved at sites where acylphosphonates are present, and thus only slight decrease in yields of oligomers with the desired chain length should be expected. It is worth mentioning that among the investigated condensing agents (7)-(11), only the chlorophosphate (11) was found to be completely unreactive toward H-phosphonate diesters even when used in large excess and during a prolonged reaction time (overnight).[53]

Some other studies related to oligonucleotide synthesis *via* H-phosphonate intermediates have also been reported recently. They include some aspects of the 2'-OH protection during oligoribonucleotide synthesis,[134] exploitation of nucleoside 3'-phosphordiamidites for the synthesis of dinucleoside H-phosphon-

ates,[135,136] conversion of dinucleoside aryl phosphite triesters into dinucleoside H-phosphonates,[137] use of nucleoside 3'-(β-cyanoethyl)-H-phosphonates as starting materials for the formation of phosphite triesters,[138] synthesis of "branched" trinucleotides using the H-phosphonate chemistry,[139] synthesis of dinucleoside H-phosphonates *via* acylphosphonate derivatives,[108] synthesis of 5'-phosphorylated oligonucleotides,[140,141] and introduction of linkers for the attachment of hybridization probes.[142]

B. Synthesis of Some Oligonucleotide Analogues

An attractive feature of oligonucleotide synthesis *via* H-phosphonate intermediates is that oligonucleoside H-phosphonates can be converted either into compounds containing natural phosphodiester linkages, or into their analogues. This can be done by changing oxidation conditions in the final synthetic cycle.

If water is replaced by an alcohol or by a primary or secondary amine during the oxidation of H-phosphonate diesters with iodine, the corresponding phosphotriesters and phosphoramidates are formed, respectively.[143] It was found that substantially better results are obtained when instead of iodine, the Atherton-Todd method[144] is used for oxidation. Typically, solid phase bound oligonucleoside H-phosphonates are treated during 5 min with carbon tetrachloride containing 10% of an appropriate amine to produce oligonucleotides with uniform phosphoramidate linkages.[143] Alternatively, phosphotriester linkages[143] can be formed if an alcohol with a tertiary amine are present during the oxidation.

There is also another way to produce phosphotriesters *via* H-phosphonate intermediates. Although H-phosphonate monoesters afford exclusively H-phosphonate diesters[7,8,10] during condensations with alcohols, it is possible by changing reaction conditions to obtain phosphate triesters as a major product.[145] This can be done by preactivation of H-phosphonate monoesters with a condensing agent (usually an acyl chloride) followed by addition of an appropriate hydroxylic component and *in situ* oxidation of the produced phosphite triester. Such a procedure was successfully applied for the synthesis of, otherwise difficult to prepare, sterically hindered phosphotriesters possessing three nucleoside moieties bound to the phosphorus centre (trinucleoside monophosphates).[145]

Another type of oligonucleotide analogue, namely phosphorothioates, can be efficiently produced by treatment of an

oligonucleotide containing H-phosphonate functions with elemental sulfur[143,146] (0.1 *M* S_8 in triethylamine/carbon disulfide, 1:9, v/v, 5 min). This method was used for preparation of several biologically active oligonucleotide phosphorothioates,[147,148] as well as for the incorporation of radioactive sulfur[149] into oligonucleotides. Some studies concerning stereochemical aspects of sulfurization of H-phosphonate diesters have recently been published.[150,151]

The P-H bond in H-phosphonate diesters can also be converted into a P-C bond *via* silylation followed by treatment with the appropriate alkyl chlorides.[50] Although usually high yields for this kind of conversion have been reported, the method failed in the synthesis of nucleoside methylphosphonate derivatives.[50]

It was recently reported that oligonucleotide analogues containing phosphoramidate internucleotidic bonds[152] can be produced *via* oxidative coupling (Atherton-Todd method) of nucleoside methyl H-phosphonate diester with 5'-aminonucleosides. The reaction is efficient and the produced dinucleoside phosphoramidates have been used as synthons[152] in further synthesis of oligonucleotide analogues *via* H-phosphonate intermediates.

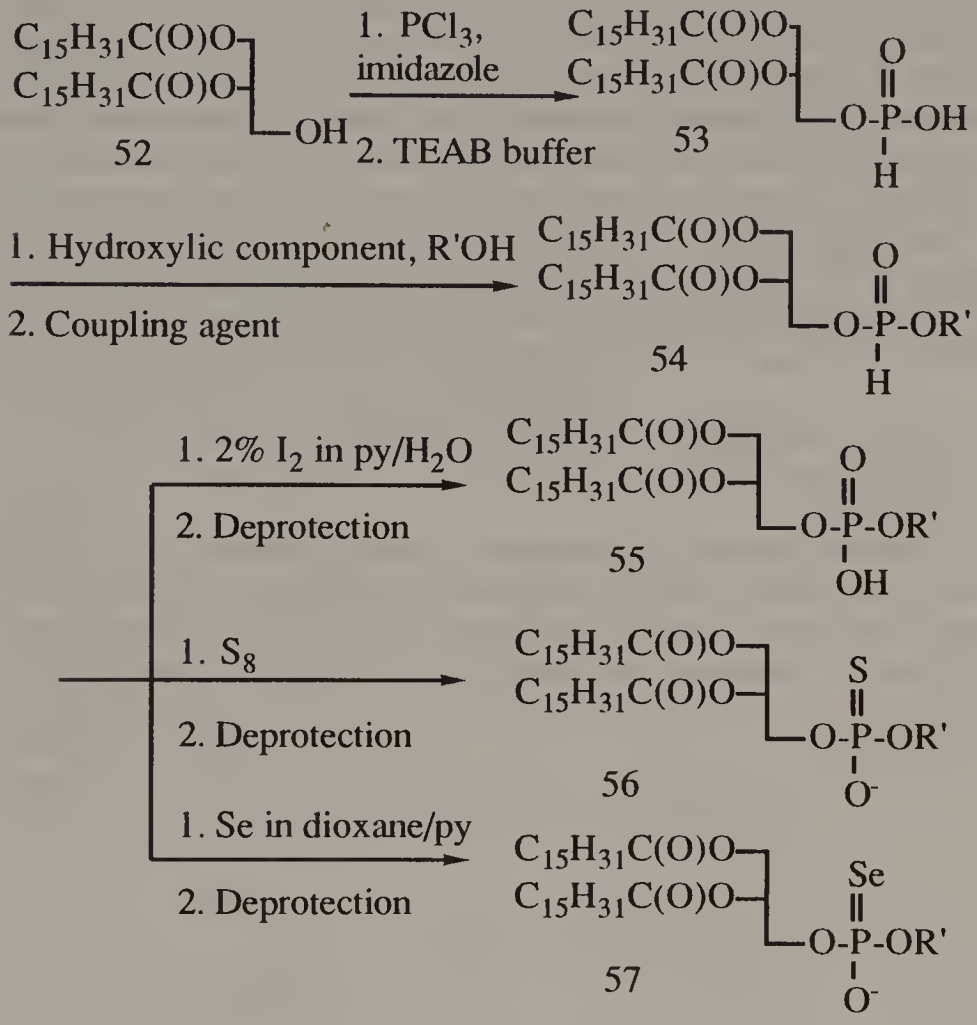
C. Other Synthetic Applications (Glycerophospholipids, Sugar Phosphates, Nucleopeptides, *etc.*)

H-Phosphonate chemistry has also been applied successfully for the preparation of a variety of natural products containing phosphodiester functions, *e.g.* phospholipids,[27] sugar phosphates,[26,38] and nucleopeptides.[37]

In Fig. 18 is presented a general scheme for the synthesis of phospholipids and their analogues *via* H-phosphonate intermediates.[27]

The 1,2-diacyl-*sn*-glycerol-3-H-phosphonate (53) can be obtained in high yield and may serve as a starting material for the preparation of various H-phosphonate diesters of type (54). These, in turn, can be converted into natural phospholipids (55) or into their thio (56) or seleno (57) analogues *via* oxidation, sulfurization, and selenization, respectively. For a routine synthesis of phospholipids, all chemical steps (coupling and oxidation) can be carried out as a "one-pot" reaction. However, if so desired, the intermediates of type (54) can be isolated, purified, and then used for subsequent transformation. The method is experimentally simple and efficient (average yields ~90%),[27] and is applicable also for the preparation

of various related compounds, *e.g.* nucleoside-[153] and oligodeoxyribonucleotide-phospholipid conjugates,[154] or glycobiosyl phosphatidylinositol derivatives.[155]



R' = choline, ethanolamine, or L-serine

Figure 18 - Synthesis of phospholipids *via* H-phosphonate intermediates

Examples of exploitation of the H-phosphonate method in the synthesis of carbohydrate phosphodiesters include a recent synthesis of a hapten corresponding to the repeat unit of the *Haemophilus influensa* capsular antigen,[156] synthesis of fragments of the cell wall polymer of *Staphylococcus lactis*,[38] synthesis of 1-6 linked poly (α-D-mannopyranosyl phosphates),[26] synthesis of

immunodominant fragments of yeast phosphoglycans,[157] synthesis of agrocinopine A,[158] and others.[159-163]

Nucleoproteins are also easily accessible *via* H-phosphonate methodology.[164] They are natural biopolymers[165] in which 5'-OH groups of nucleic acids (RNA and DNA) are covalently linked through phosphodiester linkages with the hydroxyl functions of amino acids (serine, threonine, and tyrosine) in proteins. It was reported[164] that 5'-phosphonylated oligonucleotides coupled efficiently with suitably protected amino acids in the presence of a condensing agent to produce nucleoprotein fragments. The method[164] was claimed to be superior to other approaches investigated[166] since it *inter alia* simplified the problem of synchronization of various protecting groups during synthesis.

VI. Thio Analogues of H-Phosphonate Esters

A. General

Analogues of H-phosphonate mono- and diesters in which one or two non-bridging oxygens at the phosphorus centre have been substituted by sulfur [compounds (58), (60), and (62)] seem to be quite interesting, both from theoretical and synthetic points of view.

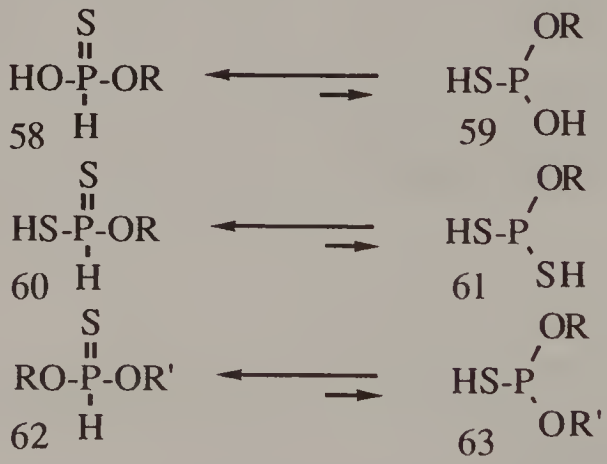


Figure 19 - Equilibria of thio analogues of H-phosphonate esters

As was the case with H-phosphonate esters, these compounds also exist predominantly in their phosphonate forms [(58), (60), and (62)],[167] but little is known about these equilibria or about the reactivity of their P-H bonds. Similarly to phosphoro-

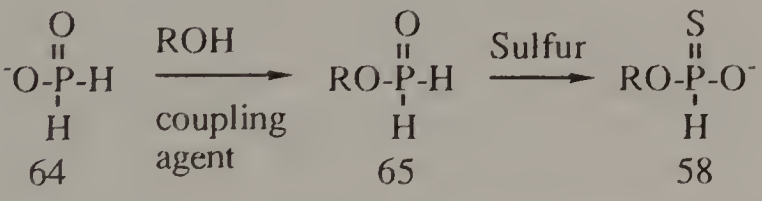
thioate analogues,[168] these compounds can be valuable tools in elucidation of some reaction mechanisms and in investigations of important processes in H-phosphonate chemistry, *e.g.* the tautomeric H-phosphonate-phosphite equilibrium, or the phosphorus-bound hydrogen exchange. It is worth mentioning that H-phosphonothioate monoesters of type (58) are chiral at the phosphorus centre, and this feature can potentially be exploited in stereospecific synthesis of chiral phosphorothioate derivatives.

B. Synthesis of H-Phospho*no**mono*Thioate Monoesters

Simple alkyl H-phosphonothioates of type (58) can be prepared by alkaline hydrolysis of the corresponding diesters.[169,170] However, this method is not suitable for the preparation of natural product derivatives.

Recently a new synthetic approach, which makes use of phosphinate intermediates,[171] has been reported for the preparation of H-phosphonothioate monoesters. Though the method was checked only with nucleoside H-phosphonothioates, it is believed to be rather general for the preparation of various natural product analogues.

As shown in Fig. 20, the triethylammonium salt of phosphinic acid (64) reacts with a nucleoside in the presence of a condensing agent in pyridine to produce the phosphinate intermediate (65) which upon *in situ* sulfurization affords the desired nucleoside H-phosphonothioate monoester (58).



R = protected ribo- or deoxyribonucleosid-3'-yl or ethyl

Figure 20 - Synthesis of H-phosphonothioate monoesters

The method[171] was used for the preparation of various deoxyribo- and ribonucleoside 3'-H-phosphonothioates (yields ~80-90% after silica gel or reversed-phase silica gel chromatography), and proved to be experimentally simple and reliable.

The H-phosphonothioates of type (58) can also be obtained *via* desulfurization of the corresponding dithioates (60) using

carbodiimides,[172] but it is difficult to say if this reaction can be of preparative value.

C. Synthesis of H-Phosphono*di*Thioate Monoesters

Methods available for the preparation of dithio analogues of H-phosphonate monoesters are summarized in Fig. 21.

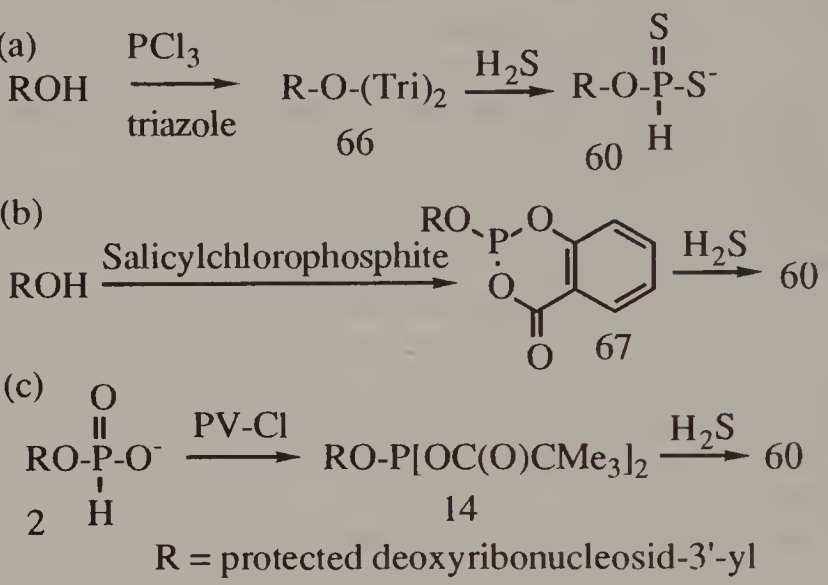


Figure 21 - Syntheses of H-phosphonodithioate monoesters

The first two approaches (Figs. 21a and 21b)[173,174] make use of the same intermediates [(66) and (67)] as in the synthesis of nucleoside H-phosphnate monoesters. However, in this case the intermediates are not hydrolyzed, but are treated with hydrogen sulfide to produce the H-phosphonodithioates of type (60). It takes ~30 min to convert the intermediates (66) (triazole or imidazole derivatives) and (67) into the product (60) by passing hydrogen sulfide through the reaction mixtures,[173] or 1-2 min by adding a stock solution of hydrogen sulfide in dioxane (yields ~65-75%).[174]

It is also possible to convert the H-phosphonate function into an H-phosphonodithioate[174] one *via* its activation with pivaloyl chloride followed by treatment with hydrogen sulfide (Fig. 21c). The yields of dithioates (60) are, however, only moderate (~65%). In the reactions b and c of Fig. 21, the monothio derivatives (58) are usually formed as side products (~10%) irrespective of the excess of hydrogen sulfide used.

D. Synthesis of H-Phosphonothioate Diesters

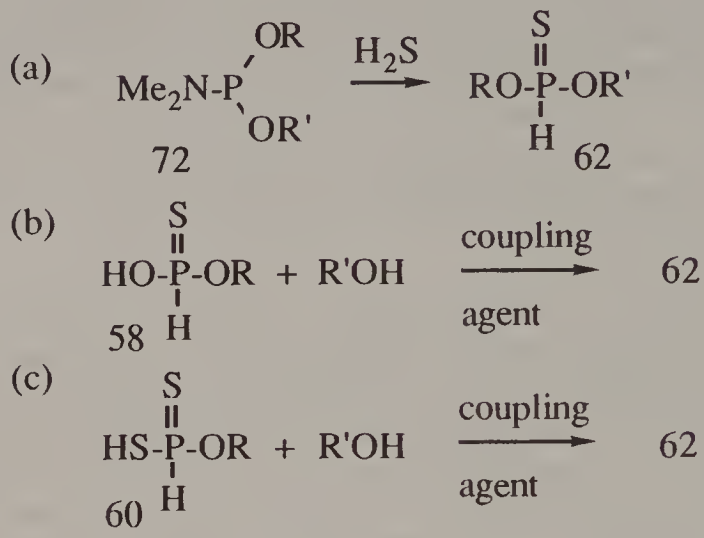
Only a limited number of synthetic methods for the preparation of simple dialkyl H-phosphonothioates are described in the literature. They include: (i) reaction of H-phosphonate diesters with phosphorus pentasulfide (P_2S_5),[175] (ii) reaction of dialkyl phosphorochloridites with hydrogen sulfide in the presence of a base,[176,177] (iii) treatment of phosphite triesters with hydrogen sulfide,[178] (iv) reaction of phosphorus sulfides with alcohols,[179] and (v) transesterification of H-phosphonothioate diesters with alcohols.[180]

Unfortunately, most of the methods suffer from various disadvantages (*e.g.* low to moderate yields of H-phosphonothioate diesters, starting materials are usually not easily accessible, or impossible to purify in the case of natural produt derivatives) and are of little use for the preparation of natural product analogues.

It seems that at present three approaches (Fig. 22a-c) can be considered as promising for the synthesis of H-phosphonothioate diesters. The first method (Fig. 22a) makes use of phosphoramidites, which can easily be converted into the corresponding H-phosphonthioate diesters by treatment with hydrogen sulfide.[181] Since phosphoramidites from various natural products are accessible *via* a phosphite approach, the method has been used for the preparation of dinucleoside H-phosphonothioates.[182] The disadvantage of this approach is that extremely anhydrous conditions have to be kept throughout the synthesis to avoid formation of the H-phosphonate diesters.

In the second and third approaches (Fig. 22b-c), H-phosphono*mono*thioates[183] and H-phosphono*di*thioates[173] are used as starting material. Both methods are experimentally simple and produce the H-phosphonothioate diesters in good yields. It was claimed that use of H-phosphonodithioates (60) offers some advantages over the method in Fig. 22b, which makes use of H-phosphonomonothioates (58). It was argued that in the latter case two centres (oxygen and sulfur) can be activated with a condensing agent, and thus H-phosphonate diesters can be formed together with H-phosphonothioates (62). In principle it is possible, but since the O-activation is apparently much faster than the S-activation, only the desired H-phosphonothioate diesters (62) are formed during the condensation of the monothioates (58) with alcohols.[183] It should be pointed out that the reaction of Fig.

22b[183] is substantially faster than the reaction of Fig. 22c,[173] which seems to reflect also higher reactivity of the O-activated intermediates (Fig. 22b) over the S-activated ones (Fig. 22c).



R = protected nucleosid-3'-yl
R' = protected nucleosid-5'-yl

Figure 22 - Synthesis of H-phosphonothioate diesters

The preliminary studies[183] on the synthesis of H-phosphonothioate diesters have shown that the P-H bond in compounds of type (62) is more reactive than that in H-phosphonate diesters. The higher reactivity of these bonds result in faster oxidation and sulfurization of H-phosphonothioate diesters.[183] Also, formation of some side-products during the condensation reactions (P-acylation, phosphite triester formation) are probably connected with this phenomenon. It seems that in the case of the thio analogues of H-phosphonate esters the choice of a condensing agent is a rather important factor.[183] Condensation of nucleoside H-phosphonomonothioate (58) with a hydroxylic component (Fig. 22b) can be carried out in the presence of pivaloyl chloride, but better results are achieved when chlorophosphates [*e.g.* (8), (10), (11)] are used as condensing agents.[183] The opposite is true for the reaction of Fig. 22c. Chlorophosphates were found to be rather poor activators for the nucleoside H-phosphonodithioates,[151] but acyl chlorides (*e.g.* pivaloyl chloride) promote condensation satisfactorily.[151,173] No

difference in terms of reaction time and formation of side products were observed when pivaloyl chloride was replaced by 1-adamantanecarbonyl chloride in this reaction.[151]

Until now only H-phosphonothioates derived from short oligonucleotides have been synthesized and successfully converted into phosphorodithioate and phosphoroselenothioate esters.[173,182,183] Some other studies on H-phosphonothioate esters have also been reported, *e.g.* oxidative coupling of nucleoside H-phosphonodithioates with nucleosides[172] in the presence of iodine, studies on sulfurization of H-phosphonothioate diesters,[185,186] and others.[167,177,187]

Recently, a simple method for the transformation of the H-phosphonate diester function into the phosphorodithioate one was described.[188] Using a chlorophosphorane as a chlorinating agent,[138] H-phosphonate diesters can be converted into the corresponding phosphorochloridites, which upon a consecutive treatment with hydrogen sulfide and elemental sulfur afford phosphorodithioate esters.[188]

VII. Concluding Remarks

The biological importance and practical significance of phosphoric acid esters have been the major driving forces for research in various areas of organic phosphorus chemistry. These have resulted in the development of numerous synthetic methods which make use of either (i) various phosphoric acid derivatives [P(V) intermediates], *e.g.* the phosphodiester and phosphotriester methods, or (ii) employ compounds with phosphorus at a lower oxidation state [P(III) derivatives], *e.g.* the phosphoramidite and H-phosphonate methods. Although both P(V) and P(III) methodologies are currently in use, the latter ones seem to gain wider application due to the higher reactivity of P(III) derivatives and higher versatility of the synthetic procedures.

The growing interest in H-phosphonate chemistry in recent years is probably due to the fact that this chemistry combines the advantages of most important methodologies that are available for the preparation of phosphorus-containing natural products, namely the phosphodiester, phosphotriester, and phosphite approaches.

The favourable tautomeric equilibria of mono- and diesters of phosphonic acids, which are practically completely shifted toward the H-phosphonate form, makes these compounds stable and resistant to air oxidation. H-Phosphonate monoesters derived from various natural products (nucleosides, sugars, lipids, and amino

acids) are easy to prepare in high yield using cheap and simple reagents for the phosphonylation. In the presence of condensing agents, these compounds become most reactive and couple efficiently with various hydroxylic components to produce H-phosphonate diesters. Due to the very fast condensation, side reactions usually associated with the use of condensing agents (*e.g.* acylation, phosphorylation, sulfonation) can practically be neglected in this approach, at least during "solution syntheses". Since H-phosphonate diesters are uncharged, they are soluble in organic solvents and can be purified on silica gel columns. Quite often, due to the high coupling yields, the purification step is superfluous, and crude condensation products can be used for further transformations after a simple work-up, or even without it. The most advantageous feature of H-phosphonate diesters is that they can be converted into the corresponding phosphodiesters *via* oxidation under mild conditions. Since no protecting group is present at the phosphorus centre, synthesis *via* H-phosphonate intermediates simplifies deprotection, which usually results in higher yields of final products. In addition, some problems connected with the synchronization of protecting groups during synthesis can be avoided.

It is also relatively easy to introduce a modification at the phosphorus centre by changing the oxidation conditions. Since oxidation is the final synthetic step before deprotection, phosphoramidate, phosphorothioate, or phosphoroselenoate derivatives can be produced from the same synthetic batch. Other types of phosphodiester analogues are also accessible by using H-phosphonothioate esters as starting materials or as intermediates.

At the present stage of development, the H-phosphonate chemistry seems to be superior to other available methodologies for the synthesis of phosphate esters and their analogues in solution. It was claimed on several occasions that syntheses *via* H-phosphonate intermediates provide substantial improvements in terms of yield, versatility, and synthetic simplicity. Concerning machine-assisted solid phase synthesis of oligonucleotides, the method has not yet been optimized, but shows great potential, especially for RNA-fragment synthesis. Since some technical problems connected with the design of machines have not yet been solved to suit H-phosphonate chemistry, it is difficult to say if the slightly lower yields occasionally reported for DNA-syntheses *via* H-phosphonate intermediates are due to technical or chemical factors. However, in the case of RNA-synthesis, condensation yields seem to be equal or

higher than those reported for the phosphoramidite approach. This may possibly be due to lower sensitivity of H-phosphonate monoesters to steric hindrance during the condensation.

Recent studies on error rates in deoxyribooligonucleotides synthesized by the H-phosphonate method[189] indicate that some kind of modifications can occur during the synthesis. Although the amidite method gives lower error rates in DNA-synthesis, the overall performance of the H-phosphonate method was claimed to be superior in speed, preparation and stability of the reagents, and cost.[189] In addition, it may be the method of choice for RNA-synthesis since the rate of condensation is only slightly affected by the presence of a 2'-OH protecting group in a nucleotidic unit. The H-phosphonate approach also seems to be valuable for the preparation of oligonucleotide phosphorothioate analogues of high degree of purity (absence of O-oxidized species).

Despite the impressive progress made during the last few years in H-phosphonate chemistry, its scope and limitations in the synthesis of phosphorus-containing natural products have not yet been explored fully. More basic studies apparently are needed in this area of organic phosphorus chemistry, and the existing experimental data have to be examined more carefully. Also, to get full benefit from this chemistry, some stereochemical aspects of condensation and oxidation of H-phosphonate esters have to be explored further.

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IX. Bibliography

1. Guthrie, J.P. (1979). Tautomerization equilibria for phosphorous acid and its ethyl esters, free energies of formation of phosphorous and phosphonic acids and their ethyl esters, and pK_a values for ionization of the P-H bond in

phosphonic acid and phosphonic esters, *Can. J. Chem.*, *57*: 236.
2. Edmundson, R.S. (1979). Dialkyl phosphites (dialkyl hydrogen phosphonates), in *Comprehensive Organic Chemistry, Vol. 2*, (Barton, D., and Ollis, W.D., eds.), Pergamon Press, Oxford, p. 1224.
3. Doak, G.O., and Freedman, L.D. (1961). The structure and properties of the dialkyl phosphonates, *Chem. Rev.*, *61*: 31.
4. Nylen, P. (1938). Acidic and basic catalysis in the reaction between dialkyl phosphites and iodine, *Z. anorg. allgem. Chem.*, *235*: 161.
5. Hall, R.H., Todd, A., and Webb, R.F. (1957). Nucleotides. XLI. Mixed anhydrides as intermediates in the synthesis of dinucleoside phosphates, *J. Chem. Soc.*: 3291.
6. Holy, A., and Sorm, F. (1966). Nucleic acid components and their analogs. LXXX. Preparation of nucleoside phosphites by reaction of nucleosides with triphenyl phosphite, *Coll. Czech. Chem. Commun.*, *31*: 1544.
7. Garegg, P.J., Regberg, T., Stawinski, J., and Stromberg, R. (1985). Formation of internucleotide bonds *via* phosphonate intermediates, *Chemica Scr.*, *25*: 280.
8. Garegg, P.J., Regberg, T., Stawinski, J., and Stromberg, R. (1986). Nucleoside hydrogenphosphonates in oligonucleotide synthesis, *Chemica Scr.*, *26*: 59.
9. Garegg, P.J., Lindh, I., Regberg, T., Stawinski, J., and Stromberg, R. (1986). Nucleoside H-phosphonates. III. Chemical synthesis of oligodeoxyribonucleotides by the hydrogenphosphonate approach, *Tetrahedron Lett.*, *27*: 4051.
10. Garegg, P.J., Regberg, T., Stawinski, J., and Stromberg, R. (1987). Nucleoside H-phosphonates. V. The mechanism of hydrogenphosphonate diester formation using acyl chlorides as coupling agents in oligonucleotide synthesis by the hydrogenphosphonate approach, *Nucleosid. Nucleotid.*, *6*: 665.
11. Froehler, B.C., and Matteucci, M.D. (1986). Nucleoside H-phosphonates: valuable intermediates in the synthesis of deoxyoligonucleotides, *Tetrahedron Lett.*, *27*: 469.
12. Froehler, B.C., Ng, P.G., and Matteucci, M.D. (1986). Synthesis of DNA *via* deoxynucleoside H-phosphonate intermediates, *Nucl. Acids Res.*, *14*: 5399.
13. Hammond, P.R. (1962). Simple preparation of alkyl ammonium phosphonates and some comments on the

reaction, *J. Chem. Soc.*: 2521.
14. Nylen, P. (1936). The monoalkyl phosphites and their saponification, *Svensk kem. Tidskr.*, *48*: 2.
15. Baddiley, J., Clark, V.M., Michalski, J.J., and Todd, A.R. (1949). Phosphorylation. V. Reaction of tertiary bases with esters of phosphoric and pyrophosphoric acids - selective debenzylation, *J. Chem. Soc.*: 815.
16. Parker, J.B., and Smith, T.D. (1961). Reaction of thiourea with dialkyl phosphites and trialkyl phosphates, *J. Chem. Soc.*: 442.
17. Cremlyn, R.J.W., Kenner, G.W., Mather, J., and Todd, A.R. (1958). Phosphorylation. XVI. Iodides as debenzylating and dealkylating agents, *J. Chem. Soc.*: 528.
18. Boyd, D.R. (1901). Action of chlorides of phosphorus on aromatic ethers of glycerol. Diaryloxyisopropylphosphorous acids, *J. Chem. Soc.*, *79*: 1221.
19. Schofield, J.A., and Todd, A. (1961). Nucleotides. XLVI. Preparation of nucleoside phosphites, *J. Chem. Soc.*: 2316.
20. Holy, A., Smrt, J., and Sorm, F. (1965). Nucleic acid components and their analogs. LIX. Preparation and properties of nucleoside phosphites, *Coll. Czech. Chem. Commun.*, *30*: 1635.
21. Hata, T., and Sekine, M. (1974). Oxidation of nucleoside phosphites by means of 2,2'-dipyridyl disulfide *via* nucleoside silyl phosphite intermediates, *Tetrahedron Lett.*: 3943.
22. Sekine, M., and Hata, T. (1975). Phenylthio group as a protecting group of phosphates in oligonucleotide synthesis *via* phosphotriester approach, *Tetrahedron Lett.*: 1711.
23. Honjo, M., Marumoto, R., Kobayashi, K., and Yoshioka, Y. (1966). Phosphorylation of ribonucleosides with phosphorus trichloride, *Tetrahedron Lett.*: 3851.
24. Holy, A., and Smrt, J. (1966). Oligonucleotidic compounds. XI. Synthesis of ribonucleoside 2'.3'-cyclophosphates from nucleosides *via* nucleoside 2',3'-phosphites, *Coll. Czech. Chem. Commun.*, *31*: 1528.
25. Sekine, M., Mori, H., and Hata, T. (1979). New type of chemical oxidative phosphorylation: Activation of phosphonate function by use of triisopropylbenzenesulfonyl chloride, *Tetrahedron Lett.*: 1145.
26. Nikolaev, A.V., Utkina, N.S., Shibaev, V.N., Ignatenko, A.V., and Kochetkov. N.K. (1988). Synthesis of 1→6

linked poly(α-D-mannopyranosyl phosphate) through the hydrogen phosphonate approach, *Bioorg. Khim.*, *14*: 555.
27. Lindh, I., and Stawinski, J. (1989). A general method for the synthesis of glycerophospholipids and their analogues *via* H-phosphonate intermediates, *J. Org. Chem.*, *54*: 1338.
28. Marugg, J.E., Tromp, M., Kuyl-Yeheskiely, E., van der Marel, G.A., and van Boom, J.H. (1986). A convenient and general approach to the synthesis of properly protected d-nucleoside-3'-hydrogenphosphonates *via* phosphite intermediates, *Tetrahedron Lett.*, *27*: 2661.
29a. Anschutz, R., and Emery, W.O. (1887). The reaction of salicylic acid with phosphorus trichloride, *Ann.*, *239*: 301.
29b. Young, R.W. (1952). A re-examination of the reaction between phosphorus trichloride and salicylic acid, *J. Am. Chem. Soc.*, *74*: 1672.
30. Tanaka, T. (1959). Phosphorylation. I. Preparation of phosphorus acid monoesters, *J. Pharm. Soc. Jpn.*, *79*: 437.
31. Sekine, M., Narui, S., and Hata, T. (1988). A convenient method for the synthesis of deoxyribonucleoside 3'-hydrogenphosphonates, *Tetrahedron Lett.*, *29*: 1037.
32. Garegg, P.J., Stawinski, J., and Stromberg, R. (1987). Activation of nucleoside hydrogen phosphonates by use of arylsulfonyl chlorides, *J. Chem. Soc., Perkin Trans II*: 1209.
33. Stawinski, J., and Thelin, M. (1990). Nucleoside H-phosphonates. XI. A convenient method for the preparation of nucleoside H-phosphonates, *Nucleosid. Nucleotid.*, *9*: 129.
34. Takaku, H., Yamakage, S., Sakatsume, O., and Ohtsuki, M. (1988). A convenient approach to the synthesis of deoxyribonucleoside-3'-hydrogen phosphonates *via* bis-(1,1,1,3,3,3-hexafluoro-2-propyl)phosphonate intermediate, *Chem. Let.*: 1675.
35. Gibbs, D.E., and Larsen, C. (1984). Bis[2,2,2-trifluoroethyl] phosphite, a new reagent for synthesizing mono- and diesters of phosphorous acid, *Synthesis*: 410.
36. Garegg, P.J., Lindh, I., Regberg, T., Stawinski, J., Stromberg, R., and Henrichson, C. (1986). Nucleoside H-phosphonates. 1V. Automated solid-phase synthesis of oligoribonucleotides by the hydrogenphosphonate approach, *Tetrahedron Lett.*, *27*: 4055.
37. Kuyl-Yeheskiely, E., Tromp, C.M., Schaeffer, A.H., van der Marel, G.A., and van Boom, J.H. (1987). A model

study directed towards the preparation of nucleopeptides *via* H-phosphonate intermediates, *Nucl. Acids Res.*, *15*: 1807.

38. Westerduin, P., Veeneman, G.H., van der Marel, G.A., and van Boom, J.H. (1986). Synthesis of the fragment GlcNAc-α(1→P→6)-GlcNAc of the cell wall polymer of *Staphylococcus lactis* having repeating *N*-acetyl-D-glucosamine phosphate units, *Tetrahedron Lett.*, *27*: 6271.
39. Thorpe, T.E., and North, B. (1890). Diethylphosphorous acid, *J. Chem. Soc.*, *57*: 634.
40. McCombie, H., Saunders, B.C., and Stacey, G.J. (1945). Esters containing phosphorus. I. *J. Chem. Soc.*: 380.
41. Atherton, F.R., Openshaw, H.T., and Todd, A.R. (1945). Phosphorylation. I. Dibenzyl chlorophosphonate as a phosphorylating agent, *J. Chem. Soc.*: 382.
42a. Zwierzak, A. (1967). Cyclic organophosphorus compounds. I. Synthesis and infrared spectral studies of cyclic hydrogen phosphites and thio phosphites, *Can. J. Chem.*, *45*: 2501.
42b. Gazizov, T.K., Kharlamov, V.A., and Pudovik, A.N. (1975). Reactions of diethyl phosphorochloridite with hydrogen chloride and of phosphorus trichloride with ethanol, *Zh. Obshch. Khim.*, *45*: 2339.
43. Bertrand, R.D., Berwin, H.J., McEwen, G.K., and Verkade, J.G. (1974). Stereochemistry of cage opening in 4-methyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane, *Phosphorus*, *4*: 81.
44. Hoffmann, F.W., and Weiss, H.D. (1957). Esterification of carboxylic acids by dialkyl phosphonates, *J. Am. Chem. Soc.*, *79*: 4759.
45. *Methoden der organischen Chemie, Vol XII/2* (1964). (Houben-Weyl), (Muller, E., ed.), Georg Thieme Verlag, Stuttgart, p. 27.
46. Oswald, A.A. (1958). Synthesis of cyclic phosphorus acid esters by transesterification, *Can. J. Chem.*, *37*: 1498.
47. Corby, N.S., Kenner, G.W., and Todd, A.R. (1952). Nucleotides. XVI. Ribonucleoside-5'-phosphite - preparation of mixed secondary phosphites, *J. Chem. Soc.*: 3669.
48. Stromberg, R., and Stawinski, J. (1987). Evaluation of some new condensing reagents for hydrogenphosphonate diester formation, *Nucl. Acids Res. symp. ser.*, *18*: 185.
49. Jager, A., Charubala, R., Pfleiderer, W. (1987). Synthesis and characterization of deoxy and ribo H-phosphonate dimers, *Nucl. Acids Res. symp. ser.*, *18*: 197.

50. de Vroom, E., Dreef, C.E., van den Elst, H., van der Marel, G.A., and van Boom, J.H. (1988). Preparation of internucleotide phosphate analogs *via* the corresponding hydrogen phosphonate diester, *Recl. Trav. Chim. Pays-Bas*, *107*: 592.
51. Garegg, P.J., Regberg, T., Stawinski, J., and Stromberg, R. (1987). Nucleoside phosphonates. Part 7. Studies on the oxidation of nucleoside phosphonate esters, *J. Chem. Soc., Perkin Trans. I*: 1269.
52. Garegg, P.J., Regberg, T., Stawinski, J., and Stromberg, R. (1987). Studies on the oxidation of nucleoside hydrogen phosphonates, *Nucleosid. Nucleotid.*, *6*: 429.
53. Regberg, T., Stawinski, J., and Stromberg, R. (1988). Nucleoside H-phosphonates. IX. Possible side-reactions during hydrogenphosphonate diester formation, *Nucleosid. Nucleotid.*, *7*: 23.
54. Garegg, P.J., Regberg, T., Stawinski, J., and Stromberg, R. (1987). Studies on the synthesis of oligonucleotides *via* the hydrogenphosphonate approach, *Nucleosid. Nucleotid.*, *6*: 283.
55. Garegg, P.J., Stawinski, J., and Stromberg, R. (1987). Nucleoside H-phosphonates. 8. Activation of hydrogen phosphonate monoesters by chlorophosphates and arenesulfonyl derivatives, *J. Org. Chem.*, *52*: 284.
56. Efimov, V.A., and Dubey, I.Y. (1990). Modification of the H-phosphonate oligonucleotide synthesis on polymer support, *Bioorg. Khim.*, *16*: 211.
57. Stawinski, J., Stromberg, R., Szabo, T., and Westman, E. (1989). Recent studies in nucleoside phosphonate chemistry, *Nucleosid. Nucleotid.*, *8*: 1029.
58. Stromberg, R. (1987). *Thesis, Chem. Comm. University of Stockholm.*
59. *Methoden der organischen Chemie, Vol. XII/2* (1964) (Houben-Weyl), (Muller, E., ed.), Georg Thieme Verlag, Stuttgart, p. 38.
60. Harvey, P.G., Myers, T.C., Jacobson, H.I., and Jensen, E.V. (1957). Phosphonic acids. V. An improved method for the preparation of sodium diethyl phosphonate and a study of its comparative reactivity with alkyl halides and R-toluenesulfonates, *J. Am. Chem. Soc.*, *79*: 2612.
61. Bruhl, J.W. (1902). Neuere Versuche mit Camphocarbonsaure, *Ber.*, *35*: 3516.

62. Dimroth, K., and Ploch, R. (1957). Eine neue Darstellungsmethode fur Ester der Phosphonsaure, *Ber.*, *90*: 801.
63. Gerrard, W., Green, W.J., and Nutkins, R.A. (1952). Dealkylation and hydrolysis of alkyl phosphites, phosphates, and phosphonates, *J. Chem. Soc.*: 4067.
64. Westheimer, F.H., Huang, S., and Covitz, F. (1988). Rates and mechanisms of hydrolysis of esters of phosphorous acid, *J. Am. Chem. Soc.*, *110*: 181.
65. Nylen, P. (1937). Kinetics of hydrolysis of dialkyl phosphites. I. Hydrolysis with hydrogen and hydroxyl ions, *Svensk kem.Tidskr.*, *49*: 29.
66. Michaelis, A., and Becker, T. (1898). Ueber die Constitution der Phosphorigen Saure, *Ber.*, *30*: 1003.
67. *Methoden der organischen Chemie, Vol. XII/1* (1964) (Houben-Weyl), (Muller, E., ed.), Georg Thieme Verlag, Stuttgart, p. 447.
68. *Methoden dre organischen Chemie, Vol. XII/1* (1964) (Houben-Weyl), (Muller, E., ed.), Georg Theime Verlag, Stuttgart, p. 463.
69. Abramov, V.S. (1957). Condensation of dialkyl phosphites with derivatives of carboxylic acids, *Dokl. Akad. Nauk, SSSR*, *112*: 868.
70. Karasch, M.S., Mosher, R.A., and Bengelsdorf, I.S. (1960). Organophosphorus chemistry. Addition reactions of diethyl phosphonate and the oxidation of triethyl phosphite, *J. Org. Chem.*, *25*: 1000.
71. *Methoden der organischen Chemie, Vol. XII/1* (1964) (Houben-Weyl), (muller, E., ed.), Georg Theime Verlag, Stuttgart, p. 487.
72. Laskorin, B.N., Yashin, V.V., and Bulgakova, V.B. (1976). Addition of salts of alkyl dihydrogen phosphites to unsaturated compounds, *Zh. Obshch. Khim.*, *46*: 2477.
73. Gevorkyan, A.A., Dyatkin, B.L., and Khunyants, I.L. (1965). Action of phosphorus esters on perfluoro *gem*-chloronitroso compounds, *Izv. Akad. Nauk, SSSR, ser. khim.*: 1599.
74. Troev, K., and Borisov, G. (1987). Characteristic reactions of the alkoxy groups of the diesters of phosphorous acid, *Phosphorus Sulfur*, *29*: 129.
75. *Methoden der organischen Chemie, Vol XII/2* (1964) (Houben-Weyl), (Muller, E., ed.), Georg Theime Verlag, Stuttgart, p. 287.

76. *Methoden der organischen Chemie, Vol. XII/2* (1964) (Houben-Weyl), (Muller, E., ed.), Georg Thieme Verlag, Stuttgart, p. 296.
77. *Methoden der organischen Chemie, Vol. XII/2* (1964) (Houben-Weyl), (Muller, E., ed.), Georg Thieme Verlag, Stuttgart, p. 37.
78. Brown, D.M., and Hammond, P.R. (1960). Studies on phosphorylation. XX. Oxidation of mono- and dialkyl phosphites, *J. Chem. Soc.*: 4229.
79. Blackburn, G.M., Cohen, J.S., and Todd, A.R. (1966). Studies in phosphorylation. XXIX. The synthesis of dialkyl phosphates from monoalkyl phosphonates: Direct oxidative esterification, *J. Chem. Soc., C*: 239.
80. Holy, A., Smrt, J., and Sorm, F. (1965). Nucleic acid components and their analogs. LXXI. Oxidation of nucleoside 5'-phosphites on treatment with halo acid derivatives and hexachloroacetone, *Coll. Czech. Chem. Commun., 30*: 3309.
81. Orlov, N.F., and Sudakova, E.V. (1969). Reaction between triorganochlorosilanes and phosphorous acid derivatives in the presence of organic bases, *Zh. Obshch. Khim., 39*: 222.
82. Hata, T., and Sekine, M. (1974). Silyl phosphites. I. The reaction of silyl phosphites with diphenyl disulfide. Synthesis *S*-phenyl nucleoside phosphorothioates, *J. Am. Chem. Soc., 96*: 7363.
83. Sekine, M., Yamagata, H., and Hata, T. (1979). Silyl phosphites. 8. Deoxygenation reactions by means of tris-(trimethylsilyl) phosphite, *Tetrahedron Lett.*: 375.
84. Michelson, A.M., and Todd, A.R. (1955). Nucleotides. Part XXXII. Synthesis of a dithymidine dinucleotide containing a 3':5'-internucleotidic linkage, *J. Chem. Soc.*: 2632.
85. Atherton, F.R., and Todd, A.R. (1947). Studies in phosphorylation. Part III. Further observations on the reaction of phosphites with polyhalogen compounds in presence of bases and its application to phosphorylation of alcohols, *J. Chem. Soc.*: 674.
86. Steinberg, G.M. (1950). Reactions of dialkyl phosphites. Synthesis of dialkyl chlorophosphates, tetraalkyl pyrophosphates, and mixed orthophosphate esters, *J. Org. Chem., 15*: 637.
87. Skowronska, A., Pakulski, M., Michalski, J., Cooper, D., and Trippett, S. (1980). The Arbuzov reaction of triethyl

phosphite with elemental iodine, *Tetrahedron Lett.*, *21*: 321.
88. Watanabe, M., Komoda, Y., Ebisuya, K., and Ozaki, S. (1990). An efficient phosphorylation method using a new phosphorylating agent, 2-diethylamino-1,3,2-benzodioxaphosphepane, *Tetrahedron Lett.*, *31*: 255.
89. Michalski, J., Okruszek, A., and Stec, W.J. (1970). Stereochemistry of oxidation of organophosphorus thiono-compounds and P(III) compounds by nitric acid and dinitrogen tetroxide, *J. Chem. Soc., Chem. Commun.*: 1495.
90. Hata, T., and Sekine, M. (1980). Silyl- and stannyl esters of phosphorus oxyacids - intermediates for the synthesis of phosphate derivatives of biological interest, in *Phosphorus Chemistry Directed Towards Biology*, (Stec, W.J., ed.), Pergamon Press, Oxford, p. 197.
91. Martin, B. (1959). The rate of exchange of the phosphorus bonded hydrogen in phosphorous acid, *J. Am. Chem. Soc.*, *81*: 1574.
92. Hammond, P.R. (1962). Ionization of the P-H bond. Deuterium-exchange studies with diethyl and ethyl H phosphonate, *J. Chem. Soc.*: 1365.
93. Luz, Z., and Silver, B. (1962). N.m.r. study of the exchange of phosphorus bonded hydrogen in dimethyl- and diethylphosphonate, catalyzed by acetate ion, *J. Am. Chem. Soc.*, *84*: 1095.
94. Luz, Z., and Silver, B. (1961). The acid catalyzed exchange of phosphorus bonded hydrogen in aqueous solutions of dialkyl phosphonates studied by nuclear magnetic resonance, *J. Am. Chem. Soc.*, *83*: 4518.
95. Nylen, P. (1938). Acidic and basic catalysis in the reaction between dialkyl phosphites and iodine, *Z. anorg. allgem. Chem.*, *235*: 161.
96. Westheimer, F.H. (1961). The magnitude of the primary kinetic isotope effect for compounds of hydrogen and deuterium, *Chem. Rev.*, *61*: 265.
97. Lewis, E.S., and Spears, L.G. (1985). Ionization of the PH bond in diethyl phosphonate, *J. Am. Chem. Soc.*, *107*: 3918.
98. Stawinski, J., and Thelin, M. (1990). Studies on the activation of phosphonic acid using acyl chlorides as activators, *J. Chem. Soc., Perkin Trans. II*: 849.
99. de Vroom, E., Spierenburg, M.L., Dreef, C.E., van der Marel, G.A., and van Boom, J.H. (1987). A general

procedure to convert H-phosphonate mono- or diesters of nucleic acids into valuable di- or triesters, *Rec. Trav. Chim. Pays-Bas*, *106*: 65.
100. Kuyl-Yeheskiely, E., Spierenburg, M., van den Elst, H., Tromp, M.T., van der Marel, G.A., and van Boom, J.H. (1986). Reaction of pivaloyl chloride with internucleosidic H-phosphonate diesters, *Rec. Trav. Chim. Pays-Bas*, *106*: 505.
101. Fitch, J.B., and Moedritzer, K. (1962). N.m.r. study of the P-C(OH)-P to P-C-O-P rearrangement: Tetraethyl 1-hydroxyalkylidenediphosphonates, *J. Am. Chem. Soc.*, *84*: 1876.
102. Prentice, J.B., Quimby, O.T., Grabenstettes, R.J., and Nicholson, D.A. (1972). Interaction of acylating agents and phosphorus(III) sources. I. Intermediacy of condensed species in the formation of ethane-1-hydroxy-1,1-diphosphonic acid, *J. Am. Chem. Soc.*, *94*: 6119.
103. Stawinski, J., and Stromberg, R., unpublished results.
104. Stawinski, J., Stromberg, R., Thelin, M., and Westman, E. (1988). Studies on the *t*-butyldimethylsilyl group as 2'-*O*-protection in oligoribonucleotide synthesis *via* the H-phosphonate approach, *Nucleosid. Nucleotid.*, *7*: 601.
105. Nifant'ev, E.E., and Fursenko, I.V. (1970). Acyl phosphites, *Russ. Chem. Rev.*, *39*: 2187.
106. Nifant'ev, E.E., and Fursenko, I.V. (1969). Alcoholysis of di- and triacyl phosphites, *Zh. Obshch. Khim.*, *39*: 1028.
107. Nifant'ev, E.E., and Fursenko, I.V. (1967). New data on the chemistry of acyl phosphites, *Zh. Obshch. Khim.*, *37*: 511.
108. Kume, A., Fujii, M., Sekine, M., and Hata, T. (1984). Acylphosphonates. 4. Synthesis of dithymidine phosphonate: a new method for generation of phosphonate function *via* aroylphosphonate intermediates, *J. Org. Chem.*, *49*: 2139.
109. Fujii, M., Ozaki, K., Kume, A., Sekine, M., and Hata, T. (1986). Acylphosphonates. 5. A new method for stereospecific generation of phosphorothioate *via* aroylphosphonate intermediates, *Tetrahedron Lett.*, *27*: 935.
110. Fujii, M., Ozaki, K., Kume, A., Sekine, M., and Hata, T. (1986). Acylphosphonates. 6. Reaction mechanism of Zn/Me_3SiCl mediated conversion of 2,2,2-trichloroethoxycarbonylphosphonates to silyl phosphites, *Tetrahedron Lett.*, *27*: 3365.

111. Fujii, M., Ozaki, K., Sekine, M., and Hata, T. (1987). Acylphosphonates. 7. A new method for stereospecific and stereoselective generation of dideoxyribonuceloside phosphorothioates *via* the acylphosphonate intermediates, *Tetrahedron*, *43*: 3395.
112. Sekine, M., Satoh, M., Yamagata, H., and Hata, T. (1980). Acylphosphonates: P-C bond cleavage of dialkyl acylphosphonates by means of amines. Substituent and solvent effects for acylation of amines, *J. Org. Chem.*, *45*: 4162.
113. Michalski, J., Modro, T., and Zwierzak, A. (1961). Anhydrides of organophosphorus acids. Part II. The synthesis of tri- and tetra-alkyl esters of phosphorous phosphoric anhydride, *J. Chem. Soc.*: 4904.
114. Daasch, L.W. (1958). The structure of the dialkyl phosphonates and some of their salts, *J. Am. Chem. Soc.*, *80*: 5301.
115. Michalski, J., and Zwierzak, A. (1965). Organophosphorus compounds. CIII. Synthesis of tetraalkyl hypophosphates, *Bull. Acad. Pol. Sci., ser. chim.*, *13*: 253.
116. Stec, W., Zwierzak, A., and Michalski, J. (1970). Organophosphorus compounds. CXLV. Reaction between sodium dialkyl phosphites and dialkyl phosphoric chloride, *Bull. Acad. Pol. Sci., ser. chim.*, *18*: 23.
117. Venijaminova, A.G., Komarova, N.I., Levina, A.S., and Repkova, M.N. (1988). Synthesis of ribonucleoside-3' and 5'-H-phosphonates *via* salicylchlorophosphine *Bioorg. Khim.*, *14*: 484.
118. Froehler, C.B., and Matteucci, M.D. (1987). The use of nucleoside hydrogen phosphonates in the synthesis of deoxyoligonucleotides, *Nucleosid. Nucleotid.*, *6*: 287.
119. Tocik, Z., Arnold, L., and Smrt, J. (1987). Automated 3'-H-phosphonate synthesis of oligodeoxyribonucleotides using amidine protected purine synthons, *Nucl. Acids Res. symp. ser.*, *18*: 193.
120. Bashuk, O.S., Zarytova, V.F., and Levina, A.S. (1988). Synthesis of oligonucleotide derivatives bearing amino and sulfhydryl groups on a polymer support. Introduction of spin, fluorescent, and other labels, *Bioorg. Khim.*, *14*: 606.
121. Gaffney, B.L., and Jones, R.A. (1988). Large-scale oligonucleotide synthesis by the H-phosphonate method, *Tetrahedron Lett.*, *29*: 2619.
122. Efimov, V.A.,, Dubey, I.Y., and Chakhmakhcheva, O.G.

(1990). NMR study and improvement of H-phosphonate oligonucleotide synthesis, *Nucleosid. Nucleotid.*, *9*: 473.
123. Isaguliants, M.G., Samoshin, V.V., and Makeeva-Smirnov, I.V. (1990). Efficient manual oligo(poly)deoxyribonucleotide synthesis in pipette tips *via* H-phosphonate approach, *Bioorg. Khim.*, *16*: 933.
124. Garegg, P.J., Henrichson, C., Lindh, I., Regberg, T., Stawinski, J., and Stromberg, R. (1987). Automated solid phase synthesis of DNA and RNA fragments by the hydrogen phosphonate approach, in *Biophosphates and Their Analogues: Synthesis, Structure, Metabolism, and Activity*, (Bruzik, K.S., and Stec, W.J., eds.), Elsevier, Amsterdam, p. 93.
125. Tanaka, T., Tamatsukuri, S., and Ikehara, M. (1987). Solid phase synthesis of oligoribonucleotides using the *o*-nitrobenzyl group for the 2'-hydroxyl protection and H-phosphonate chemistry, *Nucl. Acids. Res.*, *15*: 7235.
126. Sakatsume, O., Ohtsuka, M., Takaku, H., and Reese, C.B. (1989). Solid phase synthesis of oligoribonucleotides using the 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl (Ctmp) group for the protection of the 2'-hydroxyl functions and the H-phosphonate approach, *Nucl. Acids Res.*, *17*: 3689.
127. Venijaminova, A.G., Gorn, V.V., Zenakova, M.A., Komarova, N.I., and Repkova, M.N. (1990). Automated H-phosphonate synthesis of oligoribonucleotides using 2'-*O*-tetrahydropyranyl protecting group, *Bioorg. Khim.*, *16*: 941.
128. Rozners, E., Kumpins, V., Rekis, A., and Bizdena, E. (1988). Solid phase synthesis of oligoribonucleotides by the H-phosphonate method using 2'-*O*-benzoyl protecting group, *Bioorg. Khim.*, *14*: 1582.
129. Dan'kov, Y.V., Batchikova, N.V., Scaptsova, N.V., Besidsky, E.S., and Azhayev, A.V. (1988). H-Phosphonate solid-phase synthesis of oligodeoxyribonucleotides in syringes, *Bioorg. Khim.*, *14*: 615.
130. Sakatsume, O., Yamane, H., and Takaku, H. (1989). Use of new phosphorylating and coupling agents in the synthesis of oligodeoxyribonucleotides *via* the H-phosphonate approach, *Tetrahedron Lett.*, *30*: 6375.
131. Watanabe, T., Sato, H., and Takaku, H. (1989). New phosphite method: the synthesis of oligodeoxyribonucleotides by use of deoxyribonucleoside 3'[bis(1,1,1,3,3,3-

hexafluoro-2-propyl) phosphites] as new key intermediates, *J. Am. Chem. Soc.*, *111*: 3437.
132. Sakatsume, O., Yamane, H., Takaku, H., and Yamamoto, N. (1990). Use of new phosphorylating and coupling agents in the synthesis of oligodeoxyribonucleotides *via* the H-phosphonate approach, *Nucl. Acids Res.*, *18*: 3327.
133. Andrus, A., Efcavitch, J.W., McBride, L.J., and Giusti, B. (1988). Novel activating and capping reagents for improved hydrogen-phosphonate DNA synthesis, *Tetrahedron Lett.*, *29*: 861.
134. Stawinski, J., Stromberg, R., Thelin, M., and Westman, E. (1988). Studies on the *t*-butyldimethylsilyl group as 2'-*O*-protection in oligoribonucleotide synthesis *via* the H-phosphonate approach, *Nucl. Acids Res.*, *16*: 9285.
135. Marrug, J.E., Burik, A., Tromp, M., van der Marel, G.A., and van Boom, J.H. (1986). A new and versatile approach to the preparation of valuable deoxynucleoside 3'-phosphate intermediates, *Tetrahedron Lett.*, *27*: 2271.
136. Uznanski, B., Wilk, A., and Stec, W.J. (1987). Deoxynucleoside 3'-phosphordiamidites as substrates for solid supported synthesis of oligodeoxyribonucleotides and their phosphorothioate and DNA-triester analogues, *Tetrahedron Lett.*, *28*: 3401.
137. Eritja, R., Smirnov, V., and Caruthers, M.H. (1990). *O*-Aryl phosphoramidites: synthesis, reactivity and evaluation of their use for solid phase synthesis of oligonucleotides, *Tetrahedron*, *46*: 721.
138. Wada, T., Hotoda, H., Sekine, M., and Hata, T. (1988). 2-Cyanoethyl nucleoside 3'-phosphonates as novel starting materials for oligonucleotide synthesis, *Tetrahedron Lett.*, *29*: 4143.
139. Foldesi, A., Balgobin, N., and Chattopadhyaya, J. (1989). Synthesis of "branched" trinucleotide using the H-phosphonate chemistry, *Tetrahedron Lett.*, *30*: 881.
140. Filipov, S.A., Esipov, D.S., Kalinchenko, S.V., and Dobrynin, V.N. (1989). The synthesis of 5'-phosphorylated oligodeoxyribonucleotides by H-phosphonate method, *Bioorg. Khim.*, *15*: 527.
141. Venijaminova, A.G., Levina, A.S., Repkova, M.N., and Chenttsova, N.A. (1989). Phosphonylation of oligonucleotides by means of beta-cyanoethyl phosphite, *Bioorg. Khim.*, *15*: 844.

142. Shina, N.D., and Cook, R.M. (1988). The preparation and application of functionalised synthetic oligonucleotides: III. Use of H-phosphonate derivatives of protected amino-hexanol and mercapto-propanol or -hexanol. *Nucl. Acids Res.*, *16*: 2659.
143. Froehler, B.C. (1986). Deoxynucleoside H-phosphonate diester intermediates in the synthesis of internucleotide phosphate analogues, *Tetrahedron Lett.*, *27*: 5575.
144. Atherton, F.R., Openshaw, H.T., and Todd, A.R. (1945). Phosphorylation. II. Reaction of dialkyl phosphites with polyhalogen compounds in the presence of bases - method for the phosphonylation of amines, *J. Chem. Soc.*: 660.
145. Garegg, P.J., Lindh, I., and Stawinski, J. (1987). Synthesis of trinucleoside monophosphates using nucleoside H-phosphonates, in *Biophosphates and Their Analogues: Synthesis, Structure, Metaboilsm, and Activity*, (Bruzik, K.S., and Stec, W.J., eds.), Elsevier, Amsterdam, p. 89.
146. Fujii, M., Ozaki, K., Kume, A. Sekine, M., and Hata, T. (1986). Acylphosphonates - V. A new method for stereospecific generation of phosphorothioate *via* aroylphosphonate intermediate, *Tetrahedron Lett.*, *27*: 935.
147. Bielinska, A., Shivdasani, R.A., Zhang, L., and Nabel, G.J. (1990). Regulation of gene expression with double-stranded phosphorothioate oligonucleotides, *Science*, *250*: 997.
148. Agrawal, S., and Tang, J.-Y. (1990). Efficient synthesis of oligoribonucleotide and its phosphorothioate analogue using H-phosphonate approach, *Tetrahedron Lett.*, *31*: 7541.
149. Stein, C.A., Iversen, P.L., Subasinghe, C., Cohen, J.S., Stec, W.J., and Zon, G. (1990). Preparation of ^{35}S-labeled polyphosphorothioate oligodeoxyribonucleotides by use of hydrogen phosphonate chemistry, *Anal. Biochem.*, *188*: 11.
150. Seels, F., and Kretschmer, F.U. (1990). Stereochemistry of oxidation of diastereoisomeric d(TpA) phosphonates with sulphur and iodine - [^{18}O]water, *J. Chem. Soc., Chem. Commun.*: 1154.
151. Stawinski, J., Stromberg, R., and Thelin, M., unpublished results.
152. Gryaznov, S.M., and Sokolova, N.I. (1990). A new method for the synthesis of oligodeoxyribonucleotides containing internucleotide phosphoramidate bonds, *Tetrahedron Lett.*, *31*: 3205.

153. Lindh, I., and Stawinski, J. (1987). Synthesis of phospholipids and nucleoside-phospholipid conjugates *via* hydrogenphosphonate intermediates, *Nucl. Acids. Res. symp. ser.*, *18*: 189.
154. Shea, R.G., Marsters, J.C., and Bischofberger, N. (1990). Synthesis, hybridization properties and antiviral activity of lipid-oligonucleotide complexes, *Nucl. Acids Res.*, *18*: 3777.
155. Murakata, C. and Ogawa, (1991). Synthetic studies on glycophosphatidylinositol anchor: A highly efficient synthesis of glycobiosyl phosphatidylinositol through H-phosphonate approach, *Tetrahedron Lett.*, *32*: 101.
156. Classon, B., Garegg, P.J., and Lindh, I. (1988). Synthesis of *p*-trifluoroacetamidophenyl β-D-glucopyranoside 4-(D-ribit-5-yl phosphate) corresponding to the *Haemophilus influenzae* type A capsular antigen, *Carbohydr. Res.*, *179*: 31.
157. Nikolaev, A.V., Ryabtseva, E.V., Shibaev, V.N., and Kochetkov, N.K. (1989). Fragments of biopolymers containing glycosyl phosphate residues. 3. Use of hydrogenphosphonate approach for the synthesis of glycosyl phosphosugars, immunodominant fragments of yeast phosphoglycans, *Bioorg. Khim.*, *15*: 1649.
158. Lindberg, M., and Norberg, T. (1988). Synthesis of sucrose 4'-(L-arabinose-2-yl phosphate) (agrocinopine A) using an arabinose 2-H-phosphonate intermediate, *J. Carbohydr. Chem.*, *7*: 749.
159. Eliseyeva, G.I., Nikolaev, A.V., Shibaev, V.N., and Kochetkov, N.K. (1989). Synthesis of 6-*O*-α-D-glucopuranosylphospho)-α-D-mannopyranosides - terminal fragments of glycoprotein specific chains, *Bioorg. Khim.*, *15*: 1140.
160. Nikolaev, A.V., Ivanova, I.A., Shibaev, V.N., and Kochetkov, N.K. (1989). Hydrogenphosphonate approach in (1-2)-, (1-3)- and (1-4)-linked glycosyl phosphosugar synthesis, *Bioorg. Khim.*, *15*: 847.
161. Nikolaev, A.V., Shibaev, V.N., and Kochetkov, N.K. (1987). Glycosyl phosphosugars *via* glycosyl hydrogenphosphonates, *Bioorg. Khim.*, *13*: 1591.
162. Nikolaev, A.V., Utkina, N.S., Shibaev, V.N., Ignatenko, A.V., and Kochetkov, N.K. (1989). Cyclic and linear oligo-

(mannosyl phosphates) from partially protected α-D-manno-pyranosyl hydrogenphosphonates, *Carbohydr. Res.*, *189*: c1.
163. Nikolaev, A.V., Ivanova, I.A., Shibaev, V.N., and Kochetkov, N.K. (1990). Fragmentation of biopolymers containing glycosyl phosphate residues. 4. Synthesis of (1-2)-, (1-3)-, and (1-4)-linked glycosyl phosphosugars by the hydrogenphosphonate method, *Bioorg. Khim.*, *16*: 674.
164. Kuyl-Yeheskiely, E., Tromp, C.M., Schaeffer, A.H., van der Marel, G.A., and van Boom, J.H. (1987). A model study directed towards the preparation of nucleopeptides *via* H-phosphonate intermediates, *Nucl. Acids Res.*, *15*: 1807.
165. Hermoso, J.M., and Salas, M. (1980). Protein p3 is linked to the DNA of phage ϕ29 through a phosphoester bond between serine and 5'-dAMP, *Proc. Natl. Acad. Sci. U.S.A.*, *77*: 6425.
166. Kuyl-Yeheskiely, E., van der Klein, P.A.M., Visser, G.M., van der Marel, G.A., and van Boom, J.H. (1986). A study directed towards the preparation of nucleopeptide fragments containing covalently linked L-serine or L-threonine, *Rec. Trav. Chim. Pays-Bas*, *105*: 69.
167. Kabachnik, M.I., and Mastryukova, T.A. (1953). Organo-phosphorus compounds. Dialkyl dithiophosphates, *Izv. Akad. Nauk S.S.S.R., ser. chim.*: 163.
168. Eckstein, F., and Gish, G. (1989). Phosphorothioates in molecular biology, *TIBS*, *14*: 97.
169. Kabachnik, M.I., and Mastryukova, T.A. (1953). Theory of tautomeric equilibrium. III. Pseudomerism. Structure and properties of dialkyl thiophosphites, *Izv. Akad. Nauk S.S.S.R., ser. chim.*: 163.
170. Michalski, J., Tulimowski, Z., and Wolf, R. (1965). Synthese gemischter Thiophosphorigsaure-*O,O*-dialkylester, *Ber.*, *98*: 3006.
171. Stawinski, J., Thelin, M., Westman, E., and Zain, R. (1990). Nucleoside H-phosphonates. 12. Synthesis of nucleoside 3'-(hydrogen-phosphonothioate) monoesters *via* phosphinate intermediates, *J. Org. Chem.*, *55*: 3503.
172. Brill, W.K.-D., Yau, E.K., and Caruthers, M.H. (1989). Oxidative and nonoxidative formation of internucleotide linkages, *Tetrahedron Lett.*, *30*: 6621.
173. Porritt, G.M., and Reese, C.B. (1989). Nucleoside phos-

phonodithioates as intermediates in the preparation of dinucleoside phosphorodithioates and phosphorothioates, *Tetrahedron Lett.*, *30*: 4713.

174. Stawinski, J., Szabo, T., Thelin, M., Westman, E., and Zain, R. (1990). Studies on the preparation of nucleoside H-phosphonothioates, *Coll. Czech. Chem. Commun.*, *55*: 141.
175. *Methoden der organischen Chemie, Vol. XII/2* (Houben-Weyl), (Muller, E., ed.), Georg Thieme Verlag, Stuttgart, p. 84.
176. Michalski, J. (1955). Action of hydrogen sulfide on chloroanhydrides of organic acids of tri- and quinquevalent phosphorus. Synthesis of new types of anhydrides of organic thio acids of phosphorus. New method of synthesis of dialkyl thiophosphites and their analogs, *Roczn. Chem.*, *29*: 960.
177. Krawiecki, C., and Michalski, J. (1960). Organophosphorus compounds of sulfur and selenium. XIII. Action of H_2S on dialkyl and diaryl phosphorochloridites - synthesis of dialkyl and diaryl thiophosphites and tetraalkyl thiopyrophosphites, *J. Chem. Soc.*: 881.
178. Akhmetzhanov, I.S. (1968). On reactions of trialkyl phosphites with hydrogen sulfide, *Zh. Obshch. Khim.*, *38*: 1090.
179. Kabachnik, M.I., and Mastryukova, T.A. (1952). Organophosphorus compounds. Reaction of phosphorus sulfides with alcohols, *Izv. Akad. Nauk S.S.S.R., ser. chim.*: 727.
180. Pudovik, A.N., and Khlyupina, N.I. (1956). Synthesis of esters of phosphonic and thiophosphonic acids. XXV. Addition of mixed dialkyl phosphites, dialkyl thiophosphites, and diallyl phosphite to unsaturated compounds, *Zh. Obshch. Khim.*, *26*: 1672.
181. Petrov, K.A., Basyluk, A.A., and Mizrakh, L.I. (1962). Properties of amides of phosphorus acids. III. New method of synthesizing thiophosphites and thiophosphonites, *Zh. Obshch. Khim.*, *32*: 3062.
182. Nielsen, J., Brill, W.K.-D., and Caruthers, M.H. (1988). Synthesis and characterization of dinucleoside phosphorodithioates, *Tetrahedron Lett.*, *29*: 2911.
183. Stawinski, J., Thelin, M., and Zain, R. (1989). Nucleoside H-phosphonates. X. Studies on nucleoside hydrogenphosphonothioate diester synthesis, *Tetrahedron Lett.*, *30*: 2157.

184. Predvoditelev, D.A., Afanas'eva, D.N., and Nifant'ev, E.E. (1976). *O*-Alkyl *O,O*-1,3-propanediyl phosphorothioates from *O,O*-propanediyl hydrogen phosphorothioates, *Zh. Obshch. Khim.*, *46*: 40.
185. Porritt, G.M., and Reese, C.B. (1990). Use of the 2,4-dinitrobenzyl protecting group in the synthesis of phosphorodithioate analogues of oligodeoxyribonucleotides, *Tetrahedron Lett.*, *31*: 1319.
186. Stawinski, J., Thelin, M., and von Stedingk, E. (1990). Studies on sulfurization of nucleoside H-phosphonate and H-phosphonothioate esters using 3*H*-1,2-benzodithiol-3-one 1,1-dioxide, *Nucleosid. Nucleotid.*, in press.
187. Stawinski, J., Stromberg, R., and Zain, R. (1990). Studies on the conversion of nucleoside H-phosphonate monoesters into the corresponding H-phosphonothioates, *Nucleosid. Nucleotid.*, in press.
188. Wada, T., and Hata, T. (1990). A facile conversion of dialkyl phosphonates to dialkyl phosphorodithioates, *Tetrahedron Lett.*, *31*: 7461.
189. Vasser, M., Ng, P.G., Jhurani, P., and Bischofberger, N. (1990). Error rates in oligonucleotides synthesized by the H-phosphonate method, *Nucl. Acids Res.*, *18*: 3089.

CHAPTER 9

ADVANCES IN ^{31}P NMR

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I. Introduction

Although ^{31}P spectra were reported as early as 1951 by Dickenson[1] and Gutowsky, *et al.*[2] it was the availability of commercial multinuclear NMR spectrometers by 1955 that led to the application of ^{31}P NMR as an important analytical tool for structure elucidation.[3,4] Early spectrometers generally required neat samples in large nonrotating tubes (8-12 mm OD). In the middle 1960s more sensitive, higher field electromagnets and signal averaging led to further rapid growth in the number of reported ^{31}P spectra and the publication of the first monograph devoted to this field.[5]

With the introduction by 1970 of Fourier-transform (FT) and high-field superconducting magnet NMR spectrometers, ^{31}P-NMR spectroscopy expanded from the study of small organic and inorganic compounds to biological phosphorus compounds as well. The latest multinuclear FT NMR spectrometers (1.8-14.1 Tesla) have reduced if not eliminated the serious limitation to the widespread utilization of phosphorus NMR, which is the low sensitivity of the phosphorus nucleus (6.6% at constant field compared to ^{1}H NMR). Today, routinely, millimolar (or lower) concentrations of phosphorus nuclei in as little as 0.3 mL of solution are conveniently monitored. The ^{31}P nucleus has other convenient NMR properties suitable for FT NMR: spin 1/2 (which avoids problems associated with quadrupolar nuclei), 100% natural abundance, moderate relaxation times (providing relatively rapid signal averaging and sharp lines), and a wide range of chemical shifts (>600 ppm).

With the tremendous increase in sensitivity in modern FT NMR spectrometers, biological and medical applications of ^{31}P NMR spectroscopy grew dramatically during the 1970s and 1980s. Additional monographs[6-8] entirely devoted to ^{31}P NMR, covering theory and applications to organophosphorus, phosphorus-metal complexes, and biological and medical aspects of the field have been published.

In this review I will discuss the interpretation of various ^{31}P

NMR spectroscopic parameters, particularly chemical shifts and coupling constants. Although the general literature will be briefly reviewed, a major emphasis will be placed on new developments in ^{31}P NMR methods which have considerably expanded the utility of this important spectroscopic probe in organic and biological structure determination.

II. NMR Considerations

Today's commercial NMR spectrometers cover the ^{31}P frequency range from 32-243 MHz. Generally for small, phosphorus-containing compounds, high signal-to-noise and resolution requirements dictate the use of as high a magnetic field strength as possible since both sensitivity and chemical-shift dispersion increase at higher operating frequency (and field). However, consideration must be given to field-dependent relaxation mechanisms such as chemical shift anisotropy which can lead to substantial line broadening of the ^{31}P signal at high fields. Indeed, especially for larger biomolecules, sensitivity is often poorer at very high fields because of considerably increased linewidths. The latest probe designs provide a remarkable signal-to-noise of 420:1 on a 1% trimethyl phosphite standard sample in a 10 mm tube in a single spectral acquisition (at 202 MHz) on a Varian VXR 500 spectrometer or 200:1 on a 0.0485 *M* triphenyl phosphate standard sample in a 5 mm tube in a single spectral acquisition (at 242 MHz on a Varian VXR 600 spectrometer.

Typical acquisition times for ^{31}P free induction decays (FID) following a 90^{o} radiofrequency pulse are 1-8 sec depending on the required resolution (dictated by the line-width of the signal, $1/\pi T_2^*$, where T_2^* is the time constant for the FID). Waiting longer than $3T_2^*$ will generally not improve the signal-to-noise (S/N). Additional consideration for optimization of the S/N must be given to the time it takes for the ^{31}P spins to return to thermal equilibrium after a 90^{o} radiofrequency pulse, which is roughly 3 times the spin-lattice relaxation time (T_1). If $T_1 \sim T_2^*$ as would be true for small phosphorus containing molecules where magnetic field inhomogeneity and paramagnetic impurities do not lead to any additional line broadening, then a waiting period between pulses of $3T_2^*$ provides a good compromise between adequate resolution and signal sensitivity. If $T_1 > T_2^*$, as is often the case in larger

biomolecular systems, then waiting only $3T_2^*$ does not allow the magnetization to return to equilibrium and an additional delay must generally be introduced so that the total time between pulses is $\sim 3T_1$. This wait can be substantially shortened if the Ernst relationship[9] is used to set the pulse flip angles to $<90^o$. At low field, 60-70^o pulses, 4 to 8 K data points and 2.0-5.2 sec recycle times are generally used. The spectra are generally broadband ^1H decoupled.

The temperature of the sample can be controlled to within $\pm 1^o$ by commercial spectrometer temperature control units. Maple, *et al.*[10] have recently demonstrated the importance of temperature control and the minimization of temperature gradients in the sample, which can be a major contributor to line broadening. With proper shimming and temperature control, ^{31}P linewidths of < 100 mHz may be achieved for small organophosphorus compounds. Broadband decoupling at higher superconducting fields can also produce about 10-15^o heating of the sample above the gas stream measured temperatures, even using a gated, two-level decoupling procedure.[11] This problem may be partially circumvented by using decoupling methods such as WALTZ or MLEV decoupling. The temperature of the sample should be measured under the experimental decoupling conditions. It is incorrect to assume that the temperature of the sample and the gas used to regulate the temperature of the sample are the same because the decoupler can heat the solution substantially above the gas temperature. This is especially true for biological solutions of high ionic strength. It is therefore necessary to be able to measure directly the solution temperature using either a non-magnetic thermocouple sensor or thermister inserted into the NMR solution, or better, a sample whose ^{31}P spectrum reflects the correct temperature. Several ^{31}P "thermometers" have been proposed for this purpose.[11-13]

The ^{31}P spectra are generally referenced to an external sample of 85% H_3PO_4 or trimethyl phosphate in D_2O, which is ~3.46 ppm downfield of 85% H_3PO_4. Note that throughout this Chapter the IUPAC convention[14] is followed so that *positive values are to high frequency* (low field). One should cautiously interpret reported ^{31}P chemical shifts because the early literature (pre 1970s) and even many later papers use the opposite sign convention.

With regard to quantification of peak heights, the intensity of

a resonance can be measured in several ways: 1) peak heights and areas obtained from the standard software supplied by the spectrometer manufacturer, 2) peak heights measured by hand, 3) peaks cut and weighed from the plotted spectrum, and 4) peaks fit to a Lorentzian lineshape. For flat baselines, intensity measurements are generally straightforward. However, in the event of curved baselines, the measurements are somewhat uncertain and manual measurements are generally more reliable than intensity values obtained from computer software.

It is often necessary that experiments be performed without allowing time for full recovery of longitudinal magnetization between transients because of the limited availability of spectrometer time or of the limited lifetime of the sample. Because of variations in T_1 between different phosphorus nuclei and variation in the heteronuclear NOE to nearby protons, care should be made in interpretation of peak areas and intensities. Addition of a recycle delay of at least 5 x T_1 between pulses and gated decoupling only during the acquisition time to eliminate $^{1}H/^{31}P$ NOE largely eliminates quantification problems.

III. Phosphorus-31 Chemical Shifts

A. Introduction and Basic Principles

The interaction of the electron cloud surrounding the phosphorus nucleus with an external applied magnetic field H_o gives rise to a local magnetic field. The induced field shields the nucleus, with the shielding proportional to the field H_o so that the effective field, H_{eff}, felt by the nucleus is given by Eqn. 1.

$$H_{eff} = H_o(1-\sigma) \qquad \text{Eqn. 1}$$

The term σ in Eqn. 1 is the shielding constant. Because the charge distribution in a phosphorus molecule will generally be far from spherically symmetrical, the ^{31}P chemical shift (or shielding constant) varies as a function of the orientation of the molecule relative to the external magnetic field.[15-19] This gives rise to a chemical shift anisotropy that can be defined by three principal components σ_{11}, σ_{22}, and σ_{33} of the shielding tensor.[15] For

molecules that are axially symmetrical, with σ_{11} along the principal axis of symmetry, $\sigma_{11} = \sigma_{||}$ (parallel component), and $\sigma_{22} = \sigma_{33} = \sigma_{\perp}$ (perpendicular component). These anisotropic chemical shifts are observed in solid samples[16-20] and liquid crystals[21] whereas for small molecules in solution, rapid tumbling averages the shift. The average, isotropic chemical shielding σ_{iso} (which would be comparable to the solution chemical shift) is given by the trace of the shielding tensor as noted in Eqn. 2.

$$\sigma_{iso} = 1/3(\sigma_{11} + \sigma_{22} + \sigma_{33}) \qquad \text{Eqn. 2}$$

The anisotropy $\Delta\sigma$ is given by Eqn. 3 for the general case and for the case of axial symmetry.

$$\Delta\sigma = \sigma_{11} - 1/2(\sigma_{22} + \sigma_{33}) \qquad \text{Eqn. 3}$$

$$\Delta\sigma = \sigma_{||} - \sigma_{\perp}$$

B. Theoretical ^{31}P Chemical Shift Calculations and Empirical Observations

1. Introduction

Several attempts have been made to develop a unified theoretical foundation for ^{31}P chemical shifts of phosphorus compounds.[22-27] In one theoretical approach, Letcher and Van Wazer,[22,23] using approximate quantum-mechanical calculations, indicated that three factors appear to dominate ^{31}P chemical-shift differences $\Delta\delta$, as shown by Eqn. 4.

$$\Delta\delta = -C\Delta_{\chi\chi} + k\Delta n_{\pi} + A\Delta\theta \qquad \text{Eqn. 4}$$

Here, $\Delta_{\chi\chi}$ is the difference in electronegativity in the P-X bond,

Δn_π is the change in the π-electron overlap, $\Delta\theta$ is the change in the σ-bond angle, and C, k, and A are constants.

As suggested by Eqn. 4, electronegativity effects, bond angle changes, and π-electron overlap differences can all potentially contribute to ^{31}P shifts in a number of classes of phosphorus compounds. While these semi-empirical isotropic chemical shift calculations are quite useful in providing a chemical and physical understanding of the factors affecting ^{31}P chemical shifts, they represent severe theoretical approximations.[28] More exact *ab initio* chemical shift calculations of the shielding tensor are very difficult and very few have been reported on phosphorus compounds.[28-30] Whereas the semi-empirical theoretical calculations have largely supported the importance of electronegativity, bond angle and π-electron overlap on ^{31}P chemical shifts, the equations relating ^{31}P shift changes to structural and substituent changes unfortunately are not generally applicable. Also, because ^{31}P shifts are influenced by at least three factors, empirical and semi-empirical correlations can be applied only to classes of compounds that are similar in structure. It should also be emphasized again that structural perturbations will affect ^{31}P chemical shift *tensors*. Often variations in one of the tensor components will be compensated by an equally large variation in another tensor component with only a small net effect on the isotropic chemical shift. Interpretation of variations of isotropic ^{31}P chemical shifts should be therefore approached with great caution.

Within these limitations a number of semi-empirical and empirical observations and correlations, however, have been established and have proved useful in predicting ^{31}P chemical-shift trends.[31] Indeed, unfortunately no single factor can readily rationalize the observed range of ^{31}P chemical shifts.

2. Bond Angle Effects

The Letcher and Van Wazer theory[23] suggested that changes in the σ-bond angles should make a negligible contribution ($|A| < 1$, Eqn. 4) to the ^{31}P chemical shifts of phosphoryl compounds, with electronegativity effects apparently predominating. Several empirical correlations between ^{31}P chemical shifts and X-P-X bond angles have been noted.[32-35] Note that success here depends on

the fact that these correlations deal with only a limited structural variation: in the case of phosphate esters, the number and chemical type of R groups attached to a tetrahedron of oxygen atoms surrounding the phosphorus nucleus. As shown in Fig. 1 (bottom curve), for a wide variety of different alkyl phosphates (mono-, di-, and triesters, cyclic and acyclic neutral, monoanionic, and dianionic

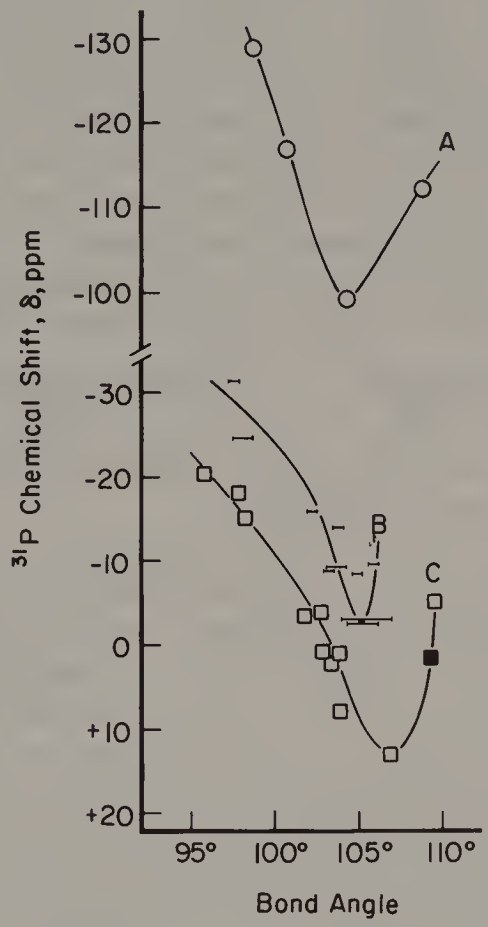


Figure 1 - (A) Phosphorus-31 chemical shifts of 2-thioxo-2-*t*-butyl-1,3,2-dithiaphospha compounds *vs.* S-P-S bond angle, derived from Martin and Robert[36] (B)Phosphorus-31 chemical shifts of PO_2N_2 tetrahedra *vs.* bond angle, derived from Contracter, *et al.*[37]. (C) Phosphorus-31 chemical shift of phosphate esters *vs.* O-P-O bond angle. Derived from Gorenstein[32] and Contracter, *et al.*[37]

esters), at bond angle < 108° Gorenstein[32] has shown that a decrease in the smallest O-P-O bond angle (obtained from X-ray data) in the molecule results in a deshielding (downfield shift) of the phosphorus nucleus. At bond angles > 108°, deshielding of the ^{31}P nucleus occurs with further increase in bond angles.

Martin and Robert[36] have shown that a similar correlation of S-P-S bond angles and ^{31}P chemical shifts in 2-thioxo-2-*t*-butyl-1,2,3-dithiaphospha compounds likely also exists (Fig. 1 top curve). Contracter, *et al.*[37] have observed a similar variation for PO_2N_2 tetrahedra, further confirming this bond angle effect in tetracoordinated phosphorus compounds (middle curve, Fig. 1).

Bond-angle changes and hence distortion from tetrahedral symmetry in tetracoordinated phosphorus should affect the chemical-shift anisotropy as well. Dutasta, *et al.*[38] experimentally have verified this bond-angle effect in a solid-state ^{31}P NMR study on a series of cyclic thioxophosphonates. The shielding tensors are very sensitive to geometrical changes, and in fact, a linear correlation appears to exist between the asymmetry parameter η and the intracyclic bond angle α. The anisotropy is also correlated to the bond angle whereas the average, isotropic chemical shielding shows a much poorer correlation.

Gorenstein and Kar[39] have attempted to calculate the ^{31}P chemical shifts for a model phosphate diester in various geometries to confirm theoretically the bond-angle correlation. Using CNDO/2 SCF molecular orbital calculations, a correlation was drawn between calculated phosphorus electron densities and isotropic ^{31}P chemical shifts, and indeed deshielding of the phosphorus atom with decreasing O-P-O bond angles was found. A slightly better correlation was achieved between observed and calculated ^{31}P chemical shifts using a Karplus-Das-type average excitation approximation semi-empirical theoretical approach.[40]

3. Stereoelectronic Effects on ^{31}P Chemical Shifts

Semiempirical molecular orbital calculations[39] and *ab initio* gauge-invariant-type, molecular orbital, chemical shift calculations[29,30] suggested that ^{31}P chemical shifts are also dependent on P-O ester torsional angles, which has been shown to be of great value in analysis of DNA structure (see section V). The two nucleic acid P-O ester torsional angles, ζ and α, are defined by the

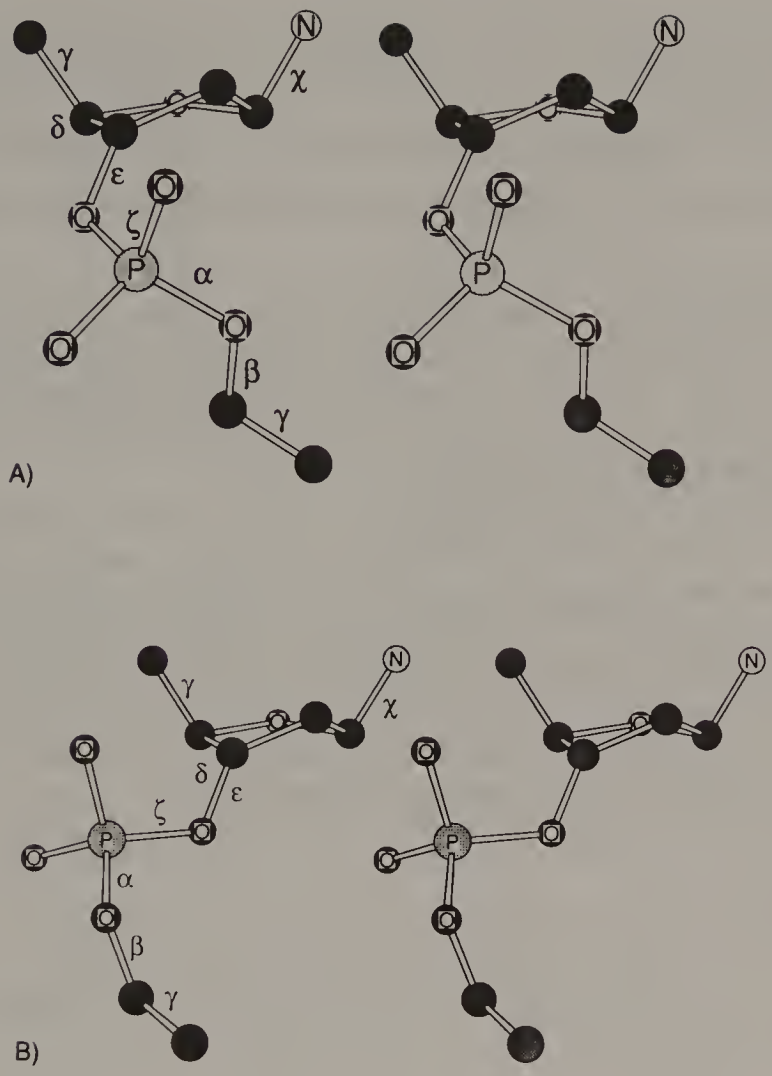


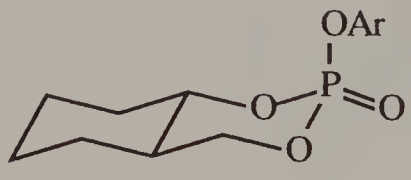
Figure 2 - Stereoview of sugar phosphate backbone in a DNA fragment. Two major conformational states are observed in the crystal structures of duplex oligonucleotides:[125] (A) the B_I conformational state (B) the B_{II} state. α, β, ε, ζ: g^-, t, t, g^- (A); g^-, t, g^-, t (B), respectively. The B_I conformation represents the low energy phosphate state normally observed in the crystal structures of B-DNA. Torsional angles gauche(-) (g^- or -60^o); *trans* (180^o). Crystal structures of duplex oligonucleotides show that these angles are only approximate and indeed the ζ angle is generally closer to -90^o for what is defined as "g^-".

R-O-P-O(R') dihedral angles (see Fig. 2)

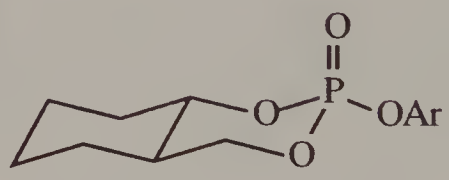
These chemical-shift calculations and later empirical observations indicate that a phosphate diester in a B_I conformation (both ester bonds gauche) should have a ^{31}P chemical shift 1.6 ppm upfield from a phosphate diester in the B_{II} conformations (α = gauche; ζ = *trans*).[41,42]

Experimentally, this torsional angle, or stereoelectronic, effect on ^{31}P shifts can be confirmed by using six-membered-ring models in which the torsional angles are rigidly defined by some molecular constraint, such as the diastereomeric phosphate triesters (1) and phosphoramidates (2).[43]

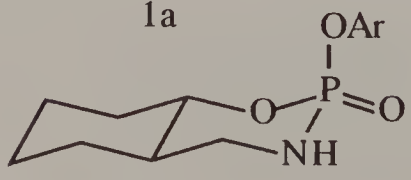
Generally those diastereomeric esters with an axial ester group [(1a) and (2a)] have ^{31}P chemical shifts as much as 6 ppm upfield from those isomeric esters with an equatorial ester group [(1b) and (2b)].[6,7,40,44] In (1b) and (2b) the "equatorial" ester group ("equatorial" insofar as the phosphorinane ring is viewed in a chair conformation) is locked into a *trans* conformation relative to the endocyclic P-O ester bond. Thus, *trans* esters (1b) and (2b) are downfield of gauche esters such as (1a) and (2a).



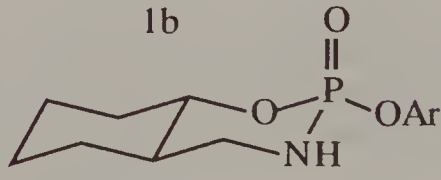
1a



1b



2a



2b

The importance of the geometry about the phosphate tetrahedron in influencing ^{31}P chemical shifts is nicely illustrated in Fig. 3.

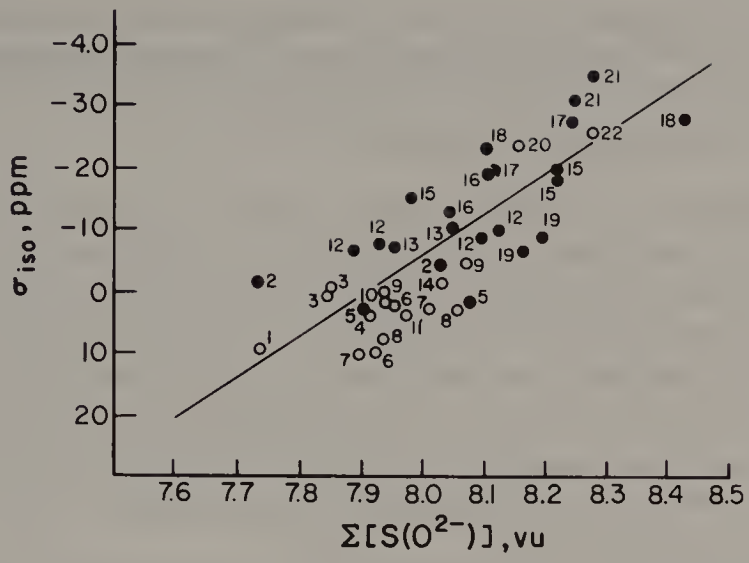


Figure 3 - Plot of the summed bond strengths at oxygen (valence units, v.u.) following the method of Brown and Shannon[138] *vs.* the ^{31}P magic angle spinning NMR isotropic chemical shifts, δ_{iso} (Eqns. 1 and 2) relative to 85% H_3PO_4. Open and closed circles are metal (M) orthophosphates (such as $M_nH_{3-n}PO_4$) and metal higher phosphates (such as $M_nP_2O_7$), respectively. Numbering and actual structures may be found in Cheetham, *et al.*[20] (Copyright 1986, The Chemical Society[20]).

Using magic angle spinning, solid-state NMR, Cheetham, *et al.*[20] have measured the ^{31}P shielding tensors, the chemical shift anisotropy and the isotropic chemical shift (Eqns. 2 and 3) for various crystalline orthophosphates and higher phosphates. From the X-ray crystallographic structures of these same phosphates, they calculated the summed bond strengths at oxygen atoms, $\Sigma[S(O^{2-})]$, term defined by Smith, *et al.*,[45] and roughly related to P-O bond lengths. As shown in Fig. 3, a reasonable correlation does appear to exist between the bond strengths at oxygen and

isotropic ^{31}P chemical shifts. The isotropic chemical shift moves upfield as the bond strength at oxygen increases. It should be noted that the variation in the individual shielding tensors is considerably larger than the isotropic shielding.[20,45]

4. Extrinsic and Other Effects on ^{31}P Chemical Shifts

Environmental effects on ^{31}P chemical shifts are generally smaller than the intrinsic effects discussed in previous sections. Lerner and Kearns[46] have shown the ^{31}P shifts of phosphate esters are modestly sensitive to solvent effects (varying as much as 3 ppm from 100% H_2O to 70% DMSO-H_2O), and Costello, *et al.*[47] have noted similar sensitivity of ^{31}P shifts of orthophosphate, diethyl phosphate, and monoethyl orthophosphate to high salt (0-5 *M* added salts).

Gorenstein, *et al.*[11,48,49] have noted that ^{31}P shifts are also sensitive to temperature, although they have analyzed this effect at least in part in terms of the stereoelectronic ^{31}P shift effect. In fact it is possible to utilize this temperature sensitivity to design a ^{31}P chemical shift thermometer (*vide supra*).[11]

Under more modest changes in solvent and salt conditions the intrinsic (and particularly stereoelectronic) effects appear to largely dominate ^{31}P chemical shifts of phosphate esters. As discussed above and in Section V.E., my laboratory has used this idea to probe the structure of nucleic acids.[6,11,31,49-53] Other possible factors that could affect ^{31}P chemical shifts in phosphate esters have been found generally to be relatively unimportant. Thus ring-current effects associated with the bases in double helical nucleic acids are expected and found[54] to have only small (<0.1 ppm) perturbations on the ^{31}P signals. This diamagnetic contribution to the ^{31}P chemical shift influences ^{1}H and heavy-atom chemical shifts to the same extent and is strongly distance dependent. The phosphorus nucleus is shielded by a tetrahedron of oxygens, and therefore aromatic groups such as nucleic acid bases can never approch close enough to cause any marked shielding or deshielding.

IV. Signal Assignments

A. Oxygen-Labeling of Phosphoryl Groups

In complex ^{31}P NMR spectra consisting of multiple signals, signal assignment can often be made by comprison of chemical

shifts to known model compounds. The wide dispersion in ^{31}P chemical shifts (Fig. 4) is quite helpful in this regard.

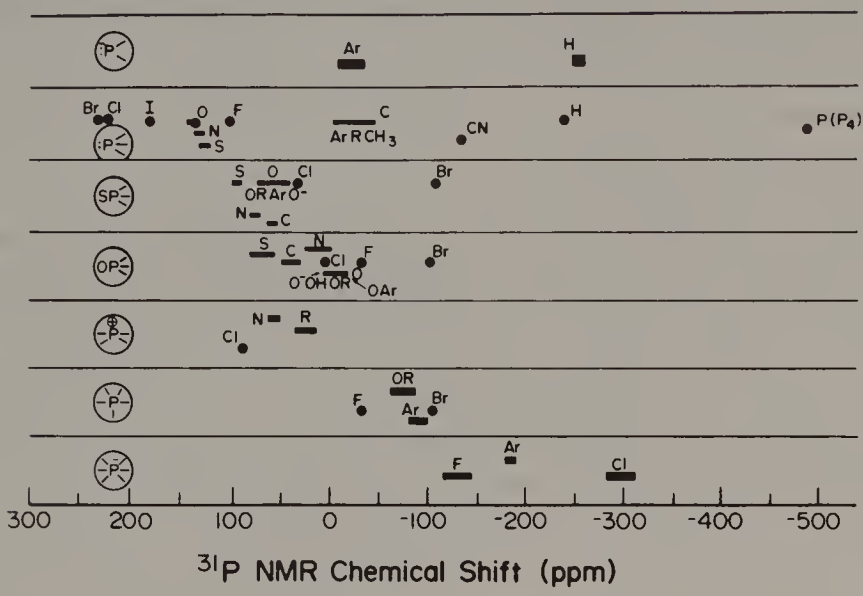


Figure 4 - Range of ^{31}P chemical shifts for substituted phosphorus compounds. Group indicated is equivalently substituted about phosphorus.

However, this is not always possible. This is especially a problem in the ^{31}P NMR signal assignment of oligonucleotides, where the dispersion in the ^{31}P chemical shifts is often less than 1 ppm.[55] A phosphoramidite ^{17}O-labeling methodology has been developed to assign the ^{31}P signals of the phosphates in a number of duplexes. Using solid-phase phosphoramidite oligonucleo- tide synthetic methods,[37] ^{17}O and/or ^{18}O-labels in the phosphoryl groups can be introduced[51,52,58,59] by replacing the I_2/H_2O in the oxidation step of the phosphite by $I_2/H_2{}^{17}O$ (40%) or $H_2{}^{18}O$. By synthesizing a mono-^{17}O phosphoryl labeled oligonucleotide (one specific phosphate is labeled along the strand), it is possible to identify the ^{31}P signal of that phosphate diester. This is because the quadrupolar ^{17}O nucleus (generally ~40% enriched) broadens the ^{31}P signal of the directly attached phosphorus to such an extent that only the high-resolution signal of the remaining 60% non-quadrupolar broadened phosphate at the labeled site is observed.[58-61] In this way each synthesized oligonucleotide with a different mono-

substituted ^{17}O-phosphoryl group allows identification of one specific ^{31}P signal and the full series of monolabeled oligonucleotides gives the assignment of the entire ^{31}P NMR spectrum.

Fig. 5A is a ^{31}P NMR spectrum of a duplex oligonucleotide, d(CGCAGAATTCGCG)$_2$.

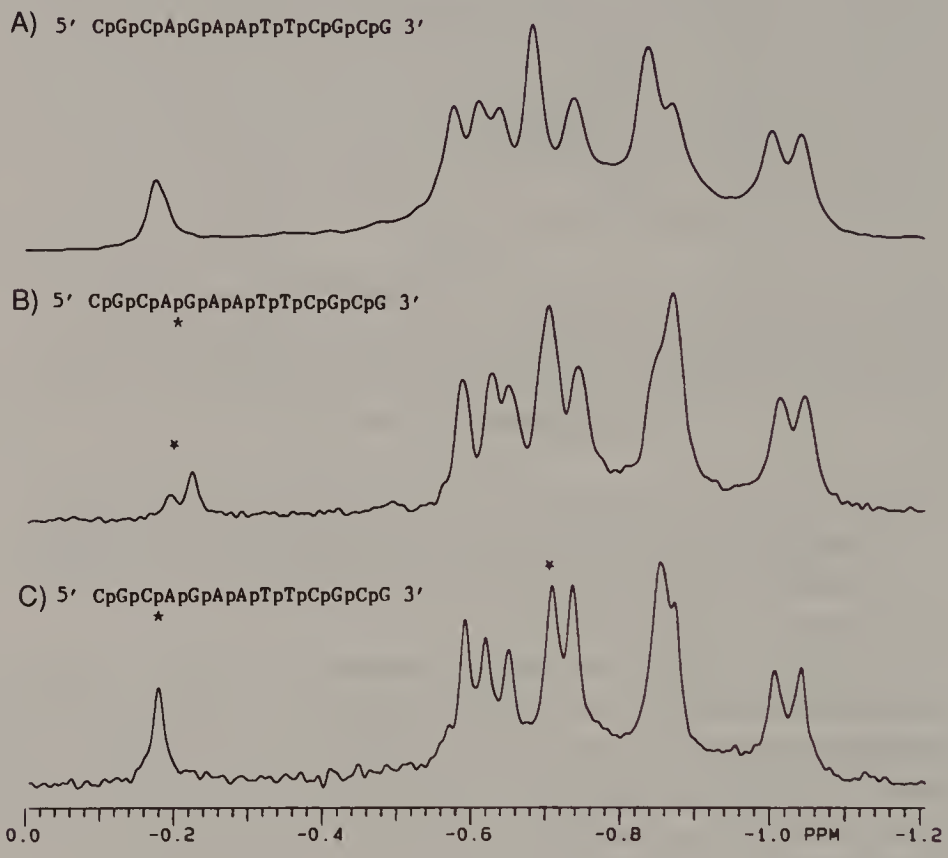


Figure 5 - ^{31}P NMR spectra of (A) 13-mer, d(CGCAGAATTCGCG). Examples of site-specific ^{17}O labeling of two of the phosphates of the 13-mer at position 4 and 3 (shown by an asterisk) are shown in (B) and (C) respectively. ^{31}P chemical shifts are reported relative to 85% phosphoric acid. Reproduced with permission.[139]

As can be seen in Fig. 5B/C for ^{17}O labeled duplex, a decrease in intensity of a single resonance is observed. Almost all of the resonances can be clearly distinguished, most integrating for a single phosphorus resonance. It is interesting to note that the

resonance of the labeled phosphate is observed as two reduced intensity, resolved peaks associated with ^{16}O (unlabeled) and ^{18}O-labeled phosphorus resonances. (The $H_2{}^{17}O$ sample also contains both $H_2{}^{16}O$ and $H_2{}^{18}O$.) This can most easily be seen in Fig. 5B where the ^{18}O-labeled phosphate ^{31}P signal is shifted slightly upfield relative to the remaining ^{16}O phosphorus resonance (*vide infra*).[62]

The ^{18}O isotope shift on ^{31}P chemical shifts[63-66] has also provided a convenient monitor of ^{18}O isotope incorporation into phosphorus compounds undergoing hydrolysis since integration of the ^{18}O signals relative to the ^{16}O-^{31}P signal yields directly the percentage ^{18}O incorporation. Separate signals are also observed for each of the multiple-^{18}O labeled species. Thus, the ^{31}P NMR spectrum of 2-hydroxyethyl phosphate formed in the base catalyzed hydrolysis of ethyl ethylene phosphate shows three ^{31}P signals. Since the ^{18}O isotope shift is always upfield[63-68] and the magnitude of it is proportional to the number of ^{18}O atoms in the molecule (~0.01-0.04 ppm/^{18}O atom), the lowest field signal represented the unenriched ester, the middle signal the mono-^{18}O labeled ester, and the upfield signal the di-^{18}O labeled ester.[69]

Cohn and Hu[70] have also shown that a rough linear correlation exists between the magnitude of the ^{18}O isotope ^{31}P shift and the bond order between phosphorus and the isotopically-substituted atom. In ADP and ATP, ^{18}O substitution on a single P-O bond produces a 0.0166 ppm upfield shift, and ^{18}O substitution on a P-O bond with half single-bond character and half double-bond character is 0.0285 ppm. This dependence on bond order has been used by Gorenstein and Rowell[68] to establish the stereochemistry of the ^{18}O-label in a phosphate diester. Thus, hydrolysis of the six-membered ring phosphate triester (1a), (Aryl = 2,4-dinitrophenyl) in $H_2{}^{18}O$ yielded a phosphate diester with a single ^{18}O atom. Methylation of the diester yielded the methyl ester of (1a). The ^{31}P NMR spectrum of this mixture (Fig. 6) of oxygen substituted axial methyl triesters shows three signals: the shift between the two large ^{31}P signals is 0.040 ppm and that between the downfield and middle signals is 0.015 ppm. The upfield signal corresponds to ^{18}O isotopic substitution into a full equatorial P=O bond and the smaller, slightly upfield shifted signal corresponds to ^{18}O substitution into a single bond. Analysis of this spectrum gave

the stereochemistry for hydroxide attack on the aryl triester.[68]

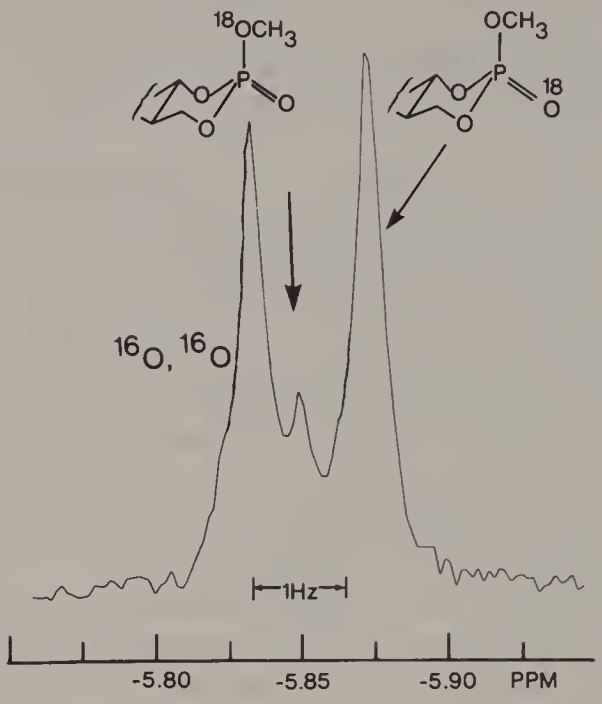


Figure 6 - 32.4 MHz ^{31}P NMR spectrum of the axial epimer of ^{18}O-labeled 2-methoxy-1,3,2-dioxaphosphorinane (1). Total monooxygen-18 enrichment into the exocyclic oxygens is 61%.[68]

Indeed, pro-prochiral phosphate monoesters may be synthesized in chiral form by substitution of the three non-ester oxygens by the three stable isotopes of oxygen.[71-75] This has made it feasible to study the stereochemistry of the hydrolysis of monophosphate esters and anhydrides.[75] In this case use was also made of the quadrupole broadening of the ^{31}P signal by a directly bonded ^{17}O atom.[76,77]

B. 2D $^{31}P/^{1}H$ Heteronuclear Correlated Spectra

Two-dimensional ^{31}P-^{1}H heteronuclear correlation NMR spectroscopy[56,79-80] can generally provide a convenient method for assigning ^{31}P chemical shifts in complex spectra.[78] Application to DNA is illustrated, although the 2D methods will of

course apply to organophosphorus compounds as well.

Conventional 2D ^{31}P-^{1}H heteronuclear correlation (HETCOR) NMR spectroscopy,[51,58,78] 2D long range COLOC experiments,[56,81] and indirect detection (^{1}H detection) HETCOR experiments[80,82] have been used successfully to assign ^{31}P signals in oligonucleotide duplexes. A novel detection experiment[82] has been applied to organophosphorus-iron spectra. Generally these 2D-experiments correlate ^{31}P signals with coupled ^{1}H NMR signals. Assuming the ^{1}H NMR spectra have been assigned, these methods allow for direct assignment of the ^{31}P signals. The heteronuclear correlation measurements, however, suffer from poor sensitivity as well as poor resolution in both the ^{1}H and ^{31}P dimensions especially for larger, biomolecular structures. The poor sensitivity is largely due to the fact that the ^{1}H-^{31}P scalar coupling constants are generally about the same size or smaller (except for organophosphorus molecules with directly bonded hydrogens) than the ^{1}H-^{1}H coupling constants. Sensitivity is substantially improved by using a heteronuclear version of the "constant time" coherence transfer technique, referred to as COLOC (COrrelation spectroscopy *via* LOng range Coupling) and originally proposed for ^{13}C-^{1}H correlations.[83] My laboratory has developed a *P*ure *A*bsorption phase *C*onstant time (*PAC*) pulse sequence to emphasize ^{1}H-^{31}P correlations in oligonucleotides as well as to give rise to pure absorption phase spectra, thereby further improving resolution.[56] This pulse sequence incorporates both evolution of antiphase magnetization and chemical shift labeling in a single, "constant time" delay period, thereby improving the efficiency of coherence transfer and increasing sensitivity. The PAC sequence also gives homonuclear decoupling during t_1 and thus improves resolution.

For example, the PAC spectrum of the self-complementary 14 base-pair oligonucleotide duplex d(TGTGAGCGTCACA)$_2$ is shown in Fig. 7. The cross peaks represent scalar couplings between ^{31}P nuclei of the backbone and the H3' and H4' deoxyribose protons (Fig. 2). Assuming that the chemical shifts of these protons have been assigned (by $^{1}H/^{1}H$ NOESY and COSY spectra) the ^{31}P signals may be assigned readily.

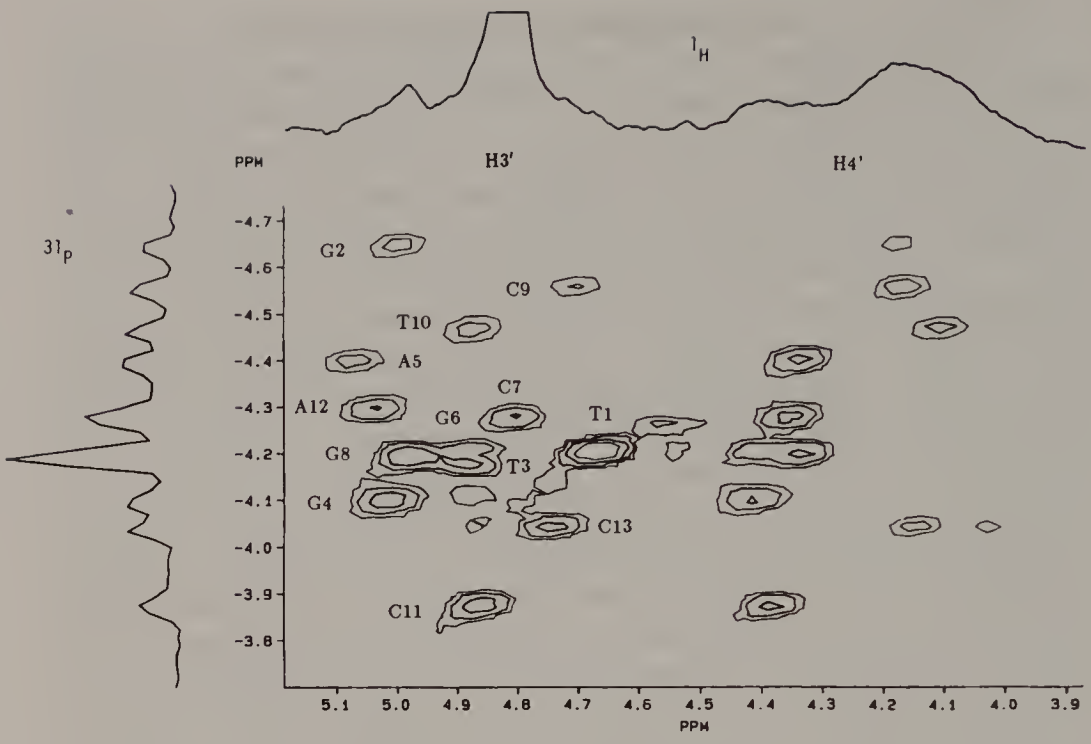


Figure 7 - Pure absorption phase ^{31}P-^{1}H PAC spectrum of d(TGTGAGCGCTCACA)$_2$, at 200 MHz (^{1}H). ^{31}P chemical shifts are reported relative to trimethyl phosphate which is 3.456 ppm downfield from 85% phosphoric acid. Reproduced with permission.[56] The pulse sequence and phase used for this spectrum was: ^{1}H - PA 90^{o} CD-t_1/2 180^{o} t_1/2 90^{o} RD/2 180^{o} RD/2 decouple; ^{31}P - PA CD-t_1/2 180^{o} t_1/2 90^{o} RD/2 180^{o} RD/2 t_2; where the composite 180^{o} pulse was a 90^{o}, 180^{o}, 90^{o} sequence applied simultaneously to ^{1}H and ^{31}P resonances, the preacquisition delay PA was 2 sec, the constant delay, CD, was 0.051 sec, and the refocussing delay, RD, was 0.035 sec. The spectrum was acquired on a Varian XL200A spectrometer (200 MHz ^{1}H).

C. DOC 2D $^{31}P/^{1}H$ Heteronuclear Correlated Spectra of Oligonucleotides

Even with the development of the PAC and indirect detection heteronuclear correlation 2D NMR methodologies, ^{31}P resonance assignments *via* heteronuclear correlation in some organophosphorus or bioorganic molecules may be difficult, largely because the resolution is often mediocre in both the proton and ^{31}P spectra, especially at lower fields.[56,84] While the PAC method certainly works, the resolution in the proton dimension is digitally limited by the constant time delay. Acceptable values of this delay are sharply constrained by the evolution of the proton-proton antiphase magnetization.

As noted above, the "constant time" PAC coherency transfer pulse sequences minimizes this delay by using the same "constant time" for chemical shift labeling and the evolution of heteronuclear antiphase magnetization. This pulse sequence reduces the problem by limiting the time for the evolution of the parasitic proton-proton antiphase magnetization. While PAC is a significant improvement over the normal HETCOR experiment. the sensitivity is still significantly reduced by the evolution of the parasitic proton-proton antiphase magnetization.

A *DO*uble *C*onstant time (DOC) sequence addresses the problem more directly by refocusing the proton-proton antiphase magnetization with a selective proton 180^{o} pulse between the two constant delays.[81] Nonselective 180^{o} pulses move through each constant time period to chemical shift label the proton coherences. Thus, the proton magnetization which is antiphase with respect to the dilute spin evolves for the entire constant delay period for protons in the region inverted by the semi-selective 180^{o} pulse. Likewise, the entire constant delay period is effectively used for chemical shift labeling. Proton-proton antiphase magnetization which evolves in the first constant time period is refocused in the second constant time period, in the case of interest, *i.e.* where one proton is within the region inverted by the semi-selective 180^{o} pulse and the other proton is outside of this region. This retains the sensitivity and resolution advantages of constant time pulse sequences and provides selectivity in the type of antiphase magnetization present at the end of the two constant time periods.

DOC not only can give much better resolution but also better sensitivity for the most difficult correlations. This sequence can thus compete effectively with indirect detection schemes.[80] The major limitation of the DOC sequence is that it may be necessary to collect the spectrum in parts and, depending on the resolution required in the proton dimension, this can take more instrument time. However, if the highest resolution and the observation of the maximum number of correlations is required, then the DOC sequence is most likely the best choice.

D. Two-dimensional NOE and Exchange ^{31}P NMR Spectroscopy

Heteronuclear and homonuclear 2D nuclear Overhauser effect spectroscopy (NOESY) may be used to correlate spins that are spatially close to each other (< 5 Å). Whereas correlated spectroscopy (COSY, COLOC, PAC, *etc.*) connect signals by their through-bonding interactions, in NOESY spectra crosspeaks are present due to the through space NOE between cross-relaxing nuclei. The two-dimensional NOESY experiments first described by Ernst, *et al.*[85,86] involve three 90° pulses. Nuclei are frequency labeled by a variable delay time (t_1) separating the first and second pulses, the mixing time is between the second and third pulses, and the detection of transverse magnetization as a function of time (t_2) follows the third pulse. During the mixing time, nuclei labeled in t_1 with a frequency corresponding to one site are converted by cross relaxation and/or exchange processes to a second site and evolve in t_2 with the frequency of the second site, giving rise to cross-peaks in the two-dimensional spectrum. Because chemical exchange also leads to magnetization transfer, chemical exchange processes can be detected by two-dimensional $^{31}P/^{31}P$ 2D exchange (NOESY) NMR.[87]

One-dimensional variations on these experiments are useful, although advantages in 2-D exchange and NOESY experiments over the selective irradiation experiment[88] are: 1) all NOE's and exchange processes can be observed in a single experiment; 2) the nonselective irradiation problem is eliminated; and 3) there is no need for a selective pulse requiring either a low power radio frequency source or a DANTE pulse which can be a limitation on

some instruments. However, the quantification of cross peak volumes is less precise than that of 1-D peak areas because of the practical limitation in the achievable signal to noise.

V. Coupling Constants

A. Introduction

Scalar ^{31}P-X spin-spin coupling constants provide important information on the nature of bonding and structure in organophosphorus compounds.[5,41,89] Compilations and discussion of phosphorus coupling constants may be found elsewhere.[7,40,90]

B. Directly Bonded Phosphorus Coupling Constants: $^1J_{PX}$

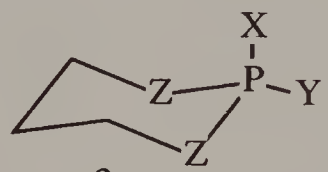
One-bond P-X coupling constants ($J_{P\text{-}X}$) generally have been rationalized in terms of a dominant Fermi-contact term:[91-97]

$$J_{P\text{-}X} = \frac{A a_P^2 a_X^2}{1 + S_{P\text{-}X}^2} + B \qquad \text{Eqn. 5}$$

where A and B are constants, a_P^2 and a_X^2 the percent s character on phosphorus and atom X, respectively, and $S_{P\text{-}X}$ the overlap integral for the P-X bond.[93-98] Because the Fermi-contact spin-spin coupling mechanism involves the electron density at the nucleus (hence the s-orbital electron density), an increase in the s character of the P-X bond is generally associated with an increase in the coupling constant. The percent s character is determined by the hybridizarion of atoms P and X, and as expected, sp^3-hybridized atoms often have $^1J_{PX}$ larger than p^3 hybridized atoms. Thus, $^1J_{PH}$ for phosphonium cations of structure $(PH_nR_{4-n})^+$ with sp^3 hybridization are ~500 Hz whereas $^1J_{PH}$ for phosphines PH_nR_{3-n} with phosphorus hybridization of approxiamtely p^3 are smaller, ~200 Hz. Furthermore, as the electronegativity of atom X increases, the percent s character of the P-X bond increases, and the coupling constant becomes more positive. In many cases, however, these simple concepts fail to rationalize experimental one-bond P-X

coupling constants (Table 1) because other spin-spin coupling mechanisms can also contribute significantly to the coupling constant.[99] For tetravalent phosphorus a very good correlation is found between $^{1}J_{PC}$ and the phosphorus 3s-carbon 2s bond orders, the percent s in the P-C bonding orbital in going from alkyl to alkenyl ($sp^3 \rightarrow sp^2 \rightarrow sp$) and $^{1}J_{PC}$.[100] Calculations and empirical observations on trivalent phosphorus compounds are *not* successful, however[101] and suggest that the Fermi-contact contribution only dominates tetravelent phosphorus compounds.

Conformationally dependent, directly bonded coupling constants may also be attributed to a stereoelectronic effect[98,102-104] as discussed earlier for ^{31}P chemical shifts. Thus, in the phosphorinane ring system (3)[98,102,105] the $|^{1}J_{PX}|$ coupling constants are 5-10 Hz smaller in the axially (gauche) substituted rings than in equatorially (*trans*) substituted rings.

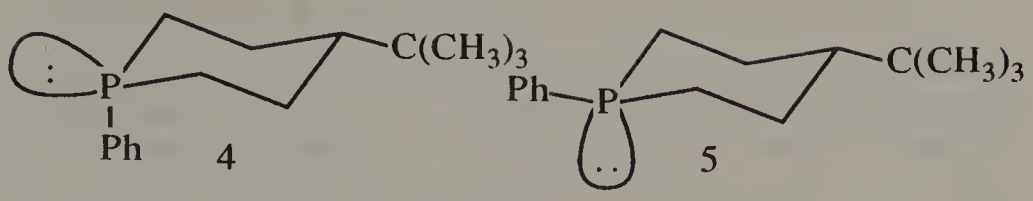


3

One-bond P-H coupling constants always appear to be positive and vary from ~+120 to +1180 Hz.[89] Other heteroatom one-bond P-X coupling constants vary over a similar wide range and can be either positive or negative. The expected ranges of values are given in Table 1.[89,90]

C. Two-bond Coupling Constants: $^{2}J_{PX}$

Two-bond $^{2}J_{P\text{-}X}$ coupling constants may be either positive or negative and are generally smaller than one-bond coupling constants (Table 2). The $^{2}J_{PCH}$ and $^{2}J_{PCF}$ constants are stereospecific and a Karplus-like dihedral dependence to the two-bond coupling constant (H or F)-C-P-X (X = lone pair or heteroatom) has been described.[89] Thus, in the *cis*- and *trans*-phosphorinanes (4) and (5) the $^{2}J_{PC}$ constants are 0 and 5.1 Hz respectively.[106] The smaller coupling constant is attributed to the *trans* orientation of the lone pair to the C-3 or C-5 atoms. Similar results for other phosphorinane ring systems have been noted.[105,107-109]



D. Three-bond Coupling Constants: $^3J_{PX}$

Three-bond coupling constants, $^3J_{PX}$, through intervening C, N, O, or other heteroatoms are generally <20 Hz (Table 3). The dihedral-angle dependence of vicinal $^3J_{POCH}$ coupling,[89,110,111] $^3J_{PCCH}$,[112,113] and $^3J_{PCCC}$[114,115] has been demonstrated. The curves may be fitted to the general Karplus equation:

$$J(\phi) = A(\cos^2\phi) + B(\cos\phi) + C \qquad \text{Eqn. 6}$$

where ϕ is the dihedral angle and A, B, and C are constants for the particular molecular framework. Caution is recommended when attempting to apply these Karplus equations and curves to classes of phosphorus compounds that have not been used in establishing these relationships because separate correlations and values for the constants A, B, and C in Eqn. 6 likely exist for each structural class. In all cases a minimum in these Karplus curves is found around 90^o.

E. Applications to Nucleic Acid Structure

The Karplus-like relationship between HCOP and CCOP dihedral angles and $^3J_{HP}$ and $^3J_{CP}$ three-bond coupling constants, respectively, has been used to determine the conformation about the ribose-phosphate backbone of nucleic acids in solution. Torsional angles about both the C-3'-O-3' and C-5'-O-5' bonds in 3',5'-phosphodiester linkages have been determined from the coupled ^1H- and ^{31}P-NMR spectra.[116]

Within the limitations just described for the general application of the Karplus relationship, the best Karplus relationship for the nucleotide H3'-P coupling constants[116] appears to be:

$$J = 15.3(\cos^2\phi) - 6.1(\cos\phi) + 1.6.$$

From the H3'-C3'-O-P torsional angle ϕ the C4'-C3'-O-P torsional angle ε (= $-\phi - 120^{o}$) may be calculated. Because of the conformational flexibility about the C-O bonds in mononucleotides and single strand oligonucleotides and the large number of conformers that may be significantly populated, analysis of a unique structure(s) from the coupling constant data is potentially problematical. Generally, only a few conformations are assumed to be important, and the observed coupling constants are analyzed to yield conformational populations. Thus, the $J_{3'P}$ coupling constant for adenylyl-3',5'-adenosine (ApA) is ~8.0 Hz.[117,118] Assuming that *only* the *trans* and gauche conformations are allowed, this result suggests that the gauche conformation is preferred. However, it is generally not possible to distinguish between the -g or +g conformations.

Coupling constants to both 5' protons are analyzed in order to determine conformations about the C5'-O bond. Again, with small H5'-P and H5"-P coupling constants (3-7 Hz), the gauche conformation appears to be preferred. The observed similarity in the two C-5' proton-phosphorus coupling constants suggests that the favored conformation has the phosphorus *trans* to the C-4' atom (-g to one of the C-5' protons and +g to the other).

The fractional population *P* of the conformation may be estimated[119,120] from the coupling constants sum:

$$\Sigma = J_{5'P} + J_{5''P} \quad \text{and}$$

$$P = (J_t + J_g - \Sigma)/(J_t - J_g).$$

For ApA with $J_{5'P}$ and $J_{5''P}$ both 4.5 Hz, it would appear that the gauche conformer population is ~80%.[118] For the deoxy-ApA, the gauche conformer population is even higher (94%).

The $J_{H3'-P}$ coupling constants in larger oligonucleotides cannot generally be determined from the coupled 1D ^{31}P or ^{1}H spectra because of spectral overlap. Recently, several 2D-J resolved long-range correlation pulse sequences[121] have been described which overcome this limitation. The Bax-Freeman selective 2D-J experiment with a DANTE sequence for a selective 180^{o} pulse on the coupled protons can be readily implemented on most newer spectrometers.

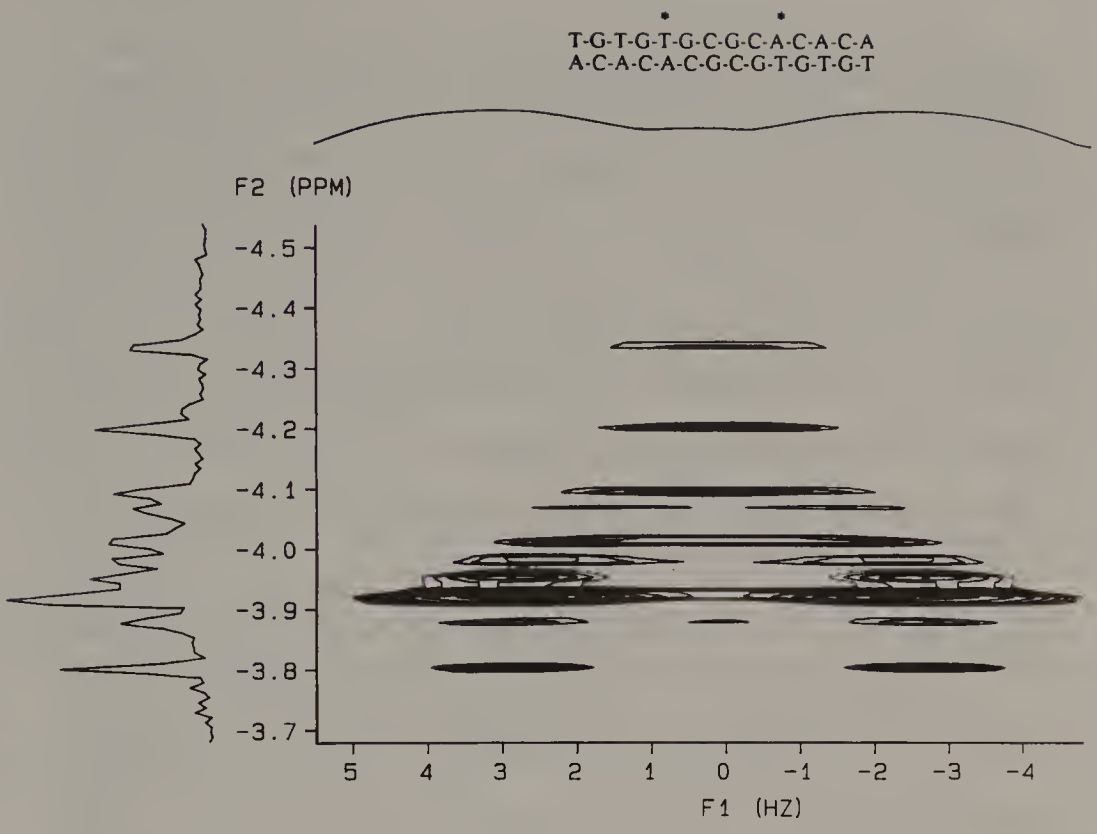


Figure 8 - 2D $^{31}P/^{1}H$ J-resolved spectra at 200 MHz (^{1}H) of duplex 14-mer d(TGTGAGCGCTCACA)$_2$. The 1D decoupled ^{31}P NMR spectrum is also shown along one axis and the H3' coupled doublets are shown along the second dimension. ^{31}P chemical shifts are reported relative to trimethyl phosphate. Reproduced with permission.[54]

This is particularly useful for measuring phosphorus-H3' coupling constants in duplex fragments, which can vary from ~1.5 to 8 Hz in duplexes as large as tetradecamers (Fig. 8). Measurement of the 4' or 5' (5") coupling constants by this pulse sequence have been less successful.[122] The larger linewidths of longer duplexes limit measurement of the small coupling constants.

As shown by Dickerson[123,124] there is a strong correlation ($R = -0.92$) between torsional angles C4'-C3'-O3'-P (ε) and C3'-O3'-P-O5' (ζ) in the crystal structures of various duplexes (ζ may be calculated from the relationship:[123,124] $\zeta = -317-1.23\varepsilon$). Thus, both torsional angles ε and ζ can often be calculated from the measured P-H3' coupling constant.

As shown in Fig. 9, the Karplus relationship provides for four different torsional angle solutions for each value of the same coupling constant. Although all four values are shown in Fig. 9, the limb which includes ε values between 0 and -270^{o} is sterically inaccessible in nucleic acids.[125] Generally it is assumed that the coupling constants all correspond to ε torsional angles on a single limb nearest the crystallographically observed average for nucleic acids[125] ($\varepsilon = -169 \pm 25^{o}$). This need not always be true, especially since phosphate ester conformations corresponding to either of the other two solutions are observed crystallographically.[125] However, as shown in Fig. 9, nearly all of the phosphates for normal Watson-Crick duplexes fall along only a single limb of the Karplus curve. In addition, it is quite interesting that the measured ^{31}P chemical shifts and coupling constants for the two phosphates at the site of a tetramer duplex actinomycin D drug complex do not fit on the main limb of the Karplus curve, although the values do nicely fit on the other two solutions of the curve (Fig. 9). Indeed, crystal structures[125] of related intercalator duplex complexes confirm that the phosphates often are constrained to conformations that best correspond to the other solutions.

Ignoring the drug-duples points that fall off the main limb of the Karplus curve, and assuming a linear correlation between the coupling constants and ^{31}P chemical shifts (effectively a linear fit to the data on the main limb of the Karplus curve), the correlation coefficient is ~-0.81.[54]

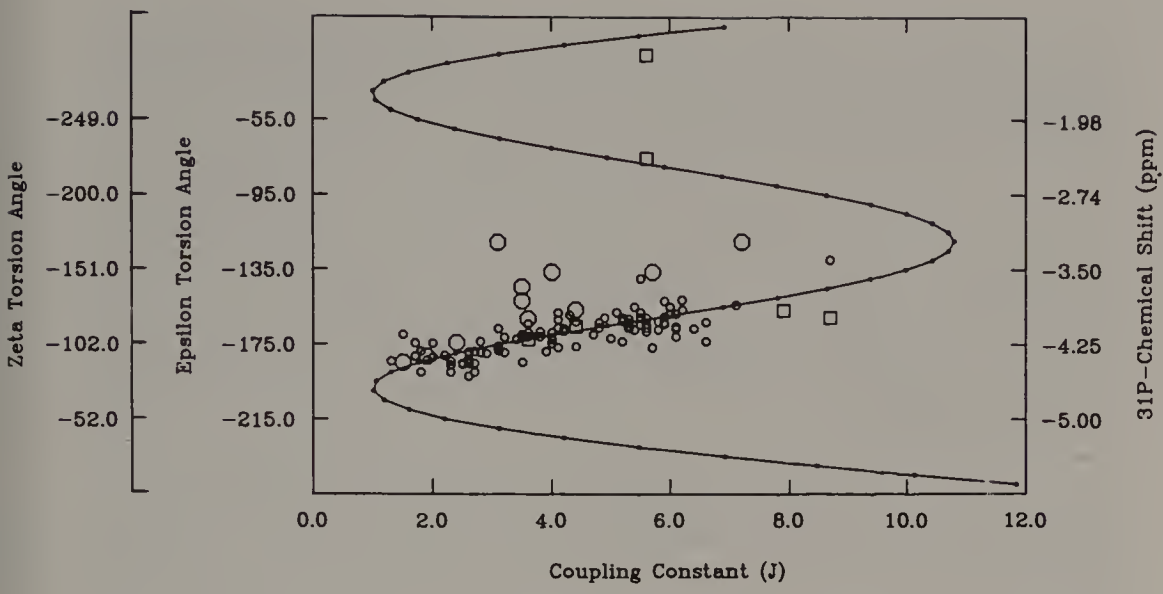


Figure 9 - Plot of ^{31}P chemical shifts for oligonucleotide sequences[54,126,139] (o) and the actinomycin-D bound $d(CGCG)_2$ tetramer complex [140] with their measured $J_{H3'-P}$ coupling constants (The O data points correspond to phosphates in a tandem GA mismatch decamer duplex[122] which shows unusual, slowly exchanging signals.) Also shown are the theoretical ε and ζ torsional angles (solid curve) as a function of coupling constant derived from the Karplus relationship (Eqn. 6) and the relationship $\zeta = -317 - 1.23\varepsilon$. ^{31}P chemical shifts are reported relative to trimethyl phosphate. Reproduced with permission.[122]

Thus, for "normal" B-DNA geometry, there is an excellent correlation between the phosphate resonances and the observed torsional angle while phosphates which are greatly distorted in their geometry must be analyzed more carefully.

It is clear from Fig. 9 that ^{31}P chemical shifts and coupling constants provide a probe of the conformation of the phosphate ester backbone in nucleic acids and complexes. If ^{31}P chemical shifts are sensitive to phosphate ester conformations, they potentially provide information on two of the most important torsional angles that define the nucleic acid deoxyribose phosphate backbone (Fig. 2).

As discussed above, one of the major contributing factors that determines ^{31}P chemical shifts is the main chain torsional angles of the individual phosphodiester groups along the oligonucleotide double helix. In duplex B-DNA, the gauche(-), gauche(g-) (g^-,g^-;ζ,α) (or B_I; Fig. 2) conformation about the P-O ester bonds in the sugar phosphate backbone is energetically favored, and this conformation is associated with a more shielded ^{31}P resonance. In both duplex and single stranded DNA the *trans*, gauche(-) (t,g^-;ζ,α) (or B_{II}) conformation is also significantly populated.

The ^{31}P chemical shift difference between the B_I and B_{II} phosphate ester conformational states is estimated to be 1.5-1.6 ppm.[48,126] As the result of this sensitivity to the backbone conformational state, ^{31}P chemical shifts of duplex oligonucleotides have been shown to be dependent both upon the sequence and position of the phosphate residue.[40,48,53,60]

Phosphates located toward the middle of a B-DNA double helix assume the lower energy, stereoelectronically favored B_I conformation while phosphodiester linkages located toward the two ends of the double helix tend to adopt a mixture of B_I and B_{II} conformations, where increased flexibility of the helix is more likely to occur. Because the B_I conformation is responsible for a more upfield ^{31}P chemical shift, while a B_{II} conformation is associated with a lower field chemical shift, the ^{31}P chemical shifts

of more conformationally restricted internal phosphates in oligonucleotides are generally upfield of those nearer the ends.[42,127] In addition, local helical distortions along the DNA chain appear to be at least partially responsible[52,54,127,128] for the correlation between ^{31}P chemical shifts of oligonucleotides and sequence-specific variations in duplex geometry.

The possible basis for the correlation between local helical structural variations and ^{31}P chemical shifts can be analyzed in terms of deoxyribose phosphate backbone changes involved in local helical sequence-specific structural variations. As the helix winds or unwinds in response to local helical distortions the length of the deoxyribose phosphate backbone must change[54] (Fig. 2) to reflect the stretching and contracting of the deoxyribose phosphate backbone between the two stacked base pairs. To a significant extent these changes in overall length of the deoxyribose phosphate backbone "tether" are reflected in changes in the P-O ester (as well as other) torsional angles.[54] These sequence-specific variations in the P-O (and C-O) torsional angles may explain the sequence specific variations in the ^{31}P chemical shifts.

VI. Utilization of ^{31}P NMR to Monitor Reaction Mechanisms: An Example of the Hydrolysis of Phosphonium Ions from Acyclic and Bicyclic Phosphorothionates

^{31}P NMR is often quite useful in delineating the mechanism of reaction of organophosphorus compounds. As an example from my own laboratory, I describe the use of ^{31}P NMR to understand the mechanism of hydrolysis of thiophosphonium ions. These salts are quite reactive intermediates and readily hydrolyze in aqueous solution.[129,130] Hydrolysis mainly proceeds through P-S rather than P-O bond cleavage.[130-132]

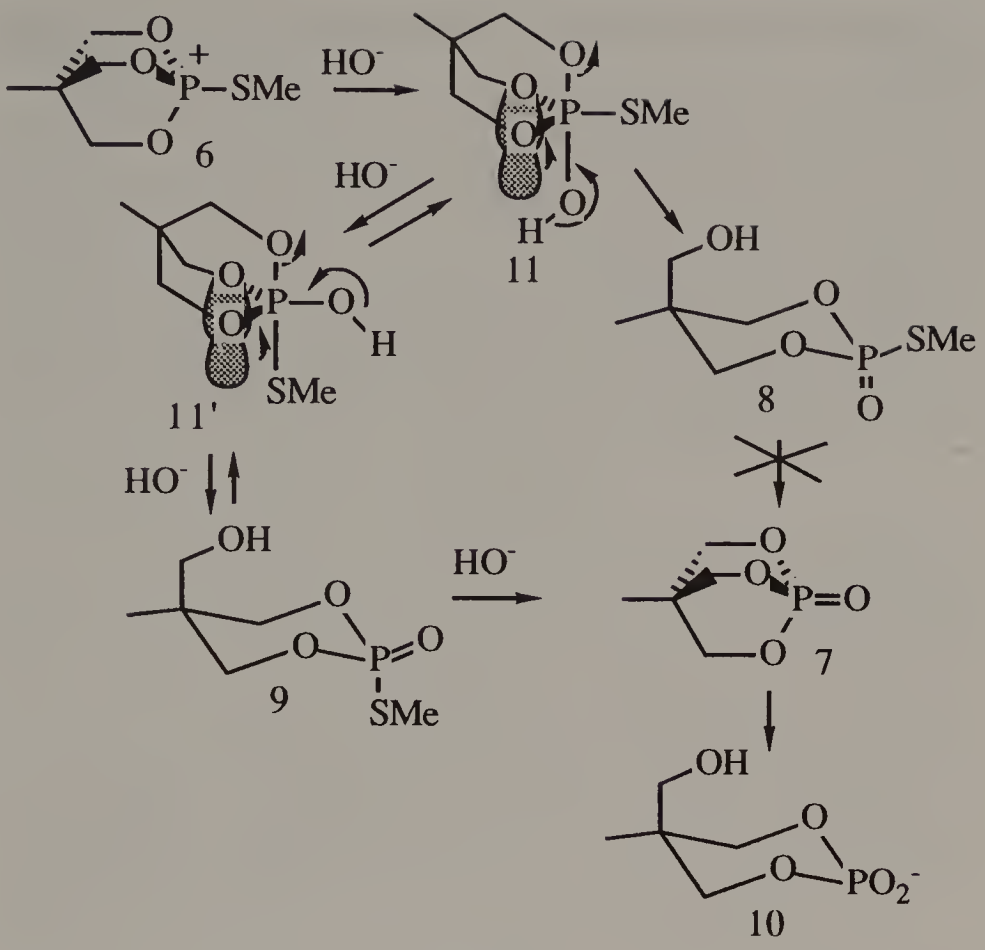
$$(R'O)_3P^+\text{-}SR + HO^- \rightarrow (R'O)_3P{=}O + RS^-$$

This preference for P-S bond cleavage is reasonable since an alkylthio group is a better leaving group (less electronegative) than an alkoxy group. Thus, 100% P-S cleavage is observed[133] in the alkaline hydrolysis of alkoxy(alkylthio)methylphenylphosphonium ions.

However, when bicyclic phosphonium ion 1-methyl-3,5,8-trioxabicyclo[2.2.2]octane-4-methylthiophosphonium hexachloroantimonate (6) is added to a 1.2 *M* sodium hydroxide solution and the reaction followed by ^{31}P NMR, three product peaks appear immediately at 25.14 ppm, 24.70 ppm, and -5.50 ppm. All of the phosphonium ion (6) was consumed during the base addition period and none remained in the first ^{31}P NMR spectrum acquired immediately after mixing. The peak at -5.50 ppm was identified as the bicyclic phosphate (7) by adding an authentic, separately prepared sample of (7) to the reaction mixture which resulted in the increase in its intensity without the appearance of a new peak. The peaks at 25.14 ppm and 24.70 ppm were assigned to epimers (8) and (9) by comparison of the ^{31}P and ^{13}C NMR spectra of the epimeric 5-chloromethyl analogs.

In alkaline solution further reactions of both thioesters (8) and (9) to (10) is observed (Scheme 1; Fig. 10).

As shown in Fig. 10, rapid hydrolysis of the phosphonium ion (6) yields within 0.5 hr not only the two epimeric thiophosphates (8) and (9) (12-14%) and 15-17% bicyclic (7), but also ~60% of the phosphate diester (10). As monitored by ^{31}P NMR over a period of several hours the thiophosphates (8) and (9) disappear with an increase in the amount of the final diester product (10). In addition, during this period of time the amount of the bicyclic phosphate (7) also increases. This suggests that at least some of the additional final product (10) that is formed derives from hydrolysis of the bicyclic phosphate(7), which in turn is produced from the recyclization of (8) and/or (9) even under basic conditions. The analysis is complicated due to the concurrent synthesis (*via* recyclization) and hydrolysis of (7) under these basic conditions. After all of (8) and (9) is consumed [with an increase in (7)], then (7) rapidly hydrolyzes to (10) (during time period 3.0-4.0 hr; Fig. 10). This shows that the 7-8% additional increase in the amount of bicyclic ester (7) during the 0.5-2.5 hr time period in the basic reaction is due to recyclization of (8) and/or (9).



Scheme 1

These ^{31}P spectral changes proved invaluable in elucidating a mechanism for the hydrolysis of the thiophosphonium ion (6). As shown in the reaction, Scheme 1, a trigonal bipyramid intermediate (11) is suggested to be formed initially by HO^- attack at phosphorus on the bicyclic thiophosphonium ion (6). Hydroxide ion attack at carbon was ruled out because no C-O bond cleavage was observed, as evidenced by carrying the hydrolysis of phosphonium ion (6) in ^{18}O labeled water where the ^{31}P NMR of the hydrolysis product mixture of (8) and (9) showed the appearance of new ^{18}O-isotope shifted ^{31}P peaks: δ 25.20 ppm [epimer (8)-^{16}O], 25.161 ppm [epimer (8)-^{18}O], 24.829 ppm [epimer (9)-^{16}O], 24.784 ppm [epimer (9)-^{18}O], -5.491 ppm [(7)-^{16}O], and -5.536 ppm [(7)-^{18}O]. The intensity of the unlabeled and ^{18}O-labeled (7)-(9) product signals was found to be in the expected

ratio based upon the amount of ^{18}O labeled water in the reaction mixture.

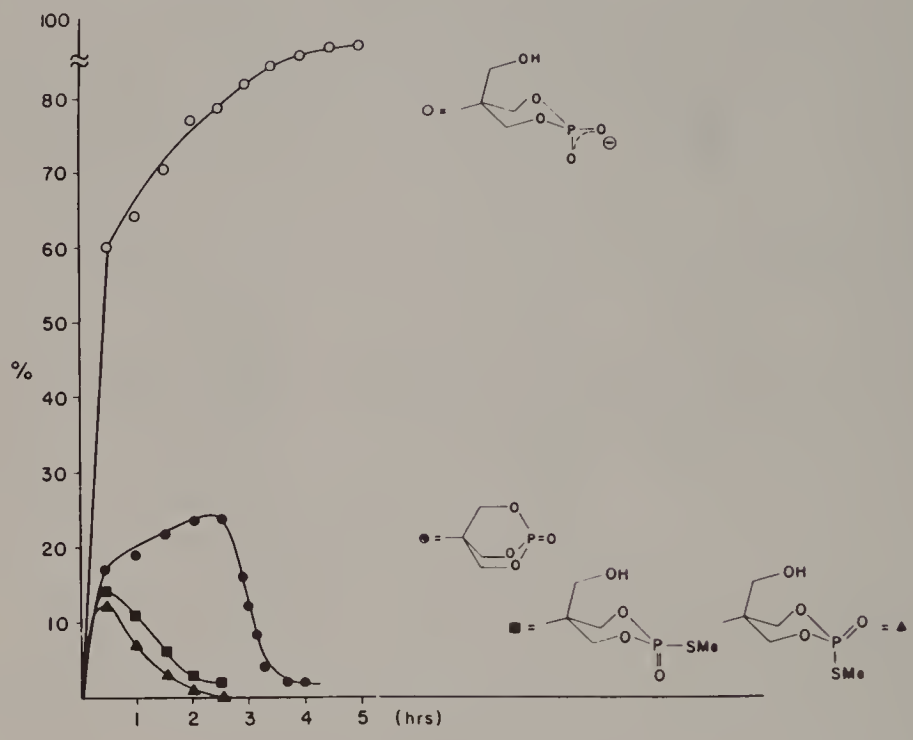


Figure 10 - Time course for the basic reaction of the products of hydrolysis of bicyclic phosphonium ion (6) as monitored by ^{31}P NMR. The basic hydrolysis of the bicyclic phosphonium ion (6) yields bicyclic phosphate (7) (•), thiophosphate esters (8) (filled squares) and (9) (filled triangles), and diester (10) (o).

The trigonal bipyramid intermediate (11) could break down through P-S bond cleavage which is usually favored for acyclic systems[133] or through P-O bond cleavage. The unusual product distribution showing considerable P-O ring cleavage and the subsequent isomerization of the hydrolysis product (9) into the other hydrolysis product (7) is consistent with the mechanism shown in Scheme 1. Immediate breakdown of the trigonal bipyramid intermediate (11) is shown to yield (8), consistent with the required cleavage of the axial P-O bond of the trigonal

bipyramid (11) (assuming applicability of the principle of expanded microscopic reversibility).[134]

The cyclic intermediate (11) can also undergo rapid pseudorotation[134] to form (11') which can break down to yield (9) with apical cleavage of the P-O bond or (7) with apical cleavage of the P-S bond. In acid, (9) can recyclize to regenerate the trigonal bipyramid intermediate which can then break down again to yield (8), (9), or (7). This ring closure is permissible for the *trans* epimer (11') which places the OR and SMe groups in the apical positions of the tbp. Ring closure should not readily be possible for (8) since this would require placing the phosphoryl oxygen into the apical position. If it is unprotonated, then the tbp will have a very unfavorable O^- group in the apical position.

It is very unusual to observe P-O bond cleavage competitive with P-S bond cleavage as demonstrated for the hydrolysis of the bicyclic thiophosphonium ion (6). Thus, the acyclic triethyl methylthiophosphonium ion hydrolyzes with complete P-S bond cleavage under the same conditions (either acid or base) to yield only triethyl phosphate. Since thioalkoxide is a much better leaving group than alkoxide (the pK's of the parent alcohols differ by >5 pK units), loss of alkoxide is expected. Ring cleavage (loss of alkoxide) is the hydrolysis of bicyclic phosphonium ion (6) is thus unexpected if analyzed solely in terms of the leaving-group ability of RO^- *vs.* SR^-.

However, ring cleavage in the bicyclic system appears to be favored due to a stereoelectronic efect: since the lone pairs on the equatorial oxygens are antiperiplanar (app) to the breaking endocyclic P-O bond, the P-O bond cleavage results in the formation of compound (8). *Ab initio* molecular orbital calculations and experiments have suggested that the stereoelectronic effect[53,135-137] involving the orientation of lone pairs on directly bonded oxygen or nitrogen atoms can significantly affect the reactivity of organophosphorus compounds.[53] Thus, consideration of the stereoelectronic effect leads to the prediction that if there are electron lone pairs antiperiplanar (app) to the P-O bond, then this bond may instead be favored to break compared to a P-S bond with no app lone pairs. Note thioalkoxide loss is not stereoelectronically favored since none of the lone pairs on the equatorial ring oxygens are app to the SMe leaving group.

VII. Conclusions

^{31}P NMR has become an indispensable tool in studying the

chemistry and reactivity of phosphorus compounds. Newer NMR instrumentation has enormously enhanced the sensitivity of the experiment and allowed two-dimensional NMR studies to provide new means of signal assignment and analysis. Through 2D heteronuclear NMR or $^{17}O/^{18}O$ labeling experiments it is now possible to assign unambiguously the ^{31}P signals of duplex oligonucleotides and other phosphate esters. Both empirical and theoretical correlations between measured coupling constants, ^{31}P chemical shifts and structural parameters have provided an important probe of the conformation and dynamics of nucleic acids and small organophosphorus compounds.

Table 1
One-Bond Phosphorus Spin-Spin Coupling Constants $^{1}J_{PX}$

Structural Class (or Structure)	^{1}J(Hz)[a]
P(II)	
PH_2^-	139
P(III)	
PH	180-225
P-C	0-45
PF	820-1450
P-P	100-400
P(IV)	
PH	490-600
PC	50-305
P(O)H	460-1030
P(M)F (M = O, S)	1000-1400
P(V)	
PH	700-1000
PF	500-1100
P(VI)	
PF_6^-	706

[a]Largely derived from Mavel.[89] Only absolute value of J is given.

Table 2
Two-Bond Phosphorus Spin-Spin Coupling Constants $^2J_{PX}$

Structural class	^2J(Hz)[a]
P(III)	
PCH	0-18
PCF	40-149
PCC	12-20
POC	10-12
P(IV)	
P(O)CH	7-30
P(O)CF	100-130
P^+CH	12-18
P^+CC	0-40
PSC	0-10
P(V)	
PCH	10-18
PCF	124-193
P(VI)	
PCF	130-160

[a]Largely derived from Mavel.[89] Only absolute value of J is given.

Table 3
Three-Bond Phosphorus Spin-Spin Coupling Constants $^3J_{PX}$

Structural Class (or structure)	^3J(Hz)[a]
P(III)	
POCH	0-15
PCCH	10-16
PNCH	3-14
P(IV)	
P^+OCH	7-11
P^+CCH	15-22
PNCH	9-17
P(O)OCH	0-13
P(M)CCH (M = O, S)	14-25
P(V)	
PCCH	20-27
POCH	12-17

[a]Largely derived from Mavel.[89] Only absolute value of J is given.

VIII. Bibliography

1. Dickenson, W.C. (1951). The time average magnetic field at the nucleus in nuclear magnetic resonance experiments, *Phys. Rev.*, *81*: 717.
2. Gutowsky, H.S., and McCall, D.W. (1951). Nuclear magnetic resonance fine structure in liquids, *Phys. Rev.*, *82*: 748.
3. Van Wazer, J.R., Callis, C.F., Shoolery, J.N., and Jones, R.C. (1956). Principles of phosphorus chemistry. II. Nuclear magnetic resonance measurements, *J. Am. Chem. Soc.*, *78*: 5715.
4. Callis, C.F., Van Wazer, J.R., Shoolery, J.N., and Anderson, W.A. (1957). Principles of phosphorus chemistry. III. Structure proofs by nuclear magnetic resonance, *J. Am. Chem. Soc.*, *79*: 2719.
5. Crutchfield, M.M., Dungan, C.H., Letcher, L.H., Mark, V., Van Wazer, J.R., Grayson, M., and Griffin, E.F. (1967). *Topics in Phosphorus Chemistry, Vol. 5*, Wiley (Interscience), New York.
6. Gorenstein, D.G. (1984). *Phosphorus-31 NMR: Principles and Applications*, Academic Press, Orlando, FL.
7. Quin, L.D., and Verkade, J.G. (1987). *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis, Vol. 8*, VCH Publishers, Inc. Deerfield Beach, FL.
8. Burt, C.T. (1987). *Phosphorus NMR in Biology*, CRC Press, Boca Raton, FL.
9. Martin, M.L., Delduech, J.J., and Martin, G.J. (1980). *Practical NMR Spectroscopy*, Heyden Son, London.
10. Maple, S.R., Carson, J.E., and Allerhand, A. (1989). Ultrahigh resolution phosphorus-31 NMR, *J. Am. Chem. Soc.*, *111*: 7293.
11. Gorenstein, D.G., Findlay, J.B., Momii, R.K., Luxon, B.A., and Kar, D. (1976). Temperature dependence of the ^{31}P chemical shifts of nucleic acids. A probe of phosphate ester torsional conformations, *Biochemistry*, *15*: 3796.
12. Dickert, F.L., and Hellman, S.W. (1980). Chemical shift thermometer for phosphorus-31 nuclear magnetic resonance measurements, *Anal. Chem.*, *52*: 996.
13. Gorenstein, D.G. (1989). Phosphorus-31 nuclear magnetic resonance of enzyme complexes: bound ligand structure, dynamics, and environment, *Meth. Enzymol.*, *177*: 295.
14. I.U.P.A.C. (1976). Presentation of NMR data for

publication in chemical journals - B. Conventions relating to spectra from nuclei other than protons, *Pure Appl. Chem.*, *45*: 217.
15. Harris, R.K. (1983). *Nuclear Magnetic Resonance Spectroscopy*, Pitman Books, London.
16. Shindo, H. (1984). Solid-state phosphorus-31 NMR; theory and applications to nucleic acids, *P-31 NMR: Principles and Applications*,(Gorenstein, D.G., ed.), Academic Press, Orlando, FL, Chapter 13.
17. Herzfeld, J., Griffin, R.G., and Haberkorn, R.A. (1978). Phosphorus-31 tensors in barium diethyl phosphate and urea-phosphatidic acid: Model compounds for phospholipid head group studies, *Biochemistry*, *17*: 2711.
18. Kohler, S.J., and Klein, M.P. (1976) ^{31}P nuclear magnetic resonance chemical shielding tensors of phosphorylethanolamine, lecithin, and related compounds: Applications to head-group motion in model membranes, *Biochemistry*, *15*: 967.
19. Tutunjian, P., Tropp, J., and Waugh, J. (1983). ^{31}P shielding tensor of deoxycytidine 5'-monophosphate, *J. Am. Chem. Soc.*, *105*: 4848.
20. Cheetham, A.K., Clayden, N.J., Dobson, C.M., and Jakeman, R.J.B. (1986). Correlations between ^{31}P N.M.R. chemical shifts and structural parameters in crystalline inorganic phosphates, *J. Chem. Soc., Chem. Commun.*: 195.
21. Ye, H., and Fung, B.M. (1983). ^{1}H, ^{31}P, and ^{13}C NMR study of phenylphosphonic dichloride in liquid-crystal solution, *J. Magn. Reson.*, *51*: 313.
22. Letcher, J.H., and Van Wazer, J.R. (1966). Theoretical interpretation of ^{31}P NMR, *J., Chem. Phys.*, *44*: 815.
23. Letcher, J.H., and Van Wazer, J.R. (1967). Quantum-mechanical theory of ^{31}P NMR chemical shifts, *Top. Phosphorus Chem.*, *5*: 75.
24. Rajzmann, M., and Simon, J.C. (1975). Theoretical study of phosphorus chemical shifts in NMR spectroscopy, *Org. Magn. Reson.*, *7*: 334.
25. Wolff, R., and Radeglia, V.R. (1980). Theoretical NMR chemical shifts of tetracoordinated central atoms. Part V. CNDO/2 EHT and empirical calculations for elucidation of the substituent effect on silicon-29, phosphorus-31, and carbon-13 chemical shifts, *Z. Phys. Chem. (Leipzig)*, *261*:

726.
26. Weller, T., Deininger, D., and Lochman, R. (1981). Studies on the calculation of phosphorus-31 anisotropies of chemical shifts for phosphine, phosphoryl chloride and trimethylphosphine oxide, *Z. Chem.*, *21*: 105.
27. Bernard-Moulin, P., and Pouzard, G. (1979). Calculation of physical molecular constants. V. Carbon-13 and phosphorus-31 screening constants and anisotropy in NMR using a modification of the CNDO/2 method, *J. Chimie Phys.*, *76*: 708.
28. Chesnut, D.B. (1987). Theoretical considerations: calculation of the chemical shift, *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis: Organic Compounds and Metal Complexes, Vol. 8*, (Verkade, J.G., and Quin, L.D., eds.), VCH Publishers, Deerfield Beach, FL, pp. 185-204.
29. Prado, F.R., Giessner-Prettre, C., Pullman, B., and Daudey, J.P. (1979). *Ab initio* quantum mechanical calculations of the magnetic shielding tensor of phosphorus-31 of the phosphate group, *J. Am. Chem. Soc.*, *101*: 1737.
30. Giessner-Prette, C., Pullman, B., Prado, F.R., Cheng, D.M., Ivorno, V., and Ts'o, P.O. (1984). Contributions of the PO ester and CO torsion angles on the phosphate group to ^{31}P nuclear magnetic shielding constant in nucleic acids: theoretical and experimental study of model compounds, *Biopolymers*, *23*: 377.
31. Gorenstein, D.G. (1984). Phosphorus-31 chemical shifts: principles and empirical observations, *Phosphorus-31 NMR: Principles and Applications*, (Gorenstein, D.G., ed.), Academic Press, Orlando, FL, pp. 7-36.
32. Gorenstein, D.G. (1975). Dependence of ^{31}P chemical shifts on oxygen-phosphorus-oxygen bond angles in phosphate esters, *J. Am. Chem. Soc.*, *97*: 898.
33. Purdela, D. (1971). Theory of ^{31}P chemical shifts. II. Bond-angle dependence, *J. Magn. Reson.*, *5*: 23.
34. Kumamoto, J., Cox, J.R., and Westheimer, F.H. (1956). Barium ethylene phosphate, *J. Am. Chem. Soc.*, *78*: 4858.
35. Blackburn, G.M., Cohen, J.S., and Weatherall, I. (1971). Phosphorus-31 nuclear magnetic resonance studies of cyclic derivatives of phosphorus oxy-acids, *Tetrahedron*, *27*: 2903.
36. Martin, J., and Robert, J.B. (1981). Eight and 16-membered ring phosphorus compounds. Ring-size dependence of the

NMR parameters, *Org. Magn. Reson.*, *15*: 87.
37. Contractor, S.R., Hursthouse, M.B., Shaw, L.S., Shaw, R.A., and Yilmas, H. personal communication.
38. Dutasta, J.P., Robert, J.B., and Wiesenfeld, L. (1981). Principal ^{31}P chemical shift tensor components as determined by solid state NMR, *Phosphorus Chemistry, Vol. 171*, (Quin, L.D., and Verkade, J.G., eds.), American Chemical Society, Washington, DC, pp. 581-584.
39. Gorenstein, D.G., and Kar, D. (1975). ^{31}P chemical shifts in phosphate diester monoanions. Bond angle and torsional angle effects, *Biochem. Biophys. Res. Commun.*, *65*: 1073.
40. Gorenstein, D.G. (1983). Nonbiological aspects of phosphorus-31 NMR spectroscopy, *Progress. Nucl. Magn. Reson. Spectro.*, *16*: 1.
41. Gorenstein, D.G., and Goldfield, E.M. (1984). Phosphorus-31 NMR of drug-nucleic acid complexes, *Phosphorus-31 NMR: Principles and Applications*, (Gorenstein, D.G., ed.), Academic Press, Orlando, FL, pp. 299-316.
42. Gorenstein, D.G., Meadows, R.P., Metz, J.T., Nikonowicz, E., and Post, C.P. (1990). Phosphorus-31 NMR, *Advances in Biophysical Chemistry, Vol. 1*, (Bush, C.A., ed.), JAI Press, Greenwich, pp.47-124.
43. Gorenstein, D.G., and Rowell, R. (1979). An unusual twist-boat conformation for a six-membered ring phosphorus heterocycle, *J. Am. Chem. Soc.*, *101*: 4925.
44. Maryanoff, B.E., Hutchins, R.O., and Maryanoff, C.A. (1979). Stereochemical aspects of phosphorus-containing cyclohexanes, *Top. Stereochem.*, *11*: 187.
45. Smith, K.A., Kirkpatrick, R.J., Oldfield, E., and Henderson, D.M. (1983). High-resolution silicon-29 nuclear magnetic resonance study of rock-forming silicates, *Am. Mineral.*, *68*: 1206.
46. Lerner, D.B., and Kearns, D.R. (1980). Observation of large solvent effects on the ^{31}P NMR chemical shifts of nucleotides, *J. Am. Chem. Soc.*, *102*: 7611.
47. Costello, A.J.R., Glonek, T., and Van Wazer, J.R. (1976). Phosphorus-31 chemical shift variations with countercation and ionic strength for the various ethyl phosphates, *J. Inorg. Chem. Soc.*, *15*: 972.
48. Gorenstein, D.G. (1981). Nucleotide conformational analysis by phosphorus-31 nuclear magnetic resonance spectroscopy, *Ann. Rev. Biophys. Bioeng.*, *10*: 355.

49. Gorenstein, D.G., Goldfield, E.M., Chen, R., Kovar, K., and Luxon, B.A. (1981). High-resolution phosphorus nuclear magnetic resonsnce spectra of yeast phenylalanine transfer ribonucleic acid. Metal ion effects and tentative partial assignment of signals, *Biochemistry*, *20*: 2141.
50. Gorenstein, D.G. (1978). Phosphorus-31 NMR of nucleic acids. Bond angle and torsional effects, *Jerusalem Symposium, NMR in Biology, Vol. 11*, (Pullman, B., ed.) D. Reidel Publishing Co., New York, pp. 1-15.
51. Schroeder, S., Jones, C., Fu, J., and Gorenstein, D.G. (1986). Phosphorus-31 NMR in nucleotide analysis, *Bull. Magn. Reson.*, *8*: 137.
52. Schroeder, S., Fu, J.M., Jones, C.R., and Gorenstein, D.G. (1987). Assignment of phosphorus-31 and non-exchangable proton resonances in a symmetrical 14 base pair *lac* pseudooperator DNA fragment, *Biochemistry*, *26*: 3812.
53. Gorenstein, D.G. (1987). Stereoelectronic effects in biomolecules, *Chem. Rev.*, *87*: 1047.
54. Gorenstein, D.G., Schroeder, S.A., Fu, J.M., Metz, J.T., Roongta, V.A., and Jones, C.R. (1988). Assignments of ^{31}P NMR resonances in deoxyribonucleotides: origin of sequence-specific variations in the deoxyribose phosphate backbone conformation and the ^{31}P chemical shifts of double helical nucleic acids, *Biochemistry*, *27*: 7223.
55. Gorenstein, D.G. DNA structures, *Meth. Enzymol.*, in press.
56. Fu, J.M., Schroeder, S.A., Jones, C.R., Santini, R., and Gorenstein, D.G. (1988). Use of pure-absorption phase $^{31}P/^{1}H$ 2D COLOC NMR spectra for assignment of ^{31}P signals of oligonucleotides, *J. Magn. Reson.*, *77*: 577.
57. Gait, M.J. (1984). *Oligonucleotide Synthesis: a Practical Approach*, IRL Press, Oxford.
58. Gorenstein, D.G., Lai, K., and Shah, D.O. (1984). ^{31}P and two-dimensional $^{31}P/^{1}H$ correlated NMR spectra of duplex d(Ap[^{17}O]Gp[^{18}O]Cp[^{16}O]T) and assignment of ^{31}P signals in d(ApGpCpT)$_2$-actinomycin D complex, *Biochemistry*, *23*: 6717.
59. Petersheim, M., Mehdi, S., and Gerit, J.A. (1984). A general procedure for assigning the ^{31}P spectra of nucleic acids, *J. Am. Chem. Soc.*, *106*: 439.
60. Connolly, B.A., and Eckstein, F. (1984). Assignment of

resonances in the ^{31}P NMR spectrum of d(GGAATTCC) by regiospecific labeling with oxygen-17, *Biochemistry*, *23*: 5523.

61. Joseph, A.P., and Bolton, P.H. (1984). A general procedure for assigning the ^{31}P spectra of nucleic acids, *J. Am. Chem. Soc.*, *106*: 437.
62. Shah, D.O., Lai, K., and Gorenstein, D.G. (1984). Facile synthesis and ^{31}P NMR spectra of a double-labeled oligonucleotide d(Ap[^{17}O]Gp[^{18}O]Cp[^{16}O]T), *J. Am. Chem. Soc.*, *106*: 4302.
63. Cohn, M., and Hu, A. (1978) Isotopic (oxygen-18) shift in phosphorus-31 nuclear magnetic resonance applied to a study of enzyme-catalyzed phosphate-phosphate exchange and phosphate (oxygen)-water exchange reactions, *Proc. Nat. Acad. Sci. U.S.A.*, *75*: 200.
64. Cohn, M. (1982). Oxygen-18 and oxygen-17 effects on phosphorus-31 NMR as probes of enzymic reactions of phosphate compounds, *Ann. Rev. Biophys. Bioeng.*, *11*: 23.
65. Lowe, G., and Sproat, B.S. (1978). ^{18}O-Isotope shifts on the ^{31}P nuclear magnetic resonance of adenosine-5'-phosphate and inorganic phosphate, *J. Chem. Soc., Chem. Commun.*: 565.
66. Lutz, O., Nolle, A., and Staschewski, D.Z. (1978). Oxygen isotope effect on phosphorus-31 NMR spectra in the phosphate ion, *Naturforsch.*, *33A*: 380.
67. Jameson, C.J. (1977). The isotope shift in NMR, *J. Chem. Phys.*, *66*: 4983.
68. Gorenstein, D.G., and Rowell, R. (1980). Isotope oxygen-18 shifts in phosphorus-31 NMR as a probe of stereochemistry of hydrolysis in phosphate triesters, *J. Am. Chem. Soc.*, *102*: 6165.
69. Gorenstein, D.G., and Taira, K. (1982). Oxygen-18 labeling evidence against a hexacoordinate phosphorus intermediate in the alkaline hydrolysis of ethyl ethylene phosphate, *J. Am. Chem. Soc.*, *104*: 6130.
70. Cohn, M., and Hu, A. (1980). Isotopic ^{18}O shifts in ^{31}P NMR of adenine nucleotides synthesized with ^{18}O in various positions, *J. Am. Chem. Soc.*, *102*: 913.
71. Knowles, J.R. (1980). Enzyme catalyzed phosphoryl transfer reactions, *Ann. Rev. Biochem.*, *49*: 877.
72. Buchwald, S.L., and Knowles, J.R. (1980). Determination

of the absolute configuration of [^{16}O,^{17}O,^{18}O] phosphate monoesters by using ^{31}P NMR, *J. Am. Chem. Soc.*, *102*: 6601.

73. Buchwald, S.L., and Knowles, J.R. (1982). Nucleophilic displacements on phosphoric monoesters: stereochemical evidence, *J. Am. Chem. Soc.*, *104*: 1438.
74. Gerlt, J.A., and Coderre, J.A. (1980). Oxygen chiral phosphodiesters. I. Synthesis and configurational analysis of cyclic [^{18}O]-2'-deoxyadenosine 3',5'-monophosphate, *J. Am. Chem. Soc.*, *102*: 4531.
75. Gerlt, J.A. (1984). Use of chiral [^{16}O,^{17}O,^{18}O]phosphate esters to determine the stereochemical course of enxymic phosphoryl transfer reactions, in *Phosphorus-31 NMR: Principles and Applications*, (Gorenstein, D.G., ed.), Academic Press, Inc., Orlando, FL, pp. 199-232.
76. Tsai, M.D. (1981). Use of ^{31}P(^{18}O), ^{31}P(^{17}O), and ^{17}O NMR methods to study enzyme mechanisms involving phosphorus, *Meth. Enzymol.*, *87*: 235.
77. Tsai, M.D. (1984). Use of chiral thiophosphates and the stereochemistry of enzymic phosphoryl transfer, in *Phosphorus-31 NMR: Principles and Applications*, (Gorenstein, D.G., ed.), Academic Press, Inc., Orlando, FL, pp. 175-197.
78. Pardi, A., Walker, R., Rapoport, H., Wider, G., and Wuthrich, W. (1983). Sequential assignments for the ^{1}H and ^{31}P atoms in the backbone of oligonucleotides by two-dimensional nuclear magnetic resonance, *J. Am. Chem. Soc.*, *105*: 1652.
79. Cheng, D.M., Kan, L.-S., Miller, P.S., Leutzinger, E.E., and Ts'o, P.O.P. (1982). An effective method for the assignment of ^{31}P-NMR resonance(s) of oligonucleotides, *Biopolymers*, *21*: 697.
80. Sklenar, V., Miyashiro, H., Zon, G, Miles, H.T., and Bax, A. (1986). Assignment of the ^{31}P and ^{1}H resonances in oligonucleotides by two-dimensional NMR spectroscopy, *FEBS Lett.*, *208*: 94.
81. Jones, C.R., Schroeder, S.A., and Gorenstein, D.G. (1988). Double constant time (DOC) pure absorption phase heteronuclear correlation spectra. ^{31}P/^{1}H 2D DOC NMR spectra for assignment of ^{31}P signals of oligonucleotides, *J. Magn. Reson.*, *80*: 370.

82. Benn, R., Brenheke, H., Frings, A., Lehmkuhl, H., Mehler, G., Rufinska, A., and Wildt, T. (1988). Indirect two-dimensional heteronuclear NMR spectroscopy. (^{31}P, ^{57}Fe) spectra of organoiron complexes, *J. Am. Chem. Soc.*, *110*: 5661.
83. Kessler, H., Griesinger, C., Zarbock, J., and Loosli, H.R. (1984). Assignment of carbonyl carbons and sequence analysis in peptides by heteronuclear shift correlation *via* small coupling constants with broadband decoupling in t_1 (COLOC), *J. Magn. Reson.*, *57*: 331.
84. Williamson, D., and Bax, A. (1988). Resolution enhanced correlation of ^{1}H and ^{31}P chemical shifts, *J. Magn. Reson.*, *76*: 174.
85. Jeener, J., Meier, B.H., Bachmann, P.J., and Ernst, R.R. (1979). Investigation of exchange processes by two-dimensional NMR spectroscopy, *J. Chem. Phys.*, *71*: 4546.
86. Bodenhausen, G., and Ernst, R.R. (1982). Direct determination of rate constants of slow dynamic processes by two-dimensional "accordion" spectroscopy in nuclear magnetic resonance, *J. Am. Chem. Soc.*, *104*: 1304.
87. Ammann, C., Pregosin, P.S., and Scrivanti, A. (1989). Applications of phosphorus-31 2D exchange NMR spectroscopy to platinum chemistry, *Inorg. Chim. Acta*, *155*: 217.
88. Post, C.B., Ray, W.J., and Gorenstein, D.G. (1988). Time-dependent ^{31}P saturation transfer in the phosphoglucomutase reaction. Characterization of the spin system for the Cd(II) enzyme and evaluation of rate constants for the transfer process, *Biochemistry*, *28*: 548.
89. Mavel, G. (1973). NMR studies of phosphorus compounds, *Ann. Rep. NMR Spectrosc.*, *5B*: 1.
90. Gorenstein, D.G., and Shah, D. (1984). Selective compliation of phosphorus-31 NMR data, in *Phosphorus-31 NMR: Principles and Applications*, (Gorenstein, D.G., ed.), Academic Press, Inc., Orlando, FL, pp.549-591.
91a. Cowley, A.H., and White, W.D. (1969). The calculation of nuclear spin coupling constants. I. Theoretical considerations, *J. Am. Chem. Soc.*, *91*: 1913.
91b. Cowley, A.H., and White, W.D. (1969). The calculation of of nuclear spin coupling constants. II. One- and two-bond couplings, *J. Am. Chem. Soc.*, *91*: 1917.
92. Jameson, C.J., and Gutowsky, H.S. (1969). Systematic

trends in the coupling constants of directly bonded nuclei, *J. Chem. Phys.*, *51*: 2790.

93. Gray, G.A., and Albright, T.A. (1977). ^{15}N and ^{17}O nuclear magnetic resonance of organophosphorus compounds. Experimental and theoretical determinations of ^{15}N-^{31}P and ^{17}O-^{31}P nuclear spin coupling constants, *J. Am. Chem. Soc.*, *99*: 3243.
94. Safiullin, R.K., Aminova, R.M., and Samitov, Y.Y. (1975). Stereochemistry of organophosphorus compounds. V. MO LCAO calculations of the spin-spin interaction constant for trimethylphosphine oxide, dimethylphosphinic acid, methylphosphonic dichloride, phosphoric acid, methylphosphine, and trimethylphosphine, *Zh. Strukt. Khim.*, *16*: 42.
95. Albrand, J.-P., Robert, J.-B., and Goldwhite, H. (1976). On the large difference between the diastereoisomeric $^{1}J(PP)$ values of 1,2-bistrifluoromethyldiphosphine, *Tetrahedron Lett.*: 949.
96. Albrand, J.-P., Faucher, H., Cagnaire, D., and Robert, J.-B. (1976). Calculation of the $^{1}J(PP)$ angular dependence in P_2H_4, *Chem. Phys. Lett.*, *38*: 521.
97. McFarlane, H.C.E., and McFarlane, W. (1978). Oxygen-17 nuclear magnetic resonance spectroscopy: spin coupling to phosphorus-31, *J. Chem. Soc., Chem. Commun.*: 531.
98. Gorenstein, D.G. (1977). A generalized gauche NMR effect in ^{13}C, ^{19}F, and ^{31}P chemical shifts and directly bonded coupling constants. Torsional angle and bond angle effects, *J. Am. Chem. Soc.*, *99*: 2254.
99. Beer, M.D., and Grinter, R. (1978). Calculations of the nuclear spin-spin coupling constants of second-row elements. II. One-bond couplings of silicon and phosphorus to carbon, *J. Magn. Reson.*, *31*: 187.
100. Albright, T.A. (1976). Theoretical calculations of nuclear spin coupling of phosphorus to carbon and hydrogen by the finite perturbation method, *Org. Magn. Reson.*, *8*: 489.
101. LeQuan, R.M., Pouet, M.J., and Simionnin, M.P. (1975). Proton and carbon-13 NMR study of α-acetylenic P^{III} and P^{IV} derivatives. Signs and magnitudes of the phosphorus-carbon and phosphorus-proton coupling constants, *Org. Magn. Reson.*, *7*: 392.
102. Stec, W.J. (1974). Heteronuclear spin-spin coupling

constants between directly bonded atoms as a probe of configuration at the phosphorus atom involved in diastereoisomeric 4-methyl-1,3,2-dioxaphosphorinanes, *Z. Naturforsch., B: Anorg. Chem., Org. Chem., 29B*: 109.

103. Stec, W.J., Kinas, R., and Okruszek, A. (1976). Configurational assignments to 2-X-2-Y-4-methyl-1,3,2- dioxaphosphorinanes, *Z. Naturforsch., B: Anorg. Chem., Org. Chem., 31B*: 393.
104. Stec, W.J., and Zielinski, W.S. (1980). ^{31}P-^{15}N spin-spin coupling as a probe for the assignment of absolute configuration in R_P- and S_P-thymidine cyclic 3',5'-phosphordimethylamidates, *Tetrahedron Lett., 21*: 1361.
105. Gray, G.A., and Cremer, S.E. (1972). Carbon-13 nuclear magnetic resonance of organophosphorus compounds. V. The effect of changes in phosphorus oxidation state in four-membered heterocycles, *J. Org. Chem., 37*: 3470.
106. MacDonnell, G.D., Berlin, K.D., Baker, J.R., Ealick, S.E., Van der Helm, D., and Marsi, K.L. (1978). Nuclear magnetic resonance studies of phosphorus inversion in and conformational analysis of *cis*- and *trans*-4-*tert*-butyl-1-phenylphosphorinane, *J. Am. Chem. Soc., 100*: 4535 (1978).
107. Featherman, S.I., and Quin, L.D. (1973). Assignment of structure to isomeric 4-phosphorinanols by ^{13}C NMR spectrometry, *Tetrahedron Lett.*: 1955.
108. Breen, J.J., Lee, S.O., and Quin, L.D. (1975). Carbon-13 nuclear magnetic resonance spectra of 4-phosphorinanones. Carbonyl hydration in oxides, sulfides, and quaternary salts, *J. Org. Chem., 40*: 2245 (1975).
109. Venkataramu, S., Berlin, K.D., Ealick, S.E., Baker, J.R., Nichols, S., and Van der Helm, D. (1978). Carbon-13 NMR study of 1-phenyl-4-phosphorinanone and derivatives. Single crystal X-ray diffraction analysis of 1-phenyl-4-phosphorinanone 1-oxide and 1-sulfide, *Phosphorus Sulfur, 4*: 133.
110. Kainosho, M., and Nakamura, A. (1969). Nuclear magnetic resonance spectrum of 2,7,8-trioxa-1-phosphabicyclo-[3.2.1]octane, *Tetrahedron, 25*: 4071.
111. Kung, W.-J., Marsh, R.E., and Kainosho, M. (1977). Crystal and solution structure of 2',5'-arabinosylcytidine monophosphate. Influence of POC bond angles on the proton-phosphorus vicinal coupling constants in the

P-O-C-H fragments, *J. Am. Chem. Soc.*, *99*: 5471.
112. Bothner-by, A.A., and Cox, R.H. (1969). The estimation of vicinal phosphorus-31-hydrogen and nitrogen-15-hydrogen spin-spin coupling constants in single conformers, *J. Phys. Chem.*, *73*: 1830.
113. Benezra, C. (1973). The variation of vicinal ^{31}P-C-C-^{1}H couplings with dihedral angles in phosphonates, *J. Am. Chem. Soc.*, *95*: 6890.
114. Quin, L.D., Gallagher, M.J., Cunkle, G.T., and Chesnut, D.B. (1980). ^{31}P and ^{13}C NMR spectra of 2-norbornyl phosphorus compounds. Karplus equations for $^{3}J_{PC}$ in several P(III) and P(IV) derivatives, *J. Am. Chem. Soc.*, *102*: 3136.
115. Duncan, M., and Gallagher, M.J. (1981). The proton, carbon-13, and phosphorus-31 NMR spectra of *EZ* pairs of some substituted alkenes, *Org. Magn. Reson.*, *15*: 37.
116. Lankhorst, P.P., Haasnoot, C.A.G., Erkelens, C., and Altona, C. (1984). Carbon-13 NMR in conformational analysis of nucleic acid fragments. 2. A reparametrization of the Karplus equation for vicinal coupling constants in CCOP and HCOP fragments, *J. Biomol. Struct. Dynam.*, *1*: 1387.
117. Tsuboi, M., Takahashi, S., Kyogoku, Y., Hayatsu, H., Ukita, T., and Kainosho, M. (1969). Phosphorus-proton spin-spin coupling and conformation of a dinucleoside phosphate, *Science*, *166*: 1504.
118. Lee, C.-H., Evans, F.E., and Sarma, R.H. (1974). The gain in conformational purity and loss in flexibility as a result of 3',5' polymerization between the component mononucleotides - A 300 MHz ^{1}H and 40.5 MHz ^{31}P comparative study of the dynamic solution conformation of dinucleoside monophosphates and their component monomers, *FEBS Lett.*, *51*: 73.
119. Wood, D.J., Hruska, F.E., and Ogilvie, K.K. (1974). Proton magnetic resonance studies of 2'-deoxythymidine, its 3'- and 5'-monophosphates and 2'-deoxythymidyl-(3',5')-2'-deoxythymidine in aqueous solution, *Can. J. Chem.*, *52*: 3353.
120. Jardetzky, O., and Roberts, G.C.K. (1981). *NMR in Molecular Biology*, Academic Press, New York.
121. Sklenar, V., and Bax, A. (1987). Measurement of ^{1}H-^{31}P NMR coupling constants in double-stranded DNA fragments, *J. Am. Chem. Soc.*, *109*: 7525.

122. Nikonowicz, E.P., and Gorenstein, D.G. (1990). Two-dimensional ^{1}H and ^{31}P NMR spectra and restrained molecular dynamics structure, *Biochemistry*, *29*: 8845.
123. Dickerson, R.E. (1983). Base sequence and helix structure variation in *B* and *A* DNA, *J. Mol. Biol.*, *166*: 419.
124. Dickerson, R.E., and Drew, H.R. (1981). Structure of a *B*-DNA dodecamer. II. Influence of base sequence on helix structure, *J. Mol. Biol.*, *149*: 761.
125. Saenger, W. (1984). *Principles of Nucleic Acid Structure*, Springer-Verlag, New York.
126. Roongta, V.A., Powers, R., Nikonowicz, E.P., Jones, C.R., and Gorenstein, D.G. (1990). Effects of distortions in the deoxyribose backbone conformation of duplex oligodeoxyribonucleotide dodecamers containing GT, GG, GA, AC, and GU base-pair mismatches on ^{31}P NMR spectra, *Biochemistry*, *29*: 5245.
127. Ott, J., and Eckstein, F. (1985). ^{31}P NMR spectral analysis of the dodecamer d(CGCGAATTCGCG), *Biochemistry*, *24*: 2530.
128. Ott, J., and Eckstein, F. (1985). The ^{31}P-NMR spectrum of the dodecamer d(GACGATATCGTC), *Nucleic Acids Res.*, *13*: 6317.
129. Emsley, J., and Hall, D. (1976). *The Chemistry of Phosphorus*, Wiley, New York.
130. Walker, B.J. (1972). *Organophosphorus Chemistry*, Penguin Books, New York.
131. DeBruin, K.E., Naumann, K., Zon, G., and Mislow, K.J. (1969). Topological representation of the stereochemistry of displacement reactions at phosphorus in phosphonium salts and cognate systems, *J. Am. Chem. Soc.*, *91*: 7031.
132. Mislow, K. (1970). Role of pseudorotation in the stereochemistry of nucleophilic displacement reactions, *Acc. Chem. Res.*, *3*: 321.
133. DeBruin, K.E., and Johnson, D.M. (1973). Preferential mode for nucleophilic attack by methoxide ion on *O,S*-dimethyl phenylphosphonothioate. A contrasting behavior to reactions on analogous phosphonium salts, *J. Am. Chem. Soc.*, *95*: 7921.
134. Westheimer, F.H. (1968). Pseudo-rotation in the hydrolysis of phosphate esters, *Acc. Chem. Res.*, *1*: 70.
135. Kirby, A.J. (1983). *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, Berlin.

136. Lehn, J.M., and Wipff, G. (1975). Stereoelectronic effects in phosphoric acid and phosphate esters, *J. Chem. Soc., Chem. Commun.*: 800.
137. Gorenstein, D.G., Findlay, J.B., Luxon, B.A., and Kar, D. (1977). Stereoelectronic control in carbon-oxygen and phosphorus-oxygen bond breaking processes. *Ab initio* calculations and speculations on the mechanism of action of ribonuclease A, staphylococcal nuclease, and lysozyme, *J. Am. Chem. Soc.*, *99*: 3473.
138. Brown, I.D., and Shannon, R.D. (1973). Empirical bond-strength-bond-length curves for oxides, *Acta Crystallogr., Sect. A: Cryst. Phys. Diffr. Theor. Gen. Crystallogr*, *29*: 226.
139. Nikonowicz, E., Roongta, V., Jones, C.R., and Gorenstein, D.G. (1989). Two-dimensional ^{1}H and ^{31}P NMR spectra and restrained molecular dynamics structure of an extrahelical tridecamer oligodeoxyribonucleotide duplex, *Biochemistry*, *28*: 8714.
140. Delepierre, M., Van Heijenoort, C., Igolen, J., Pothier, J., LeBret, M., and Roques, B.P. (1989). Reassessment of structural characteristics of the $d(CGCG)_2$:actinomycin D complex from complete proton and phosphorus-31 NMR, *J. Biomol. Struct. Dyn.*, *7*: 557.

CHAPTER 10

PHOSPHOLES AND RELATED COMPOUNDS

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I. Introduction

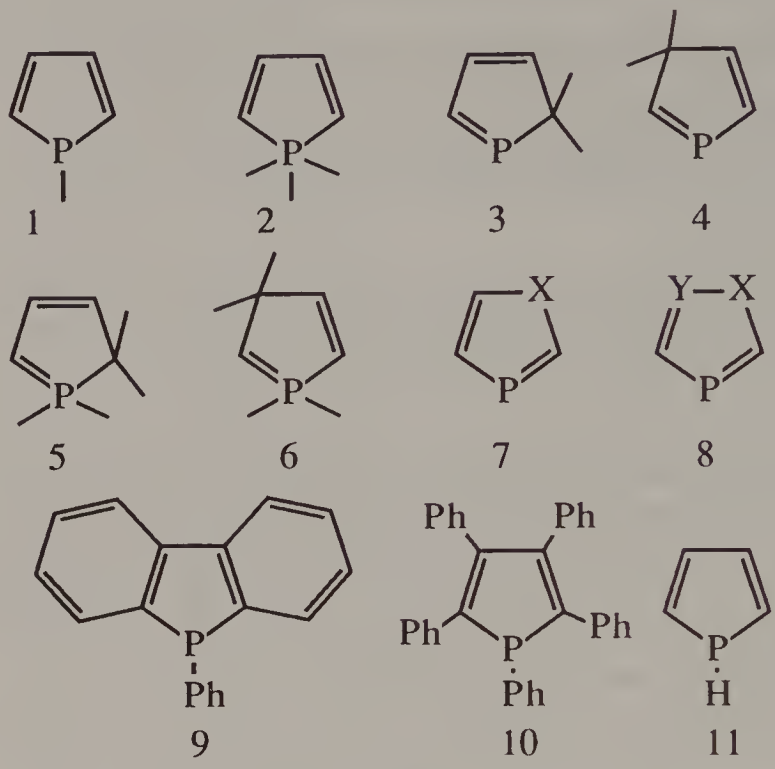
Phospholes are a class of compounds based upon a fully unsaturated, five-membered ring containing a phosphorus atom. Since phosphorus can have an oxidation state of 3 or 5 and, in rings, a coordination number of 2-5, or even 6, this general definition allows for considerable structural variety. Furthermore, in addition to carbon and phosphorus, the five-membered ring may also incorporate other elements. This survey covers the above structural types in which the phosphorus atom is bonded only to ring carbon. Phospholes in which the phosphorus is bonded to a ring heteroatom are largely outside the scope of the discussion and such systems have been recently reviewed elsewhere.[1]

The systems under review here are those in which the phosphorus is singly bonded to all attached atoms [$\sigma^3\lambda^3$- and $\sigma^5\lambda^5$-phospholes of types (1) and (2)], phospholes containing 2-coordinate or 4-coordinate phosphorus [$\sigma^2\lambda^3$- and $\sigma^4\lambda^5$-phospholes of types (3), (4), (5), and (6)], fused ring derivatives of (1)-(6), and phospholes containing additional heteroatoms [*e.g.* (7) and (8)] together with fused-ring derivatives thereof. Topics covered will include synthetic routes, electronic structure where appropriate, any reactions of the various systems which are of particular interest, and metal complexes of certain of the systems. While the coverage is thorough and includes references into early 1990, it is not intended to be exhaustive and some topics are presented more as a general overview than as a detailed account.

II. History

Phospholes are comparative newcomers to the literature of heterocyclic chemistry. Thus, while furan, thiophene, and pyrrole had been studied extensively during the first decades of this century, the first $\sigma^3\lambda^3$-phosphole derivative [the dibenzophosphole (9)] was not reported until 1953.[2] Six years elapsed before the first

simple $\sigma^3\lambda^3$-phosphole, (10), was reported in 1959.[3,4]

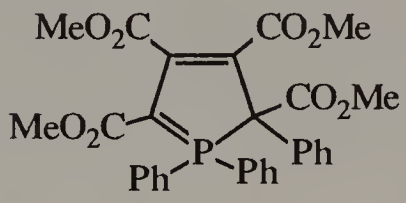


More general synthetic routes to this system were developed in the period 1967-1981[5-8] as were routes to $\sigma^3\lambda^3$-phospholes functionally substituted upon the ring carbon atoms[9,10] or the P atom.[11] However, it was not until 1987 that the parent compound (11) was prepared in pure form and fully characterized.[12]

With regard to the other phosphole systems, the first synthesis of a $\sigma^4\lambda^5$-phosphole appeared in the 1961 literature[13] although the product (12) was not recognized as such until 1969.[14] Many such systems are now known. Even more recent additions to the phosphole family are the $\sigma^2\lambda^3$- and $\sigma^5\lambda^5$- derivatives which were both characterized for the first time in 1981[15,16] although structures of the latter type had been postulated [*e.g.* (14)] much earlier as intermediates in certain reactions leading to the formation of $\sigma^4\lambda^5$-phospholes.

During the 1960s and early 1970s, much attention was given to the question of whether $\sigma^3\lambda^3$-phospholes could be regarded as aromatic systems similar to the common heterocyclopentadienes

such as pyrrole, and, while this point is no longer the subject of much current interest, it did stimulate a great deal of work and it will be discussed later in this survey. From the mid 1970s, however, most of the published work has concerned the reactivity of $\sigma^3\lambda^3$-phospholes (including metal complexes thereof) and, later, both the synthesis and reactivity of $\sigma^2\lambda^3$-phospholes. It is in this last area that much of the current activity is taking place. Indeed, the whole area of low-coordination phosphorus chemistry is developing very rapidly.



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It can be seen that phosphole chemistry has developed in several distinct phases and, as a result, subject reviews have been published fairly regularly.[17-23] In addition, other reviews devoted to or including specialized aspects of phosphole chemistry have appeared at intervals.[24-27] These reviews contain a wealth of highly detailed information.

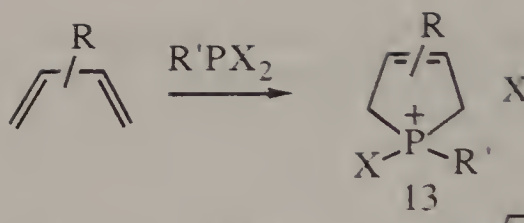
III. $\sigma^3\lambda^3$-Phosphole Derivatives

A. Synthesis

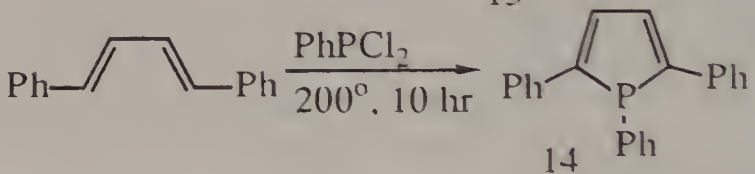
1. Simple Phospholes

The starting point for the most versatile synthetic routes to the phosphole ring is the McCormack reaction[28] in which the five-membered ring is assembled *via* a cycloaddition reaction of a diene and a phosphonous dihalide (Eqn. 1). The resulting 3-phospholenium salt (13) can be dehydrohalogenated directly or indirectly to give a phosphole.

An early example of this[29] is the synthesis of 1,2,5-triphenylphosphole (14) from 1,4-diphenyl-1,3-butadiene and phenylphosphonous dichloride (Eqn. 2). The intermediate phospholenium salt is not isolated and smooth dehydrohalogenation may be achieved solely by heating the reaction mixture.



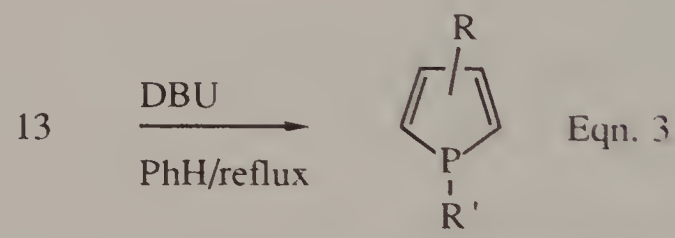
13 Eqn. 1



14 Eqn. 2

The reaction is slow but yields are good (>60%) and may be further improved[30] by using an excess of $PhPCl_2$ as the solvent for the reaction. However, while several other attempts at this kind of reaction have been made,[29,31,32] this direct thermal dehydrohalogenation can only be achieved for the synthesis of (14) and the pentaphenyl derivative.

On the other hand, dehydrohalogenation in the presence of a nitrogen base (*e.g.* DBU) is much more general and represents what has so far been the most generally useful route to $\sigma^3\lambda^3$-phospholes. The process was developed by Mathey[6] and is illustrated in Eqn. 3. Three useful modifications to the synthesis have been made since.

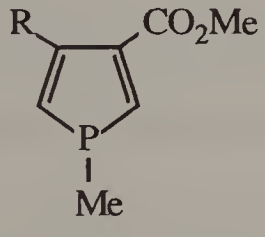


Eqn. 3

Thus, changing the solvent from benzene to a more polar hydrocarbon/dichloromethane mixture permits[7] the reaction to occur at room temperature and, thereby, improves both the yield and the purity of the product. Also, changing the dehydrohalogenating base to a pyridine derivative such as 2-picoline further improves the yield[8] to around 80% and large scale syntheses are now possible[33] using these various improvements in the procedure. The most recent modification to the synthesis concerns the formation of the 3-phospholenium salt prior to dehydrohalogenation. In this connection, it has been found[34,35] that application of pressure to the diene/phosphonous dihalide mixture reduces the

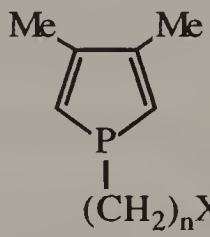
time for formation of the 3-phospholenium salt from days (or even weeks) to hours. Reaction times are typically[34] cut from ~12 days at 1 bar pressure to 10 hours at 4 kbar or 1 hour at 7 kbar. The second advantage to the pressure technique is that whereas the usual McCormack reaction produces the phospholenium salt as a very hard aggregate which is difficult to disperse for the dehydrohalogenation step, the application of high pressure leads to the formation of the cycloadduct as a finely divided material which is easily washed clean and dispersed.

The Mathey method for the dehydrohalogenation of 3-phospholenium salts is very versatile and some quite complex phospholes such as the functionally substituted (15)[9] and (16)[36] as well as the polycyclic derivatives (17)[37] and (18)[37] have been prepared by variations on this approach.



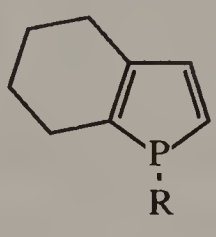
R = H or Me

15



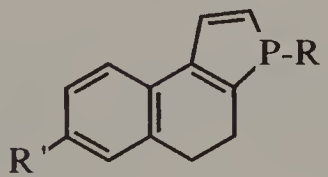
n =1, X = OR or SR
n = 2, X= CN

16



R = Me or Ph

17

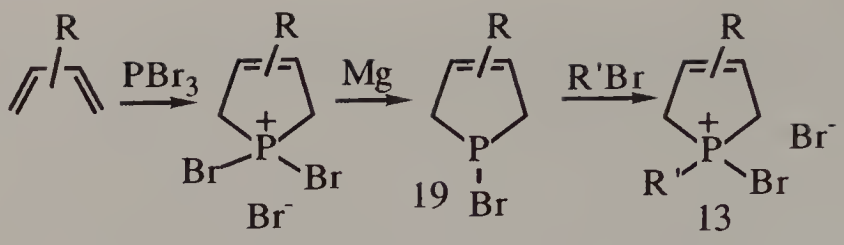


R = Me or Ph
R' = H or OMe

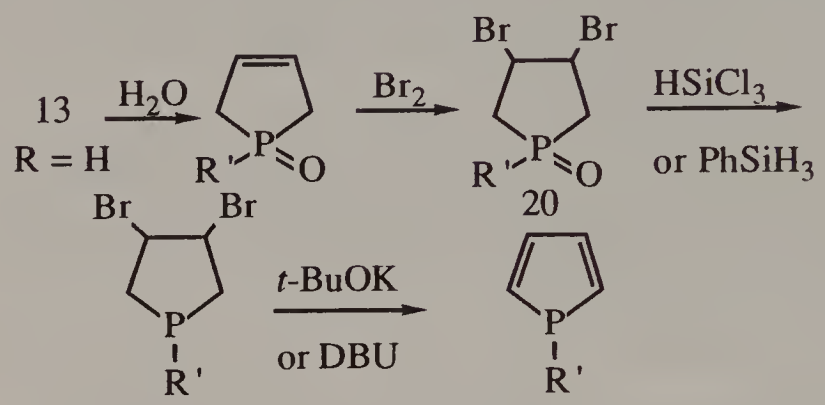
18

It should be noted, however, that the synthesis of (15) involves many steps and six such steps precede the formation of the phospholenium salt which is dehydrohalogenated to give (15).

Quin, *et al.*[5,9,38] and Markl, *et al.*[39] have also used McCormack type adducts in phosphole synthesis but in a somewhat different manner. Thus, the 3-phospholenium salt, formed either by the method outlined already or [9] by the route summarized in Eqn. 4, is hydrolyzed to the corresponding 3-phospholene oxide which then undergoes the series of transformations outlined in Eqn. 5. The method is particularly suited to the synthesis of phospholes with no substituents upon ring carbon.

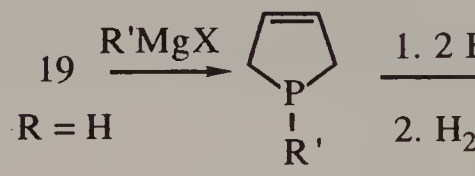


Eqn. 4



Eqn. 5

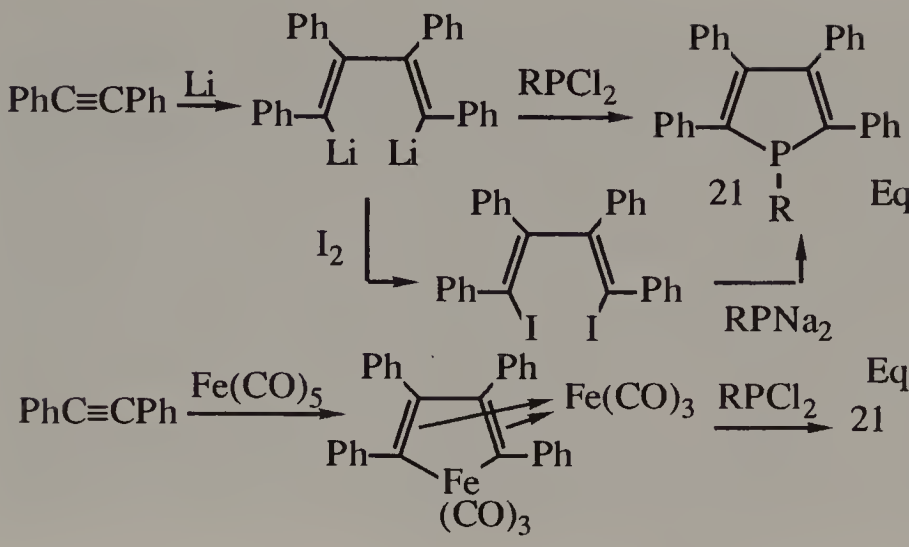
The dibromophospholane oxide (20) may also be prepared[9] from (19) as shown in Eqn. 6.

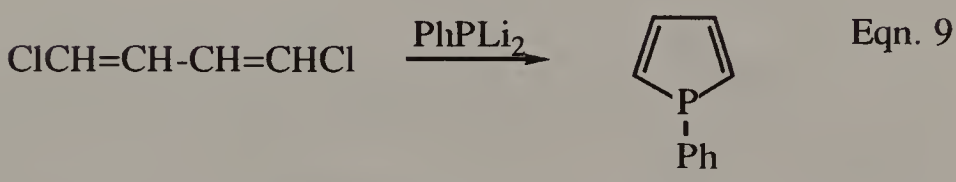


Eqn. 6

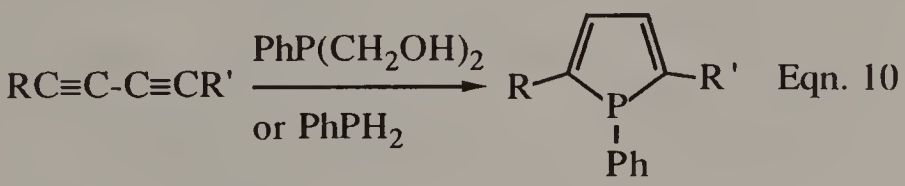
It should be noted that in syntheses of the type outlined in Eqn. 5, the phosphine oxide grouping in (20) must be reduced before dehydrobromination occurs since most simple phosphole oxides dimerize[6,7,9,39,40] by a [4+2] cycloaddition spontaneously and very rapidly.

Numerous other simple $\sigma^3\lambda^3$-phosphole syntheses have been reported but most, while interesting, are of limited value except that they may lead to phospholes of particular interest. Among these are several reactions which use diene or diyne derivatives as starting materials or key intermediates. This category includes the first two reported routes to monocyclic, albeit heavily substituted, phospholes[3,4] which are summarized in Eqns. 7 and 8 respectively. A more recent synthesis[41] based upon the same idea, and leading to ring-carbon unsubstituted phospholes in low yield, is shown in Eqn. 9.



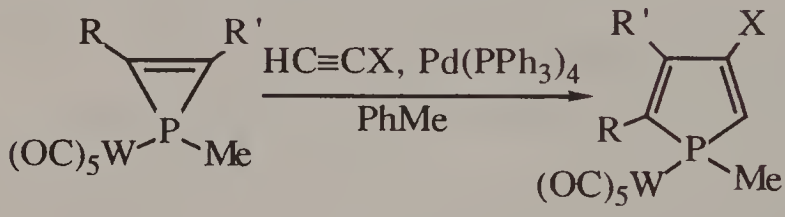


The same group has also shown in earlier work[42] that diynes will undergo cycloaddition reactions with primary phosphines, or reactive sources thereof, to give $\sigma^3\lambda^3$-phospholes (Eqn. 10) but only systems with a 1,2,5-substitution pattern can be obtained by this route. If phenylphosphine is used, its poor nucleophilic characteristics can be overcome by addition of small amounts of *n*-butyllithium,[42] KOH,[11] or Cu(I) or Hg(II) salts.[11] While the synthesis has several limitations, it has been used[43] as a route to unsymmetrically substituted phospholes prepared for some pyramidal inversion studies of considerable interest. These will be discussed later.



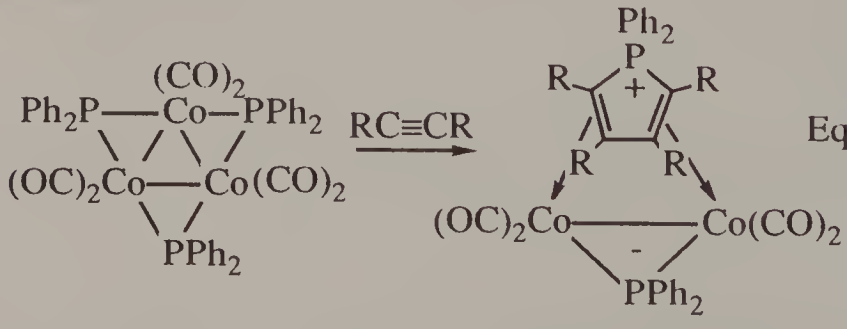
The reactions in the next group of $\sigma^3\lambda^3$-phosphole syntheses are mechanistically unrelated to one another but have in common the fact that a metal center is involved. All are quite recent and probably the most versatile is the ring expansion of tungsten

carbonyl-phosphirene complexes.[44] The reaction is outlined in Eqn. 11 and eight phospholes have been prepared [as the -$W(CO)_5$ complexes] in moderate to excellent yield by this method. Only a trace of the catalyst $Pd(PPh_3)_4$ is required. The main value of this route is that X can be a variety of functional groups and the method represents, therefore, one of relatively few routes to functionally substituted $\sigma^3\lambda^3$-phospholes. The group X, however, can only occupy the 4-position and only terminal alkynes can be used in the reaction. The fact that phospholes are obtained in complexed form is of little importance since methods have been developed[45] for decomplexation in similar complexes. The synthesis is the first discussed in which the 4-carbon skeleton is not assembled prior to incorporation of the phosphorus atom.



Eqn. 11

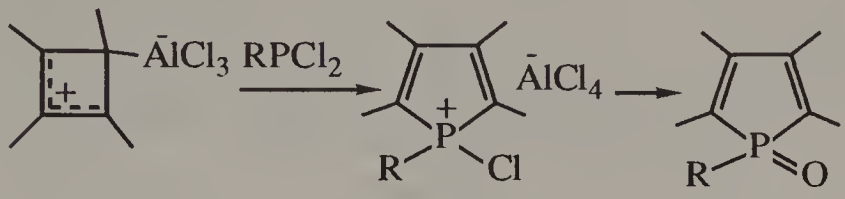
Another route to phospholes based upon metal complexes uses a phosphido-bridged trimetallic complex (Eqn. 12) as the unit about which the phosphole ring construction occurs.[46] In this case, the phosphole is obtained in both a quaternized and complexed form. Similar results have been obtained with phosphido-bridged manganese complexes.[46] The authors remarked upon the potential synthetic value of this route in the preliminary communication and this is apparently under investigation.



Eqn. 12

The third route which employs metal complexes is based upon an aluminum complex in which the 4-carbon skeleton is

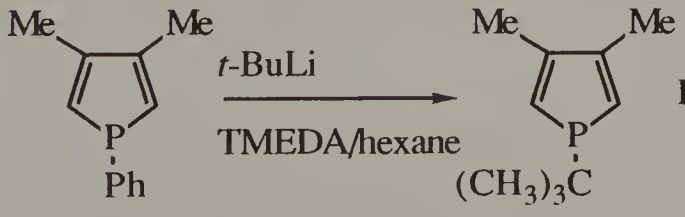
already present.[47] The reaction is limited to the formation (Eqn. 13) of phospholes as the oxides substituted on all ring carbon atoms but within that restriction, some fairly complex phospholes can be prepared. As mentioned earlier, many phosphole oxides dimerize spontaneously but with the heavy substitution obtained here, this does not occur. Phosphine oxides in general are readily reduced[48] to the corresponding phosphines by silane derivatives and the fact that phosphole oxides rather than phospholes are produced in the above reaction is therefore of little importance.



Eqn. 13

Several other syntheses of $\sigma^3\lambda^3$-phosphole derivatives using metal complexes appeared in the literature and one of these will be discussed shortly with another group of reactions. The remaining syntheses in this category are of very minor importance. They are related to the reaction outlined in Eqn. 13 in that they involve the construction of a phosphole ring as an oxide or quaternary salt with the aid of cobalt[49,50] or manganese[51] complexes.

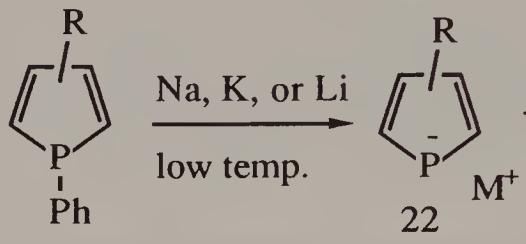
The next group of simple $\sigma^3\lambda^3$-phosphole syntheses involves the transformation of one simple phosphole into another. These transformations may involve reactions at the phosphorus atom, at a ring carbon atom, or at a site on a substituent. Dealing first with reactions at the phosphorus atom, there are apparently two variants. Thus, direct displacement of one P-substituent by another may occur[52,53] in a reaction in which the P atom of the phosphole acts as an electrophile. The process is illustrated in Eqn. 14 but the detailed mechanism is uncertain.



Eqn. 14

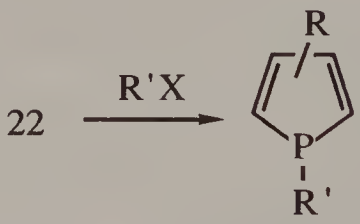
This kind of reaction is something of a rarity and most ligand exchange reactions at the P atom of phospholes involve the inter-

mediacy of a phospholyl anion. Such anions have been known[11] since the early days of phosphole chemistry and they are readily formed in excellent yield by treatment of *P*-phenylphospholes with an alkali metal (Eqn. 15). Phospholyl anions of type (22) have an electronic structure which is quite different[54] from that of $\sigma^3\lambda^3$-phospholes in that it is apparently a true 6π electron system. More will be said about the electronic structure of this system later in the context of metal complex formation.



Eqn. 15

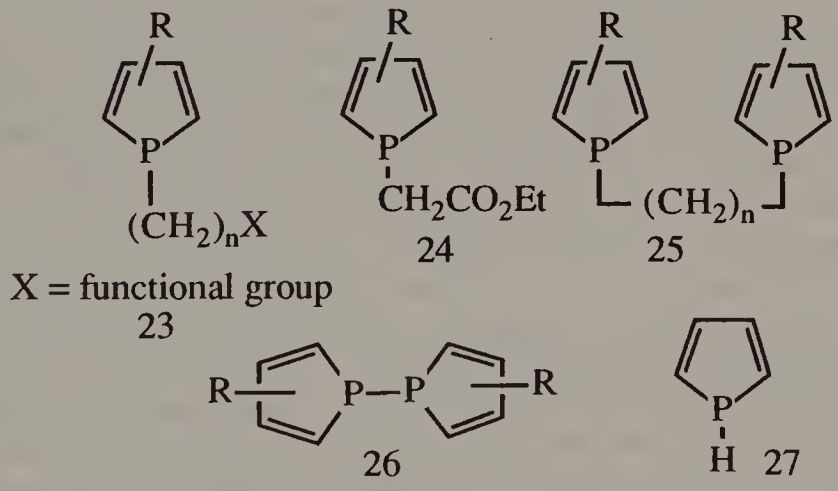
The phospholyl anions, once formed as shown in Eqn. 15, are then treated with an electrophile to yield a $\sigma^3\lambda^3$-phosphole derivative (Eqn. 16). However, before this can be done, the problem of the presence of the highly nucleophilic phenyl anion (Eqn. 15) must be solved. This was initially done by addition of 2-chloro-2-methylpropane[11] but, while moderately effective in destroying the phenyl anion, this process is not entirely satisfactory. More recently, the problem has been tackled by adding to the reaction mixture produced by Eqn. 15 salts of metals which are less electropositive than the alkali metals used in the cleavage reaction.[55-57] Aluminum trichloride is the most efficient such reagent found so far.[57]



Eqn. 16

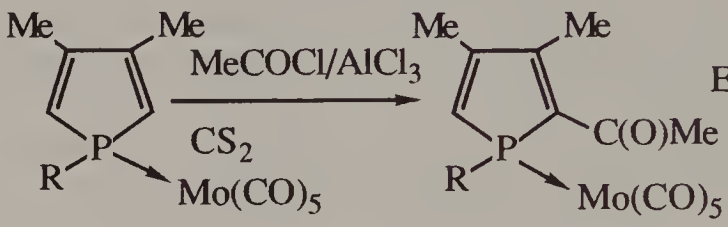
Once formed, phospholyl anions react readily with a variety of alkyl halides,[11,43,57] α,ω-dihalogenoalkanes,[11,12,58-61] halogenoalkanes containing additional functional groups,[55] ethyl bromoacetate,[11] ethylene oxide,[54] iodine,[62] or phosgene.[63]

Among the product types formed are (23), (24), (25), and (26). The first two are interesting as examples of $\sigma^3\lambda^3$-phospholes having reactive substituents upon the phosphorus atom while (25) (n = 2) is of particular interest for two reasons. First, it too can be cleaved[12,61] by an alkali metal to give the phospholyl anion but the significance of this is that the product is uncontaminated with other anions since the $-CH_2CH_2-$ bridge is eliminated as ethylene. Second, in the case where R = H, protonation with trifluoroacetic acid at low temperatures gives[12] the pure parent phosphole (27). Full spectroscopic characterization of (27), previously prepared in impure form[64] by protonation of the parent phospholyl ion generated by the more conventional methods noted above, has been carried out.[12] Compounds of type (26) can also be cleaved by alkali metals to give[64] phospholyl anions. Cleavage of (26) can also be achieved[63] by treatment with bromine and the resulting *P*-bromophospholes will react[63] with alcohols to give *P*-alkoxyphospholes.



Other $\sigma^3\lambda^3$-phosphole syntheses involving transformations of one phosphole derivative into another are also known. For example, direct substitution on the phosphole ring (as a metal complex) can be made[65] using the Friedel-Crafts reaction. Acetylation occurs smoothly (Eqn. 17) on 3,4-dimethylphospholes unless R is larger than Ph. Benzoylation does not occur with the 3,4-dimethyl systems but occurs smoothly (but only in the 3-position) with ring-unsubstituted phospholes. 2-Substitution followed by 2,5-disubstitution occurs in acetylation reactions with the ring-un-

substituted complexes. This reaction is particularly useful in that it leads in one simple step to phosphole derivatives functionally substituted upon ring carbon. Such phospholes were not readily available until this synthesis was developed. After the substitution reaction, the phospholes are still in complexed form. This, however, presents no problem since decomplexation can be achieved smoothly by treatment with CO under pressure.[65]

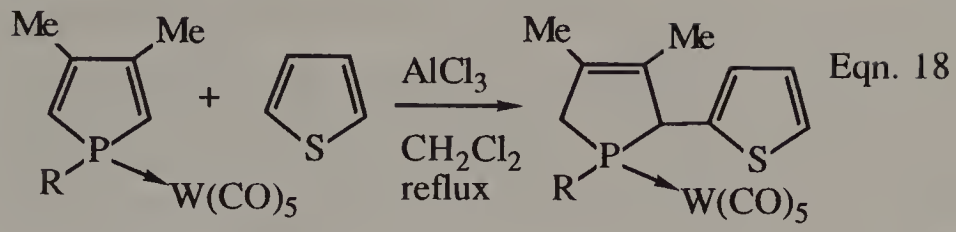


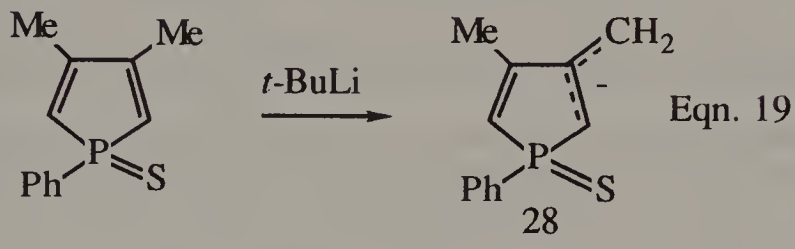
Eqn. 17

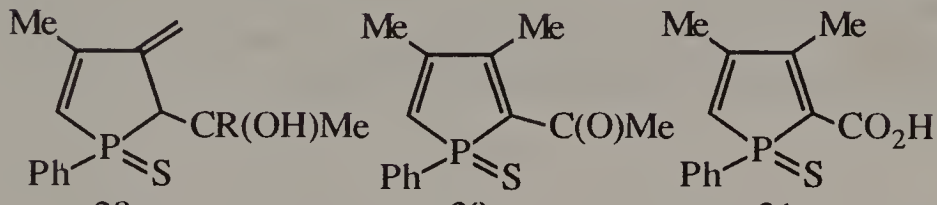
R = Me or Ph

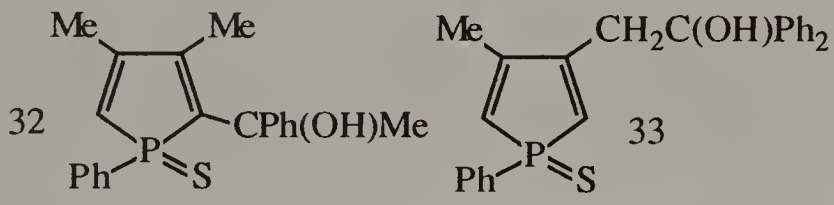
Friedel-Crafts reactions between phospholes and arenes or heteroarenes follow a different course in which the phosphole acts[66] as an alkylating agent (Eqn. 18). The reaction has been examined further[67] and substitution reactions of the type outlined in Eqn. 18 occur readily in high yield with other electron rich arenes such as anisole and furan using both tungsten and molybdenum carbonyl complexes. The corresponding 2-arylphospholes can be derived from these 2-arylphospholene complexes by a procedure[67] involving decomplexation, reduction of the resulting 3-phospholene oxides or sulfides, bromination and, finally, dehydrobromination of the type illustrated in Eqn. 3.

A somewhat older approach[10,68] to phospholes with functional groups upon the ring carbons is limited to 3,4-disubstituted phosphole sulfides in which one of the substituents is a methyl group. This disubstitution is necessary to prevent the phosphole sulfides from dimerizing.[69] The principle upon which the synthesis is based is outlined in Eqn. 19 and relies upon the fact that the protons of the 3-methyl groups are slightly acidic. The anion produced is delocalized and subsequent reaction with electrophiles leads to the formation of $\sigma^3\lambda^3$-phosphole sulfides in which the electrophile has attached itself directly to the 2-position or to the side-chain in the 3-position. Thus, reaction of (28) with acetaldehyde, acetone, ethyl acetate, CO_2/H^+, acetophenone, and benzophenone give, respectively (29) [R = H, Me], (30), (31), (32), and (33).



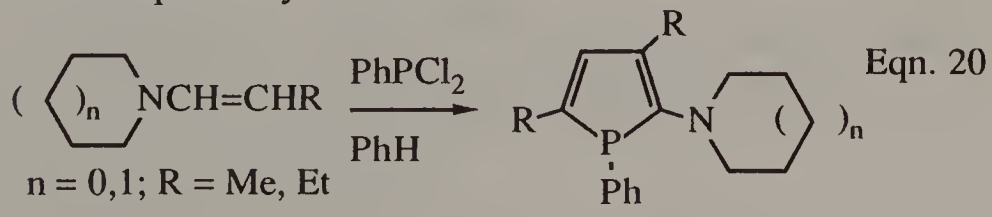






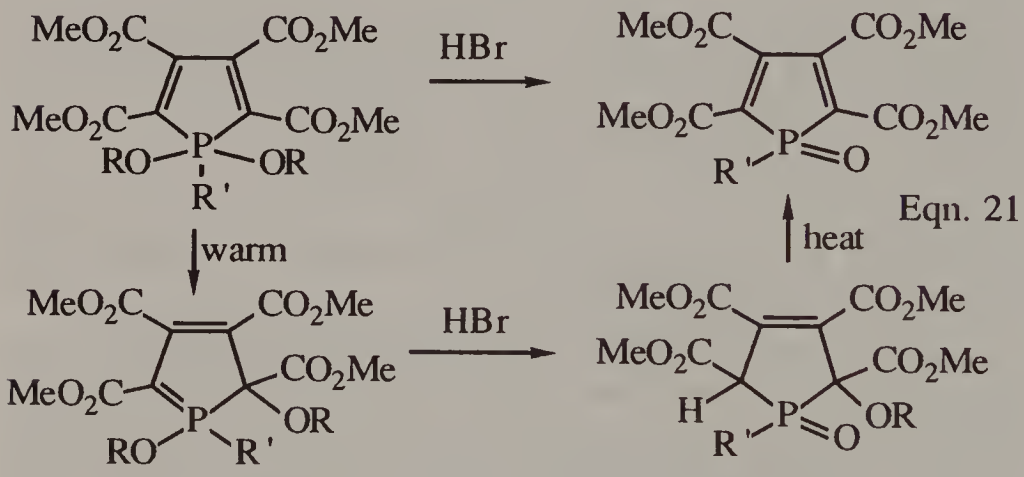
These sulfides are readily desulfurized by reaction with dimethylphenylphosphine.[70]

Several other routes to simple $\sigma^3\lambda^3$-phospholes have been reported but, for the most part, they are of limited value as synthetic methods. Perhaps the most useful of these is the reaction of enamines with dichlorophenylphosphine to give[71] 2-aminophosphole derivatives (Eqn 20). No aminophosphole derivatives have yet been reported by other workers.



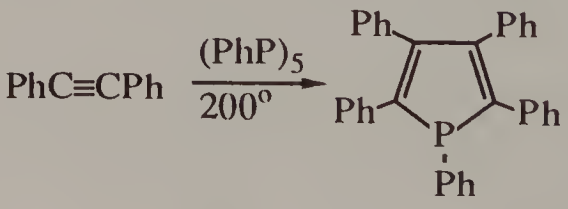
Also of some interest are the syntheses of $\sigma^3\lambda^3$-phospholes

(as the oxides) from both $\sigma^5\lambda^5$- and $\sigma^4\lambda^5$-phospholes. These $\sigma^5\lambda^5$- and $\sigma^4\lambda^5$-systems will be discussed in more detail later but there have been three brief reports[72-74] on the above-mentioned syntheses, the essentials of which are summarized in Eqn. 21. The syntheses are limited to the phosphole oxide tetracarboxylates and, while phosphine oxides are normally reducible to the corresponding phosphines,[48] this has not yet proven possible with the tetracarboxylates because of the ease with which they undergo addition reactions.[73] The two remaining simple $\sigma^3\lambda^3$-phosphole syntheses in the literature are of only minor interest. They are the reaction of diphenylacetylene with $(PhP)_5$ (Eqn. 22), which produces[75] pentaphenylphosphole in very low yield, and the pyrolysis of phosphole dimers[76,77] which produces (Eqn. 23) phospholes in low to moderate yields *via* a retro-Diels-Alder reaction.

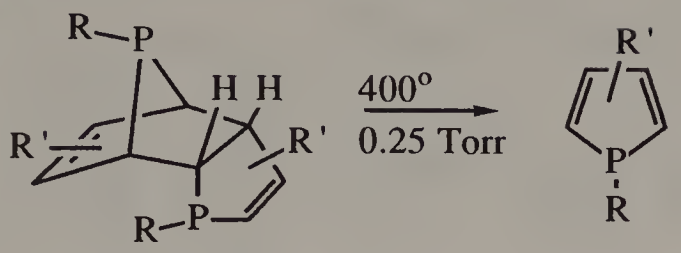


Eqn. 21

R = Me, Et, *i*-Pr; R' = Me, Ph, OMe, OEt, O-*i*-Pr



Eqn. 22

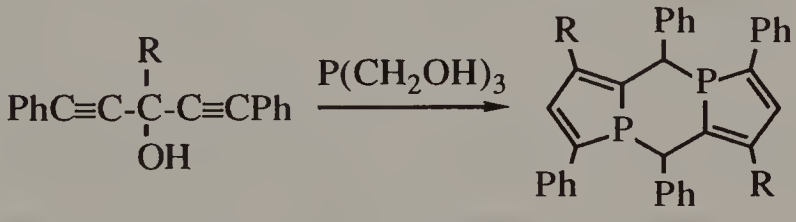


Eqn. 23

2. Phospholes Containing More Than One Phosphole Ring

Such systems are, for the most part, of comparatively recent origin. Compounds which contain more than one $\sigma^3\lambda^3$-phosphole ring, *e.g.* (25) and (26), have already been mentioned briefly. However, this section is concerned primarily, though not exclusively, with $\sigma^3\lambda^3$-phosphole rings which are linked through the ring carbon atoms. Several of the reactions are thermally induced and some proceed *via* transient $\sigma^2\lambda^3$-phosphole intermediates which will receive further discussion in a later section.

The first example of such a system was reported in 1974 and was produced by a variant of the reaction, already described, in which phenylphosphine (or more reactive derivatives thereof) reacts with 1,3-diynes to give 1,2,5-trisubstituted phospholes (Eqn. 10). In the reaction under discussion, 1,4-diyne-3-ols are treated with tris(hydroxymethyl)phosphine to give (Eqn. 24) a tricyclic system containing two $\sigma^3\lambda^3$-phosphole rings. The heavy substitution means that the system is only of minor interest.

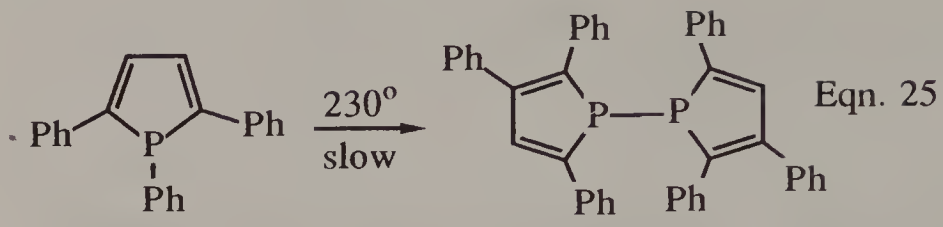


Eqn. 24

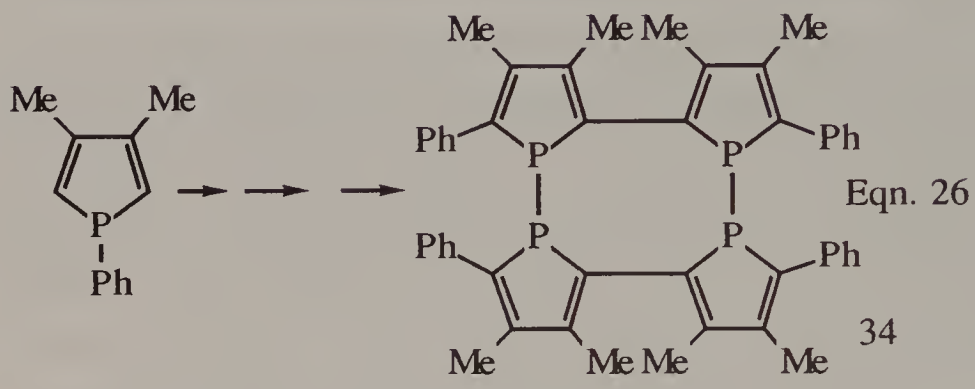
Bicyclic[79] and tetracyclic[80] systems have been prepared by a heat-initiated process. Thus, 1,2,5-triphenylphosphole gives, at 230° over 10 days, a good yield of an unsymmetrically substituted 1,1'-biphospholyl (Eqn. 25).

In the case of the less heavily substituted phospholes, such as 3,4-dimethyl-1-phenylphosphole, the process is much faster (60 hours), the temperature required is lower (170°), and the reaction proceeds further to give a tetrameric system (Eqn. 26), the crystal

structure of which has been determined.[81]



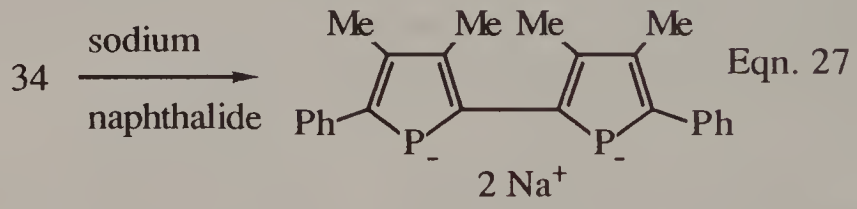
Eqn. 25



Eqn. 26

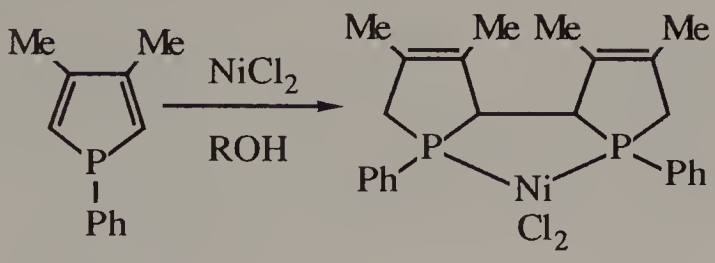
34

As with other 1,1'-biphospholyls mentioned earlier, the P-P bond in the tetramer (34) is easily cleaved (by sodium naphthalide in this instance) to give a 2,2'-biphospholyl dianion (Eqn. 27) which, on treatment with alkyl halides yields[80] the corresponding biphospholyl isolated as the sulfide.



Eqn. 27

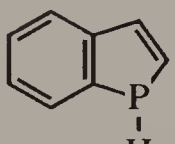
2,2'-Biphospholyls may also be prepared by a less direct route in which the initial step[82,83] is a reductive dimerization of a phosphole in the presence of nickel(II) chloride at 140-170° in an alcohol solvent (Eqn. 28). This is followed[84] by decomplexation, *P*-bromination, and dehydrobromination to give the corresponding 2,2'-biphospholyl.



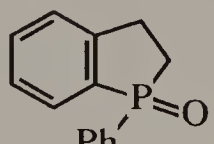
Eqn. 28

3. Phospholes Containing Additional Fused Aromatic Rings

While the range of simple $\sigma^3\lambda^3$-phospholes known is now quite large and several useful syntheses have been reported, fused-ring derivatives of these simple phospholes have received comparatively little attention. Virtually, all such compounds known are derivatives of the phosphindole (35) and dibenzophosphole (9) systems and a brief summary of synthetic approaches to each type will be given.



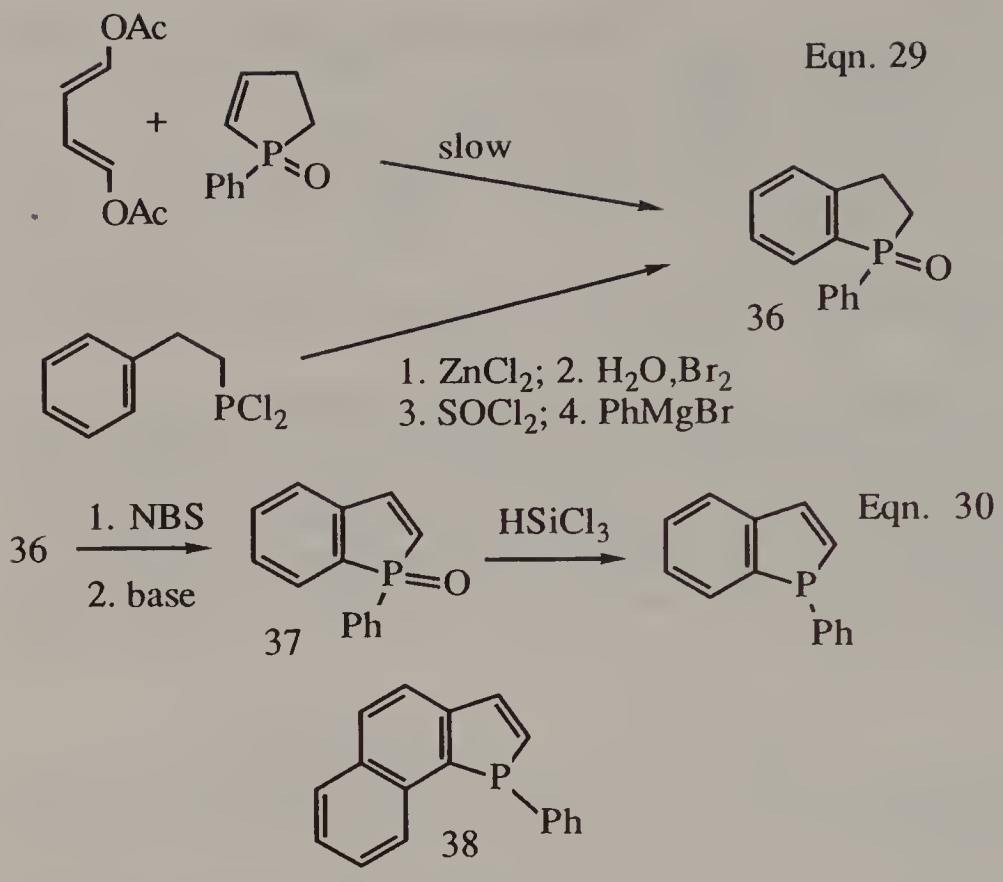
35



36

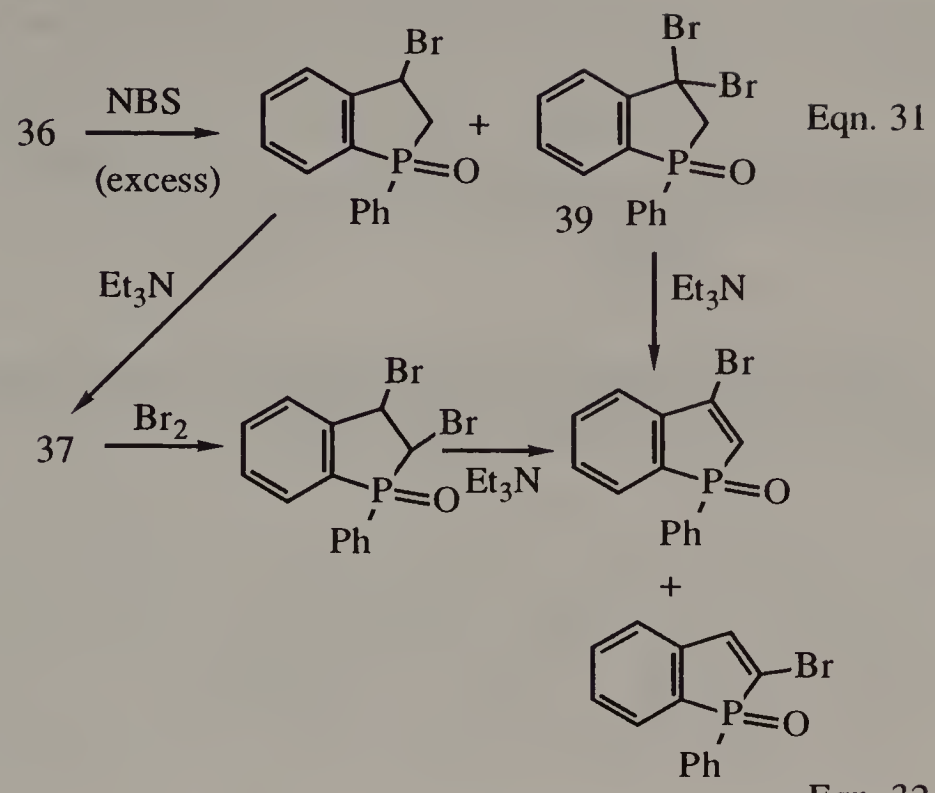
No truly general syntheses of phosphindoles have been developed although a variety of substitution patterns, some of which involve the attachment of functional groups, have been achieved by a variety of methods. Perhaps the most useful synthesis of the system is from the phosphindoline oxide (36). This is readily synthe- sized[85,86] by two routes which are outlined in Eqn. 29. While the cycloaddition route would seem to be the easier, the starting 1,4-di- acetoxy-1,3-butadiene is not readily available and the reaction is slower.

Conversion of (36) into the corresponding phosphindole oxide (37), and then the phosphindole is a straightforward[85,87] process (Eqn. 30) and the same basic reaction sequence has also been used[88] to prepare 1-benzylphosphindole. A similar NBS bromination followed by dehydrobromination and reduction has been used[37] to prepare the benzophosphindole (38) from the corresponding benzophosphindoline oxide.



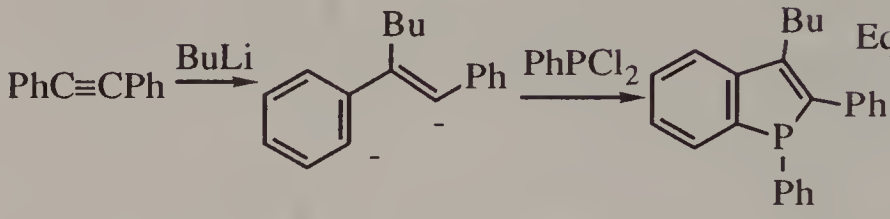
The chief advantage of this route is that it can be adapted to the synthesis[87] of functionally-substituted phosphindoles. The two published approaches to such systems are shown in Eqn. 31 and it can be seen that functional substitution can be introduced at either the 2- or 3-positions of the five-membered ring. The 3,3-dibromophosphindoline oxide (39) has not been characterized. While mixtures of products are obtained in both approaches, separation is straightforward.[87]

Another, recently-developed[89] route which can probably be modified to yield functionally-substituted phosphindoles is shown in Eqn. 32. While it does not lead directly to phosphindole derivatives in which the P atom is bound only to carbon, modification of the synthesis along the lines outlined in the lower part of Eqn. 29 could achieve this goal and, for this reason, the synthesis is given some prominence here.



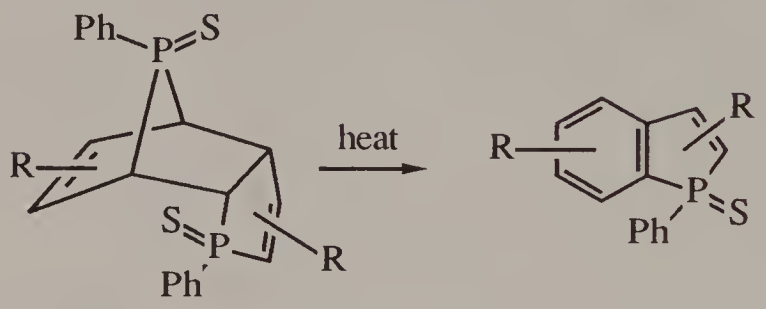
The other published syntheses are of little general value because they lack any generality, because yields are very low, and/or because the products obtained are very heavily substituted. The easiest of these syntheses[90] is a two-step process (Eqn. 33) which, while it gives a very heavily substituted phosphindole, has proven useful as a source of phosphindoles for ligand exchange reactions[43] at the P atom or reactions of the phosphindole system

with dimethyl acetylenedicarboxylate[91] which will be discussed later.

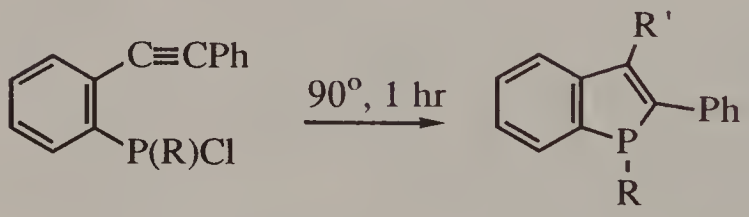


Eqn. 33

Other reactions which lead to the formation of phosphindole derivatives are shown in Eqns. 34-38.[69,92-95]

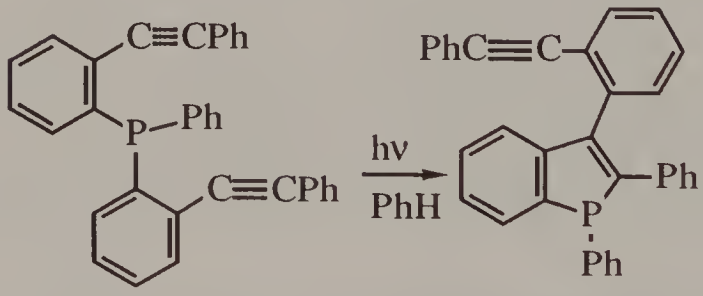


Eqn. 34

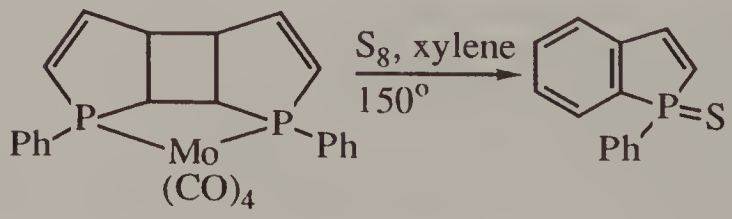


Eqn. 35

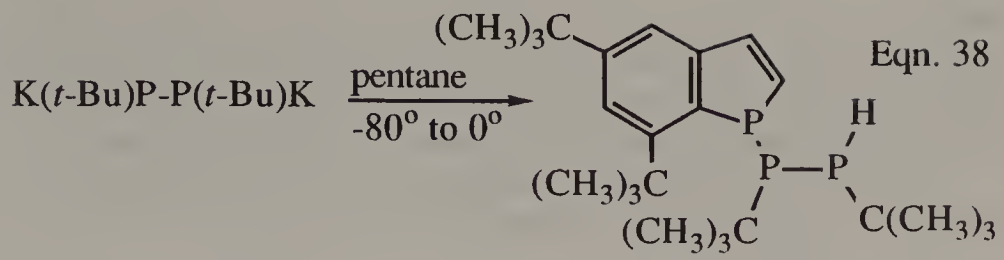
R = Ph; R' = H, Cl or R = PhC≡C(*o*-C_6H_4); R' = Cl



Eqn. 36



Eqn. 37

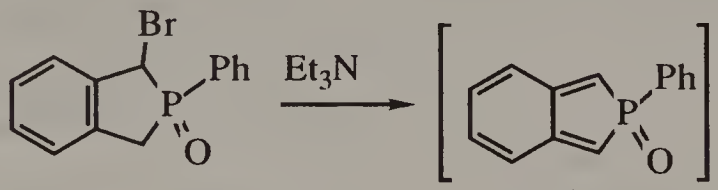


Eqn. 38

(very minor product)

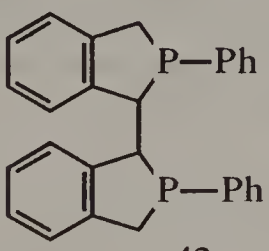
In Eqn. 37, the intermediate is probably an *exo* phosphole sulfide dimer whereas in Eqn. 34, an *endo* dimer is involved. In Eqn. 38, the phosphindole formed is present in little more than trace amounts.

Two attempts have been made[96,97] to prepare the isomeric isophosphindole system. In the first of these,[96] attempts were made to prepare the system as the *P*-oxide (Eqn. 39). However, while it is clear that the desired compound (40) was formed in the reaction (it can be trapped as a Diels-Alder adduct with dimethyl acetylenedicarboxylate), it very rapidly undergoes the type of [4+2] dimerization observed[6,7,9,39,40] for simple phosphole oxides.

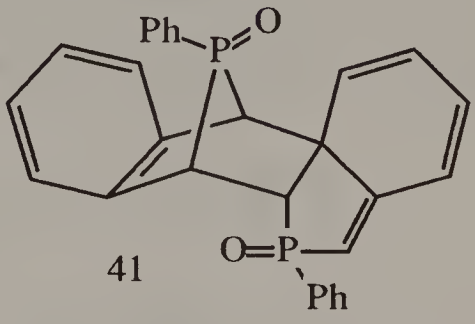


Eqn. 39

40



42



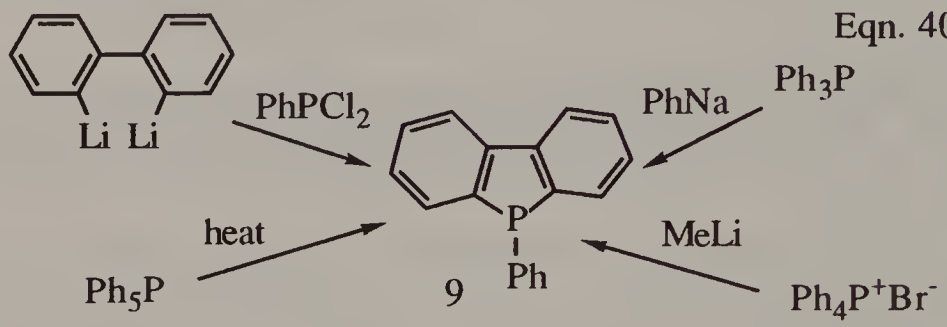
41

The second attempt[97] involved reduction, with trichlorosilane, of the dimer (41) with the thought that the deoxygenated dimer might be susceptible to a thermally induced retro-Diels-Alder reaction as has already been discussed (Eqn. 23) for simple phosphole dimers. Instead, however, C-C bond cleavage also occurs to give (42).

Although the dibenzophosphole (9) was the first phosphole

derivative of any kind to be reported, there are few synthetic routes to the system known and even fewer of these have been reported in the 20 years since the first major review of the system appeared.[17] Thus, only a brief overview of the system will be given here.

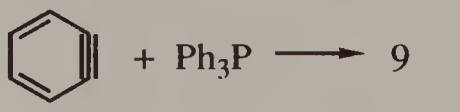
In the first report,[2] four approaches to the system were documented and these are summarized in Eqn. 40.



Eqn. 40

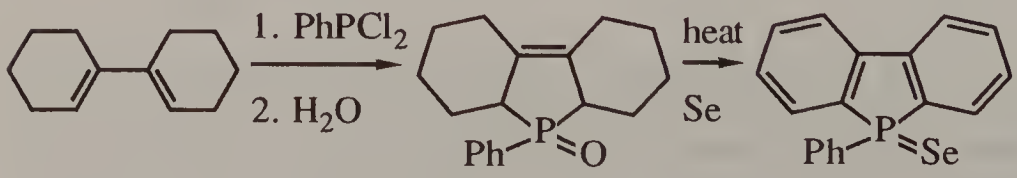
These initial syntheses gave very poor yields and some of the reactions were very slow. Several of them, however, have been modified and improved and, for the most part, these have been discussed thoroughly elsewhere.[17] Recent developments in this respect are two significant improvements in the preparation of tetraphenylphosphonium bromide and its cyclization to give (9).[98,99] Yields of (9) of 87% are now obtainable.[99] Also, the reaction of dilithiobiphenyl with arylphosphonous dihalides has been adapted to give *P*-(2-thienyl)dibenzophospholes.[100]

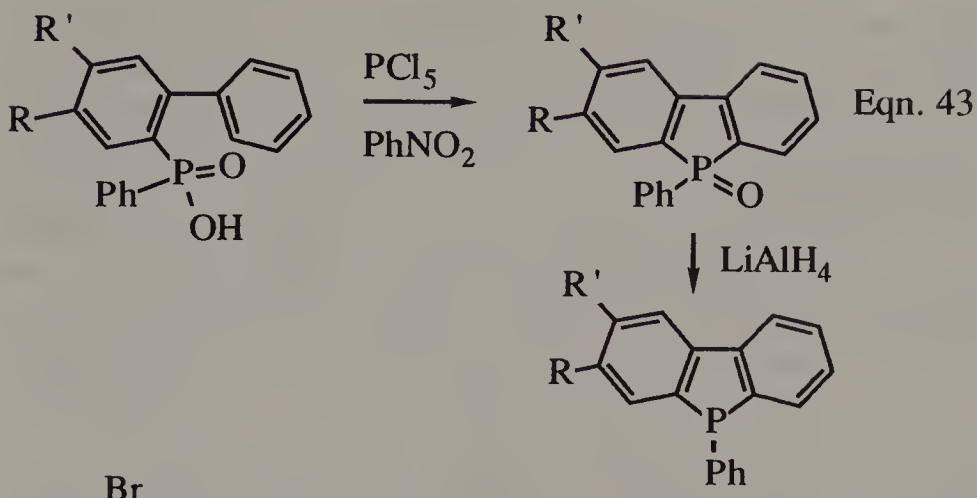
Other routes to dibenzophospholes are shown in Eqns. 41,[101,102] 42,[29] 43,[103] 44,[104] 45,[105] and 46.[106] All of these are quite old, although some have been used in more recent work to prepare (9) or derivatives thereof, for reactivity studies.

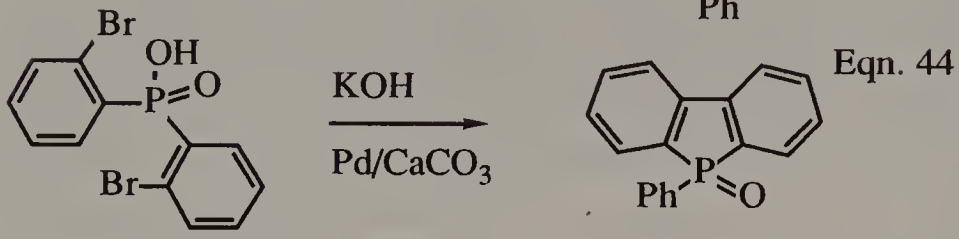


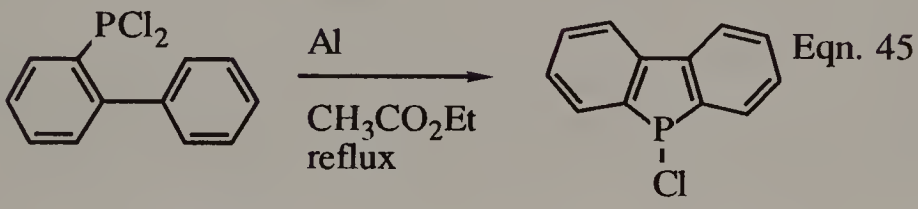
Eqn. 41

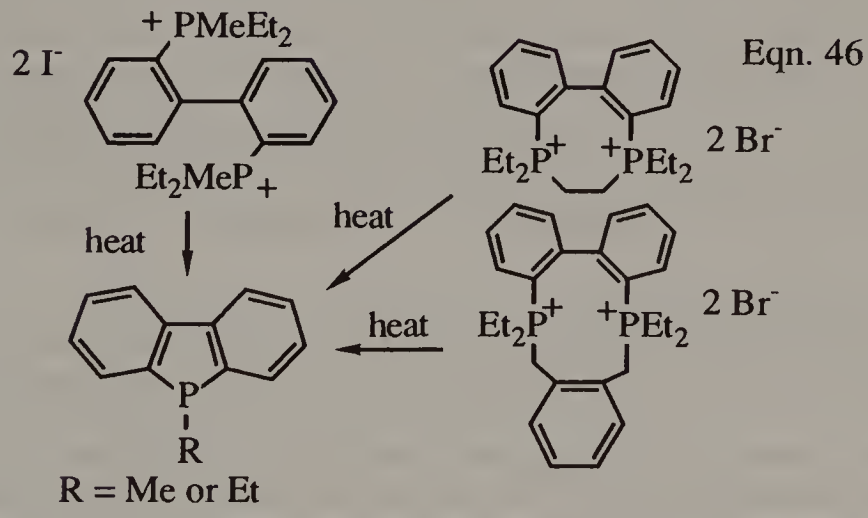
Eqn. 42











A more recent synthesis of some very heavily substituted dibenzophospholes involves[107] the treatment of 2',2''-diiodo-*m*-quaterphenyls successively with butyllithium, phosphorus trichloride, water, and hydrogen peroxide. The method is of interest

only because it leads to 4,6-diaryl derivatives.

B. Electronic Structure

1. Introduction

$\sigma^3\lambda^3$-Phospholes bear a superficial similarity to the common heterocyclopentadienes furan, pyrrole, and thiophene. Since the phosphorus atom possesses a non-bonding electron pair, there is the possibility that full 6π electron delocalization of the Huckel type could occur to give an aromatic system. Clearly, the situation is not as simple as this because $\sigma^3\lambda^3$-phosphorus is pyramidal with, unlike the nitrogen atom in amines in general and pyrrole in particular, a fairly high inversion barrier. Furthermore, the valence shell orbitals of phosphorus are larger and much more diffuse than those of nitrogen. Nevertheless, the possibility of some Huckel-type delocalization in $\sigma^3\lambda^3$-phospholes prompted numerous investigations. The majority of these took place in the period 1965-1975 and have been exhaustively reviewed elsewhere.[18-20,22] However, while no significant developments regarding this facet of phosphole chemistry have occurred recently, it is appropriate that a brief survey of these studies be given here even though the opinion that phospholes have little or no aromatic character has remained unchanged for almost fifteen years.

The investigations relating to this problem can be divided into the three main areas of chemical studies, spectroscopic and structural studies, and theoretical studies. A selection of the more important of these will be given here and a brief overview of the electronic structure of phospholyl anions will also be presented.

2. Chemical Studies

It should be noted at the outset that chemical studies can be misleading in this context since the electronic structure of a molecule at the moment of reaction is greatly perturbed by the attacking species. Thus, while chemical investigations of the aromaticity problem yield results which are largely meaningless within the context of aromatic character, they have on occasion afforded results which are intrinsically interesting, which have some bearing upon the electronic structure, and which require explanation.

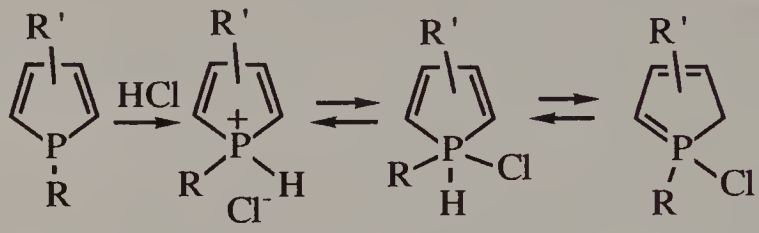
$\sigma^3\lambda^3$-Phospholes, like acyclic tertiary phosphines, readily

form oxides and quaternary salts. However, it has been remarked that in the oxides of certain phospholes, the P=O bond is significantly weaker than for similar acyclic phosphine oxides.[108] Similarly, phospholes and phosphindoles readily form quaternary salts but, in some instances at least, the rate of quaternization is slower[9] than for conventional tertiary phosphines. These results have been taken[9,108] to indicate that the P non-bonding electron pair is, to some degree, delocalized. However, they may simply reflect the degree of s character in the non-bonding pair orbital or variations in σ- and π-orbital energies.

Perhaps the most interesting reactions at the P atom relating to the electronic structure are protonation studies and retrocyanoethylation reactions. Dealing first with protonation, seven studies[11,30,37,38,53,109,110] have been performed which address various aspects of the protonation of $\sigma^3\lambda^3$-phospholes. The first of these[38] was a study of the basicity of simple $\sigma^3\lambda^3$-phospholes and it was found that 1-methylphosphole has a pK_a value of 0.5, which is several orders of magnitude lower than those of trialkylphosphines (~7), divinylphosphines (5.2), and even triphenylphosphine (2.73). Pyrrole, a known aromatic system, has a pK_a value of -3.8. These results were taken[38] to be consistent with 6π Huckel-type delocalization but again, they simply reflect factors such as the degree of s character in the non-bonding orbital and/or the relative energies of the n and π orbitals.

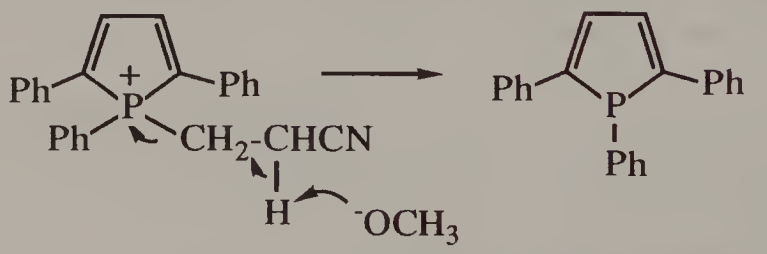
Thereafter, more attention was given to the site of protonation of $\sigma^3\lambda^3$-phospholes and two reports on this topic came in 1971. Thus, it was shown unambiguously,[109] by IR spectrophotometry, that under strictly anhydrous conditions and in the presence of $TaCl_5$, 1,2,5-triphenylphosphole protonates at the P atom to give the $TaCl_6^-$ salt. Braye's group[11] presented evidence in the same year that 2,5-diphenylphosphole behaves similarly. The IR evidence[109] was later confirmed[22,30] by NMR studies which showed a P-H coupling in phospholium salts of 502 Hz, typical of the R_3P^+-H linkage. In contrast, others[37,53] produced evidence to show that more simply substituted $\sigma^3\lambda^3$-phospholes protonate, like pyrrole,[111] on the α-carbon suggesting the accumulation of

electron density at that site through a delocalization process. This apparent conflict was resolved in 1986[110] when it was shown conclusively that, at low temperatures, $\sigma^3\lambda^3$-phospholes with simple substitution patterns protonate first at the P atom but that, at higher temperatures, a [1,5] sigmatropic shift of H occurs (Eqn. 47) and further reaction of the C-protonated system can then occur.



Eqn. 47

Considering now retrocyanoethylation reactions, the results of these complement the observation made earlier in this survey that quaternization of phospholes, in general, proceeds more slowly than for more conventional phosphines. Thus, dequaternization (as exemplified by retrocyanoethylation, Eqn. 48) occurs[112] much more rapidly for phospholium salts than conventional phosphonium salts with phosphindolium salts being intermediate[112] in character. These results, and those of the protonation studies discussed above, show clearly that the P lone pair in $\sigma^3\lambda^3$-phospholes has much less nucleophilic and basic character than one would expect from a tertiary phosphine. However, the fact that protonation occurs at the P atom suggests that some electronic factor other than Huckel-type delocalization applies.



Eqn. 48

3. Structural and Spectroscopic Studies

Again, there have been few recent developments and previous surveys[20,22] have covered the field thoroughly. Therefore, only a brief synopsis will be given here. Dealing first with structural analyses, there have been five reports[70,81,113-115] of X-ray crystal structures of $\sigma^3\lambda^3$-phosphole derivatives. The

structures examined were the ring-unsubstituted 1-benzylphosphole,[113,114] 1,2,5-triphenylphosphole (14),[115] the $\sigma^3\lambda^3$-phosphole-2-carboxylic acid obtained by desulfurization of (31),[70] and the tetrameric system (34). In all cases, the arrangement about the P atom is pyramidal and the intracyclic C-P-C angle is small, ranging from 89.2° to 91.8°. In addition, there is considerable variation in the intracyclic P-C bond lengths. Thus, for 1-benzylphosphole it is 1.783 Å while in (14) it is 1.822 Å. All of these observations are of interest. First, the pyramidal nature of the P atom in the solid state indicates that lone pair/diene interactions should be small and, therefore, phospholes should behave more like tertiary phosphines than aromatic heterocyclopentadienes. Second, the small intracyclic C-P-C angle suggests that P-protonation or quaternization of the system could introduce significant ring strain on going from the pyramidal phosphine state to the tetrahedral phosphonium arrangement. Indeed, it has been suggested[116] that it is primarily for this reason that phospholes are weaker bases and poorer nucleophiles than are conventional phosphines. Finally, the variations in the intracyclic P-C bond length are of considerable interest. In all cases, this bond length is less than the sum of the single bond covalent radii (1.84 Å) and in the case of 1-benzylphosphole, it is considerably less (by 0.057 Å). This was taken[113] to suggest signficiant lone-pair delocalization despite the pyramidal nature of the P atom. On the other hand, at the other extreme, is 1,2,5-triphenylphosphole in which this bond length is only marginally less than in a conventional phosphine. These differences could indicate some dependence of the degree of delocalization upon the substitution pattern or, more likely, steric effects arising from bulky substituents and the interaction of these substituents with the four-carbon framework of the ring.

Turning now to spectroscopic studies of the $\sigma^3\lambda^3$-phosphole system, numerous investigations of this type have been undertaken. Most of these were performed some time ago, and have yielded conflicting data, at best. They have been reviewed thoroughly elsewhere. Only those which make a clear contribution to our understanding of the electronic structure of phospholes will be surveyed here. Those studies which fall into this category are photoelectron spectroscopic investigations and various aspects of the NMR spectra of phospholes.

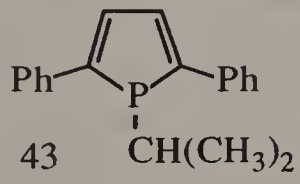
Regarding photoelectron spectroscopic properties of $\sigma^3\lambda^3$-

phospholes, there have been two reports[119,120] on this topic. The principal conclusions are that the lone-pair orbital energy is very similar to that of the corresponding orbital in the fully-saturated phospholane system and that the n and highest π orbitals are also of very similar energies. Indeed, with some substitution patterns, the n orbital may not be the HOMO. The first of these conclusions is suggestive of a non-delocalized structure and, in this context, it is interesting to note that dipole moment measurements[121] indicate that the negative end of the dipole in $\sigma^3\lambda^3$-phospholes is at the P atom, an observation more consistent with a localized rather than a delocalized electron pair.

The NMR spectroscopic studies have been quite varied. One of the earliest of these was the measurement, by NMR temperature coalescence techniques, of the pyramidal inversion barriers in $\sigma^3\lambda^3$-phospholes, phosphindoles, and dibenzophospholes.[43] Examples of the molecules used are (43) and (44) which, because of their dissymmetry and inversion about the P atom, allow diastereotopically non-equivalent proton signals to become equivalent at the coalescence temperature. Inversion barriers around 16 kcal/mol were found for simple $\sigma^3\lambda^3$-phospholes, rising to 24 kcal/mol for phosphindoles and 26 kcal/mole for dibenzophos- pholes. This was taken as evidence of an aromatic planar inversion transition state (in which the P atom is sp^2 hybridized) since a non-aromatic model would be expected[43] to have an inversion barrier well in excess of 30 kcal/mol. This implies a delocalization energy in the transition state of ~20 kcal/mol and could explain why, at room temperature, $\sigma^3\lambda^3$-phospholes are pyramidal. However, this interpretation has been challenged on theoretical grounds.

The ^{31}P chemical shift data have been taken to be consistent with aromatic character but since they allow for no firm conclusions to be drawn and since they have been reviewed extensively elsewhere, no more will be said here. One-bond phosphorus-carbon and phosphorus-proton coupling data, however, do give some useful information. For example, while ^{13}C chemical shift values for a variety of phosphole and dibenzophosphole derivatives[122-125] are inconclusive but not inconsistent with a delocalized system, values of $^1J_{P-C}$ (negative)[122] for the intracyclic bonds of the monocyclic systems are, at around 5 Hz, very low for anything other than a single bond. Similarly, one-bond P-H

coupling constants for *P*-unsubstituted phospholes indicate[64] low s character in the P-H bond (and presumably, the ring P-C bonds) and, therefore, a high s character for the lone-pair orbital. This would argue against significant lone-pair delocalization. One might expect these one-bond couplings to change with rising temperature since inversion at P would occur *via* a potentially aromatic planar transition state. Such a temperature dependence is observed[64] for 3,4-dimethylphosphole where, in THF, $^{1}J_{P\text{-}H}$ decreases as the temperature increases. The temperature dependence is also, however, solvent-dependent with no significant variation with temperature observed for toluene solutions. That the variation of this coupling constant with temperature in THF solution is due to increased delocalization in the planar transition state therefore seems unlikely.



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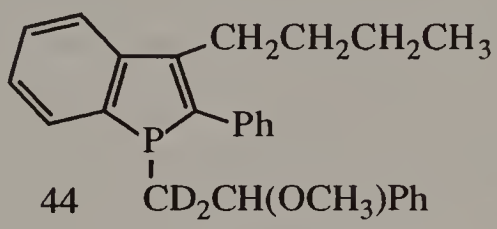

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4. Theoretical Studies

There have been ten published reports[120,126-134] concerning various attempts at theoretical analysis of the electronic structure of the $\sigma^3\lambda^3$-phospholes with particular reference to the possible aromatic character of the system. All of these are quite old with the latest appearing in 1976. However, while the whole topic has been thoroughly discussed elsewhere,[18-20,22] it is appropriate that a brief summary be given here. To say the least, the various reports give a very confused picture in that some yielded results entirely consistent with significant aromatic character for the system while others showed, apparently quite conclusively, that phospholes are non-aromatic. Clearly, no reliable conclusions can be drawn from the bulk of the studies (with one possible exception) except that knowledge of the geometry of the phosphole system was inadequate at the time the studies were performed, that good basis sets were not available, and that computational methods were not sufficiently well evolved. Nevertheless, it is worth noting (in chronological order) the variety of treatments used.

The first such treatment[126] was a simple HMO calculation performed in 1962. This was followed much later (1971) by

calculations[127] of pyramidal inversion barriers at P using the Pople CNDO/2 approach and the same group published[129] an extension of this study in 1974. The CNDO/2 approach was also used by others[128] in 1973 to calculate orbital energies and sequences in the context of conformational effects in simple phospholes. In 1974, two further studies[130,131] appeared concerning, respectively, an analysis by the LCAO-MO-CNDO/2 approach of the effect of conformational changes upon delocalization[130] and a detailed *ab initio* treatment of the system.[131] This last treatment was further extended[132] in 1975. The year 1976, the last in which theoretical treatments of the phosphole system were published, saw three reports concerning, respectively, an extended CNDO/S and MINDO/2 analysis[120] of phospholes performed in conjunction with the photoelectron spectroscopic studies already discussed, an *ab initio* many-body approach to the problem,[133] and an explicit SCF-MO-CNDO/2 treatment of phospholes and arsoles.[134]

As remarked above, few firm conclusions can be drawn from the widely differing results of these studies with the possible exception of the treatments performed[131,132] by Palmer, *et al.* where, as has been noted elsewhere,[22] the calculations were based upon accurate geometrical information and were highly detailed. The Palmer group concluded that $\sigma^3\lambda^3$-phosphole is essentially a non-aromatic system with a very low delocalization energy (~13 kcal/mol in the pyramidal state). Furthermore, an explanation (a valence force-field effect in a non-aroamtic system) for the low pyramidal inversion barriers measured by others, and discussed earlier, was offered.[132] While the deductions made by Palmer, *et al.* may not be entirely accurate, they are in agreement with the deductions made from the structural and spectroscopic investigations already discussed.

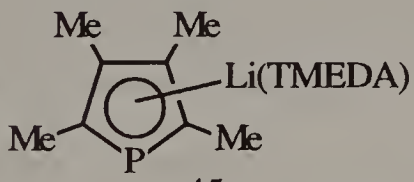
It should perhaps be mentioned that a theoretical treatment of phospholes using the 6-311* basis set and the Gaussian 86 computational method is in progress[135] in our laboratories with a view to calculating optimized geometries for the pyramidal and planar states, the inversion barrier, and the delocalization energy.

5. Phospholyl Anions

Phospholyl anions are closely related to $\sigma^3\lambda^3$-phospholes and, indeed, are readily derived from them (Eqn. 15). It is appropriate, therefore, that what is known of the electronic structure of

these chemically interesting and synthetically useful species be discussed here. Based on a simple electron count, the phospholyl anion is isoelectronic with thiophene and, as will be seen shortly, it appears to be, like thiophene, a genuinely aromatic species. In short, the picture is much clearer for phospholyl anions than for phospholes.

Until recently, structural information was available only for transition metal complexes of the system. However, while it is still the case that no X-ray analyses of completely free phospholyl anions have been performed, the Li-tetramethylethylenediamine (TMEDA) salt (45) of the 2,3,4,5-tetramethylphospholyl anion has recently[136] been the subject of an X-ray study. The anion is η^5-coordinated to Li, it is essentially planar, the P-C bond lengths are very short at 1.750 and 1.752 Å, and the 2-3 (also 4-5) and 3-4 C-C bonds are 1.396 and 1.424 Å in length respectively. The transition metal η^5-phospholyl complexes mentioned above also have short P-C bonds together with 2-3 and 3-4 C-C bonds which are very similar in length and the general characteristics of the phospholyl moiety with regard to both the bond lengths within the ring and the nature of the complexes formed are very similar to those of the cyclopentadienyl anion. Further reference to these transition complexes will be made later.



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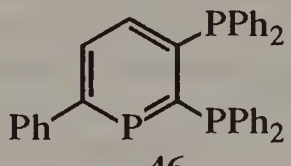

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The remaining information available regarding the electronic structure of phospholyl anions comes from spectroscopic and theoretical studies. Dealing first with spectroscopic studies, ^{31}P chemical shift data (unlike those for the corresponding phospholes) give some useful information. There have been five such studies[61,63,64,84,137] for a variety of phospholyl and 2,2'-biphospholylyl anions and the shifts observed range from δ 56.7 (for the biphospholylyl system[84]) to δ 102.5 for the 2,3,5-triphenylphospholyl anion.[63] The parent unsubstituted ion has a shift of δ 76.6.[64] These shifts are considerably downfield of those

arising from acyclic phosphides (δ ~0) and, even allowing for the ring size effect associated[138] with five-membered rings containing phosphorus, indicate significant delocalization into the ring as has been noted elsewhere.[137]

More recently, strong evidence has been obtained[61] from ^{13}C NMR spectra for charge delocalization into the ring. Thus, the ^{13}C spectrum of pure lithium 3,4-dimethylphospholyl, obtained[61] from structures of type (25), shows that $^{1}J_{P\text{-}C}$ is much greater (45 Hz *vs.* 7.3 Hz) than for the corresponding 1-phenylphosphole. Coupling constants of this magnitude are typical[139] of phosphaalkenes and the conclusion is that there is considerable π electron density in the P-C bonds. In this context, it is worth noting that intracyclic $^{1}J_{P\text{-}C}$ values for (46) (which also contains 2-coordinate P in a delocalized 6 π electron framework) are similarly high at around 58 Hz.[140]

There have been three theoretical treatments of the phospholyl anion.[54a,54b,130] The first of these[130] was based upon the known geometry of 1-benzylphosphole and used the CNDO/2 approach. The second and third treatments used the geometries of a variety of η^5-phospholyl complexes which provided a more accurate basis for the calculcations. All three analyses, however, concluded that the phospholyl anion is a clear Huckel-type 6 π electron system with the negative charge localized mainly at the P atom.[54b]

Thus, the situation is much more clear cut for phospholyl anions than for phospholes in that structural, spectroscopic, and theoretical data all strongly indicate a highly delocalized and aromatic system.

C. $\sigma^3\lambda^3$-Phosphole Reactions of Particular Interest

1. Introduction

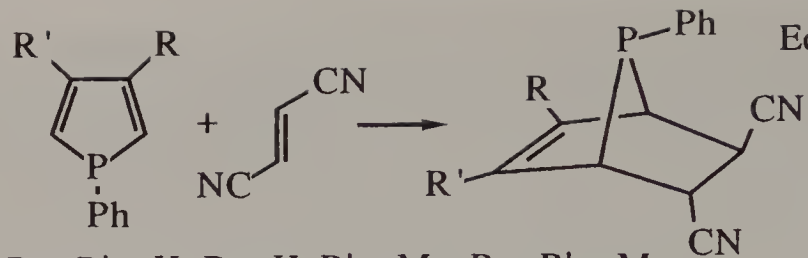
The reactions of $\sigma^3\lambda^3$-phosphole oxides and sulfides, with a few exceptions already noted (*e.g.* Eqn. 19), are largely outside the scope of this survey since, for the most part, they are reactions of a *cis* diene and the presence of the phosphorus atom is usually incidental to the outcome. Such reactions have recently been

reviewed elsewhere[22] and no significant developments have occurred since. Some reactions of simple $\sigma^3\lambda^3$-phospholes have already been discussed in the context of transformations of one phosphole derivative into another, as in Eqns. 14-18, and 19 leading to structures (29)-(33), and Eqns. 25-28. Others are best left to the sections on $\sigma^2\lambda^3$- and $\sigma^4\lambda^5$-phospholes. Those reactions remaining which are of major interest are [4+2] cycloadditions, ring expansions, miscellaneous reactions which occur at ring carbon, and metal complex formation with both phospholes (including fused-ring derivatives) and phospholyl anions.

2. [4+2] Cycloaddition Reactions

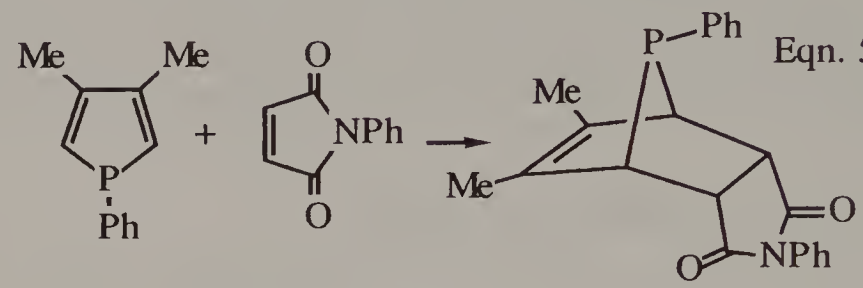
Early work[4,29] with 1,2,3,4,5-pentaphenyl- and 1,2,5-triphenylphosphole indicated that the phosphole ring would undergo the Diels-Alder [4+2] reaction with maleic anhydride or dimethyl acetylenedicarboxylate only under high-temperature (>170°) conditions with the severity of the conditions leading to elimination of the phosphorus-containing bridge from the adduct. However, while detailed studies have not yet been performed, it is clear that high temperatures are certainly not required in all cases. Thus, high-pressure reactions (9 kbar) performed[35] between several simple phospholes and fumaronitrile at 30° over a period of 10-24 hours gave good yields (~60%) of the corresponding [4+2] adducts (Eqn. 49) although, in some cases, the products were contaminated with the *P*-oxides formed during work-up. An even simpler Diels-Alder reaction is that of 3,4-dimethylphosphole with *N*-phenylmaleimide (Eqn. 50) which occurs[141] in dichloromethane at 40° over a period of four hours (50% yield).

Perhaps the most significant developments regarding the Diels-Alder reactivity of $\sigma^3\lambda^3$-phospholes have come from such reactions performed within the coordination sphere of a metal. An early example of this[142] is shown in Eqn. 51. This reaction is of interest in two respects. First, unlike[22] the products of similar reactions with phosphole oxides and sulfides, the bridged systems obtained by the route outlined in Eqn. 51 are stable at room temperature. Second, they will extrude the P-containing bridge under controlled conditions to give[143] terminal phosphinidine complexes, $RP{=}M(CO)_5$, which have proven to be useful in a variety of contexts. Several examples are in the literature and the subject has been reviewed recently.[144]

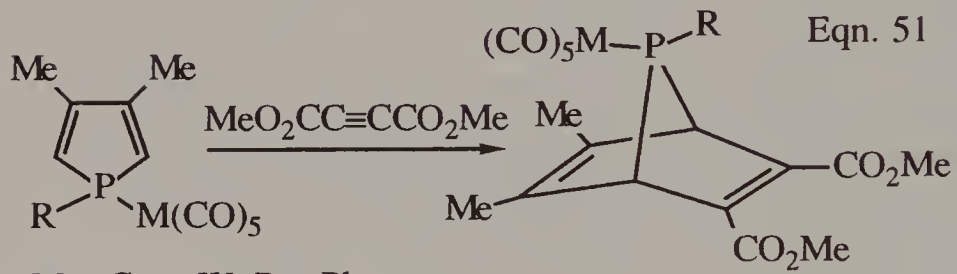


Eqn. 49

R = R' = H; R = H, R' = Me; R = R' = Me



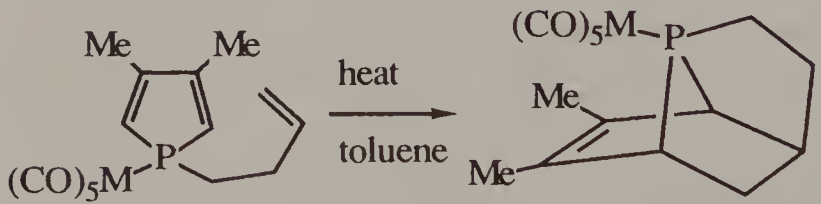
Eqn. 50



Eqn. 51

M = Cr or W, R = Ph
M = W, R = Me

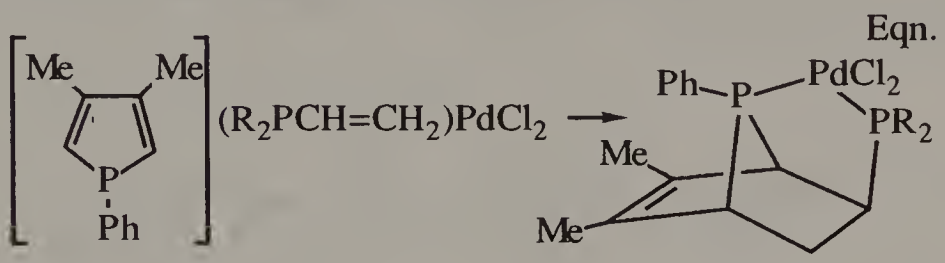
An intramolecular cycloaddition[145] related to that shown in Eqn. 51 is outlined in Eqn. 52.



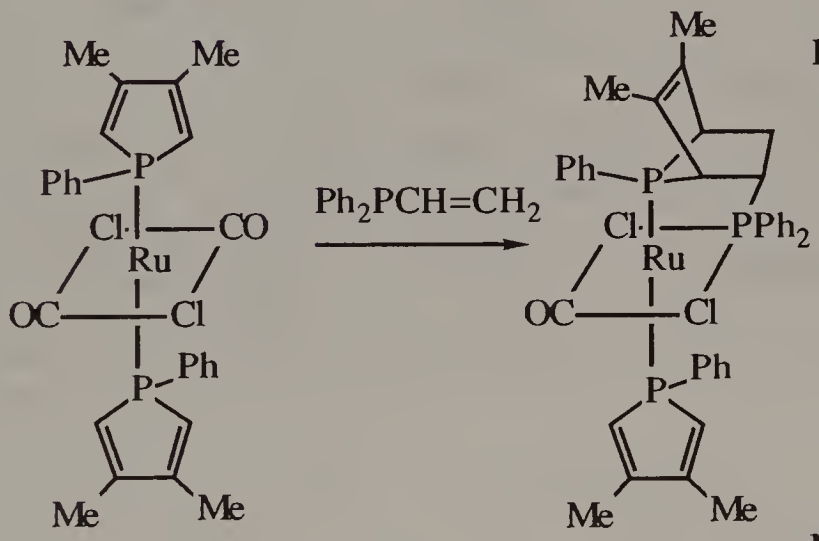
Eqn. 52

Other intramolecular [4+2] cycloadditions of phospholes have been reported but they are intramolecular in the sense that the phosphole and the dienophile are separately coordinated to the same metal center. An early example,[146] using a palladium center, is shown in Eqn. 53. Two later examples,[147,148] using a ruthenium center, are shown in Eqns. 54 and 55 and these reactions have been extended to include dienophiles such as $PhP(CH{=}CH_2)_2$,[148]

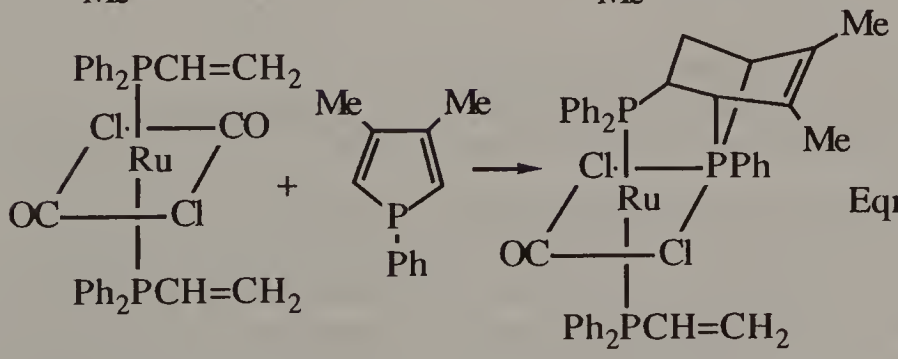
$Et_2PCH{=}CH_2$,[148] and $PhS(O)CH{=}CH_2$.[147,148] Related intramolecular [4+2] cycloaddition reactions using palladium,[149] platinum,[149] nickel,[150] and molybdenum[151] centers have also been reported recently. For the most part, the reactions proceed smoothly at room temperature in high yield although heat is required in the cases of Ni and Mo.



Eqn. 53



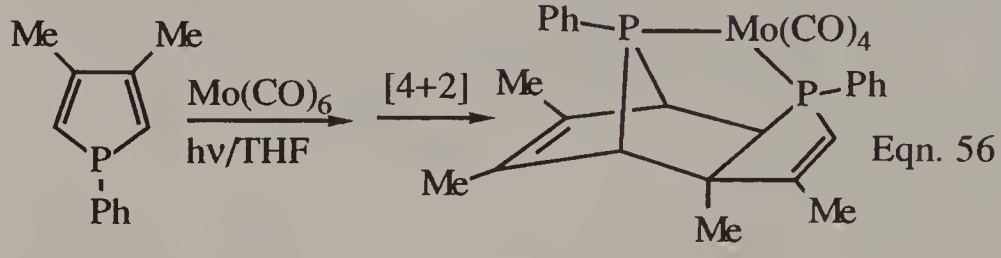
Eqn. 54



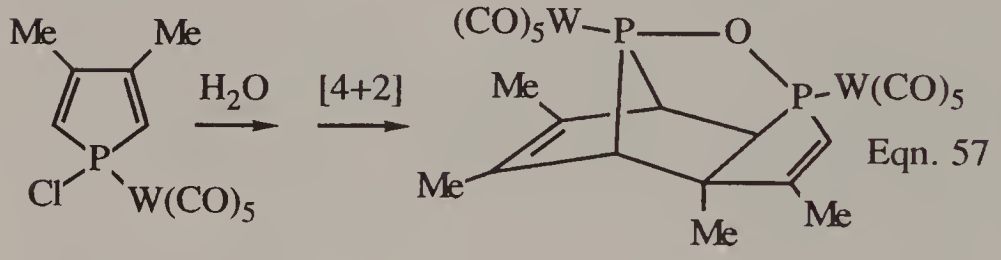
Eqn. 55

Two further [4+2] cycloadditions will be noted here. The first is the photochemically-induced reaction[94] of 3,4-dimethyl-1-phenylphosphole with $Mo(CO)_6$. The photochemical step produces

(Eqn. 56) the (phosphole)$_2$Mo(CO)$_4$ complex which then undergoes an intra-complex reaction to give a complexed phosphole Diels-Alder dimer with the unusual *exo* geometry shown. A similar intra-complex *exo* dimerization occurs, this time *via* an entirely thermal process,[152] by the reaction outlined in Eqn. 57. Other Diels-Alder dimerizations of phosphole derivatives (oxides, sulfides, quaternary salts), which often occur spontaneously, give only the *endo* dimers.[22]



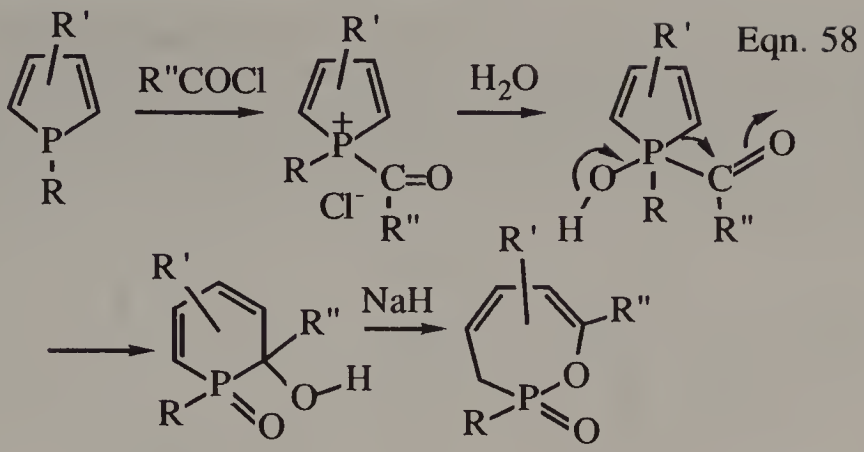
Eqn. 56



Eqn. 57

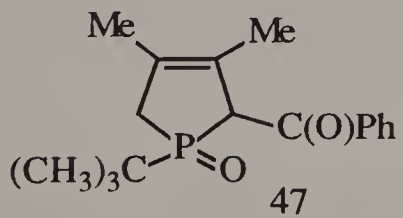
3. Ring-expansion Reactions

Several routes to the ring expansion of phospholes have been developed. Only six of these will be discussed in this section since the others are more appropriately discussed in the context of $\sigma^4\lambda^5$-phosphole chemistry. Of these six, only one has been shown to have any generality and, in this approach,[153] a double ring expansion is feasible in many instances. The general scheme is outlined in Eqn. 58 and the key step is the 1,2-migration of the apical carbon atom in the five-membered ring of the five-coordinate intermediate.



Eqn. 58

Several other reports of such ring expansions have been made for simple phospholes[36,56,153-156] and the reaction can also be applied to both phosphindoles[157] and dibenzophospholes.[158] However, while the second, hydride induced, expansion works well with phosphindoles,[157] this reaction appears to follow a different course with dibenzophospholes.[157] With simple phospholes there are some interesting exceptions to this general process which occur when the *P*-substituent is a *t*-butyl group. In such cases[53,153] the benzoyl group in the phospholium salt migrates upon hydrolysis to the 2- or 3-position (depending on the ring substitution pattern) to give compounds of types (47) and (48). As will be seen shortly, similar migrations occur in some other reactions of phospholium salts.



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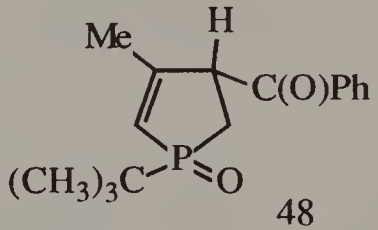
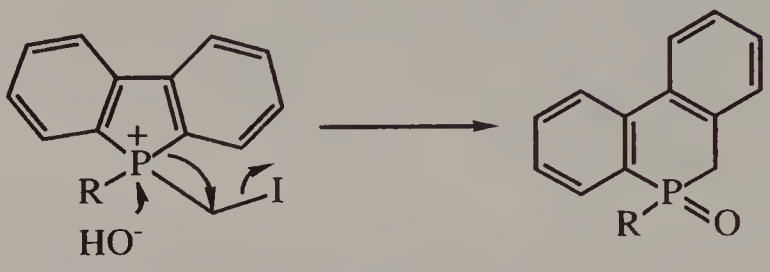


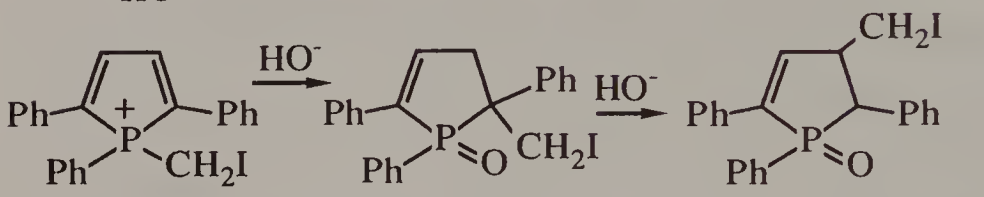
48

Another phosphole ring expansion[158] which initially offered some promise of general applicability is shown in Eqn. 59. Again, an apical C atom in the five-coordinate, five-membered ring intermediate undergoes a 1,2-migration similar to that which is illustrated in Eqn. 58. However, iodomethyl phosphindolium salts undergo[157] ring opening rather than ring expansion under these conditions while the corresponding salt of 1,2,5-triphenylphosphole undergoes[159] an interesting migration of the -CH_2I group

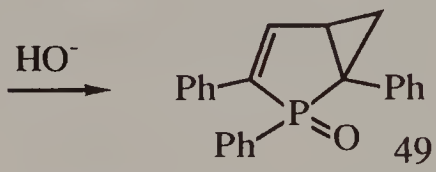
followed by formation of a bicyclic system as shown in Eqn. 60. Unfortunately, these reactions are not easily attempted with very simple iodomethyl phospholium salts since most such phosphole quaternary salts dimerize spontaneously and rapidly[160] to give [4+2] adducts.



Eqn. 59



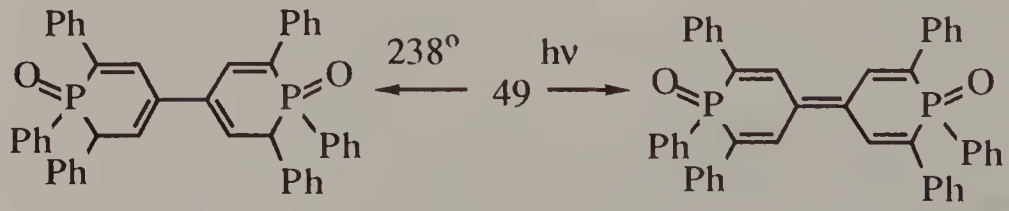
Eqn. 60



49

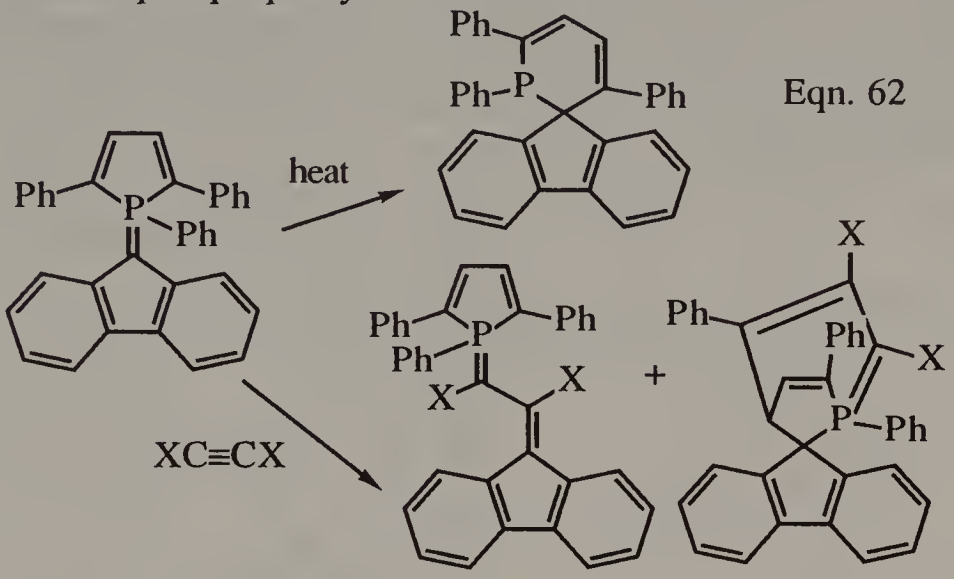
The third ring expansion is, in fact, based upon Eqn. 60 in that the bicyclic system (49) can undergo[161] both thermal and photochemical ring enlargement (Eqn. 61), and it is worth noting here that (49) can also be obtained by an entirely different route[29] involving the reaction of 1,2,5-triphenylphosphole oxide with diazomethane.

Eqn. 61

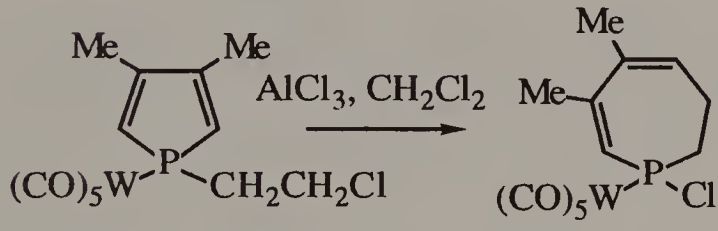


The fourth and fifth ring enlargements noted in the literature[162,163] are one-carbon and two-carbon expansions respectively. They have a common starting point and the two processes are summarized in Enq. 62. Again, there appears to be no general synthetic value to these reactions.

Finally, another two-carbon phosphole ring expansion has recently appeared in the literature.[60] Like many other recently-reported and interesting phosphole reactions, it utilizes a metal complex and may prove to have some general application. The process is illustrated in Eqn. 63 and it provides a potentially useful route to the phosphepin system.



Eqn. 62



Eqn. 63

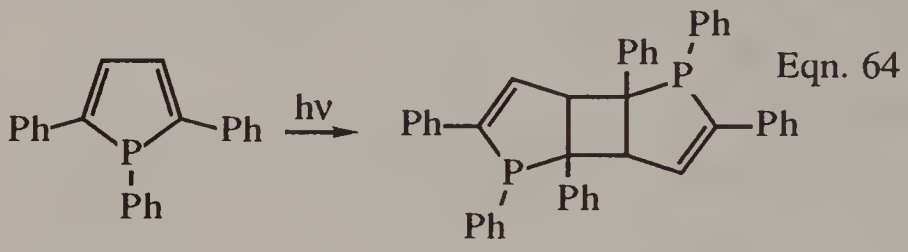
4. Other Reactions at Ring Carbon

Several reactions at the ring carbon atoms of phosphole derivatives have already been mentioned, in addition to those discussed in the two preceding subsections, and some examples of these are shown in Eqns. 17, 18, 26, 28, and 32. Others are best discussed in the section on $\sigma^2\lambda^3$-phospholes. However, a few such reactions, both thermal and photochemical, remain to be discussed here.

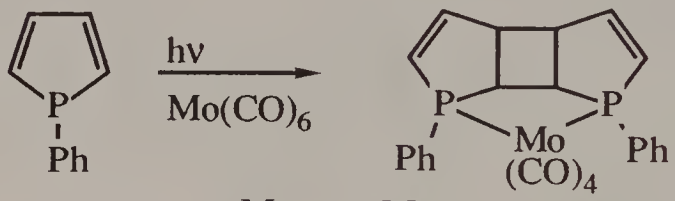
Dealing first with photochemical reactions, there are two [2+2] cycloadditions which should be mentioned and a very early example[164] is shown in Eqn. 64. Another such cycloaddition, giving this time a "head to head" dimer, is believed[94] to occur as an intermediate just prior to the formation of the [4+2] adduct in the

sequence outlined in Eqn. 56. Indeed, 1-phenylphosphole has been shown to undergo a similar reaction (Eqn. 65) and the adduct has been characterized.

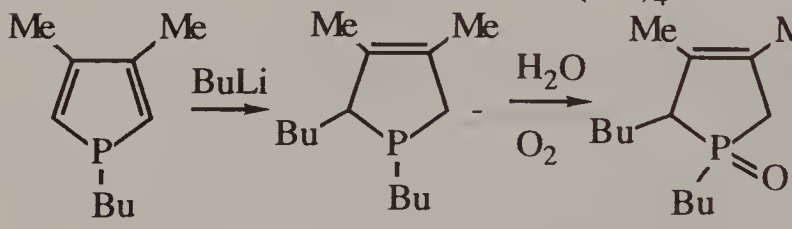
Considering now thermal reactions, there are two of these for simple phospholes and one for a phospholyl complex which should be mentioned briefly. The two phosphole reactions are summarized in Eqns. 66 and 67,[52,61] while that for the phospholyl complex is represented in Eqn. 68.[165] It can be seen that each of the transformations involves a negatively charged phosphorus-containing species.



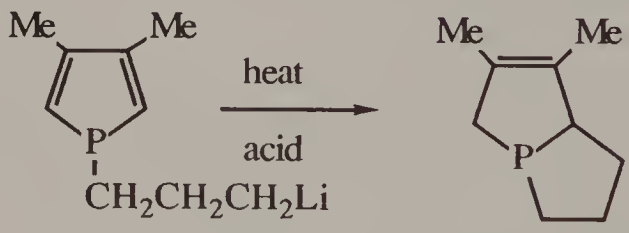
Eqn. 64



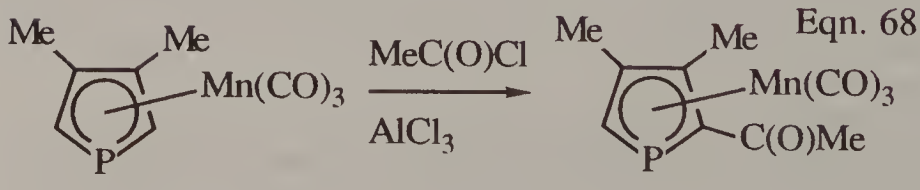
Eqn. 65



Eqn. 66



Eqn. 67



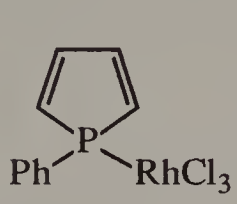
Eqn. 68

5. Metal Complex Formation

Over the past decade or so an enormous amount of inform-

ation has been published regarding metal complexes of $\sigma^3\lambda^3$-phospholes, dibenzophospholes, and phospholyl anions, and a thorough survey would demand a major review article for this topic alone. Such review articles have appeared from time to time[25,27,166] and since the topic is one of many facets of phosphole chemistry, only a general overview will be given here. For the older work, references will be made to the review articles and only more recent work will be separately referenced.

Dealing first with phosphole complexes, the phosphole ring can act as a 2-, 4-, or 6-electron donor in σ-, π-, and σ,π-complexes respectively. All three types of complexes are known and examples are shown as (50)-(52).



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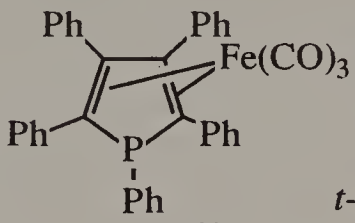

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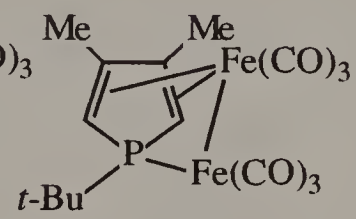


52

Most of the known phosphole complexes are of the 2-electron donor type[25,27] and the variety of metals and oxidation states with which such complexes have been formed is very large. Thus, in the most recent survey[27] of phosphole complexes it was recorded that simple phospholes form σ-complexes with Cr(0), Mo(0), W(0), Mn(0), Re(III), Fe(II), Fe(0), Ru(III), Ru(II), Co(II), Rh(III), Rh(II), Rh(I), Ir(III), Ir(I), Ni(II), Ni(0), Pd(II), Pt(II), Cu(I), and Hg(II). Others have shown[109] that metals in higher oxidation states, such as Ta(V) and Nb(V), will also form phosphole σ-complexes. Up to three simple phosphole rings can coordinate (depending upon the structure of the phosphole and the actual metal ion) in this fashion to a metal center.[27] Few examples of the π- and σ,π-complexes are known.[27]

Since this last major survey several developments have occurred. Many of the more important of these have already been discussed, notably those illustrated in Eqns. 11, 12, 17, 18, 51-57, and 63, in the context of phosphole syntheses and chemistry, but some other interesting reports have also appeared. Thus, further work has been published[167,168] on Ru(II) complexes of 3,4-di-

methylphospholes with the emphasis being upon the geometries of the systems, their NMR properties, and their catalytic activity in hydrogenation and alkene isomerization processes. The catalytic activity (and regioselectivity) of Rh(I)-1,2,5-triphenylphosphole-CO complexes in hydroformylation reactions of alkenes has also received attention.[169,170] In other investigations, studies of the solid state ^{31}P NMR and X-ray properties of Au(I)[171] and Pt(II)[172] complexes of simple phospholes have been published. This is the first mention of phosphole complexes of gold to appear in the literature.

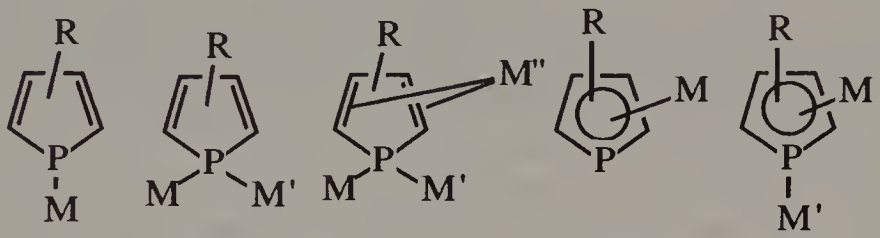
No publications devoted to the chemistry of phosphindole complexes have appeared, but, while the attention given to dibenzophospholes in this context has been much less than for simple phospholes, some work on metal complexes of this system has been published. As might be expected, dibenzophospholes act as 2-electron σ-donors in all of the known complexes. The early work has been thoroughly surveyed[25] and there have been relatively few recent developments of note. Among these is a comparison of the donor properties of the dibenzophosphole system with those of triphenylphosphine in Ni(II) complexes where it was found[173] that triphenylphosphine is the poorer donor. Much more recently, the Nelson group (which, together with the Mathey group, has dominated the whole field of phosphole and phospholyl anion coordination chemistry) has reported[174] the synthesis and some spectroscopic and X-ray properties of a range of the phenyldibenzophosphole complexes of Cr(0), Mo(0), and W(0) carbonyls and has also published[175] a study of the electrochemistry of these complexes. The same group has also commented on the synthesis, structural characteristics, and spectroscopic properties of phenyldibenzophosphole complexes of Ru(II),[168] Au(I),[171] and Pt(II).[172]

In other studies, phenyldibenzophosphole complexes of Rh(I) have received attention as hydrogenation[176] or hydroformylation[177] catalysts and the interaction of the (phenyldibenzophosphole)$_4$RhH system with carbon monoxide has also been reported[178] as have some related investigations.[179]

Turning now to metal complexes of phospholyl anions, a very detailed review of syntheses, theoretical and physical data, and chemical properties has appeared recently.[166] Five types of complexes, the structural characteristics of which are shown in (53)-(57), are known. The coverage is excellent in this review and, apart from a little background material, only the few studies

published since it appeared will be covered here.

By far the most common type of complex contains the η^5 mode of complexation shown in (56). Thus, both η^5-phospholyl-metal carbonyl complexes (with, W, Mn, Re, and Co), *e.g.* (58), and phosphorus-containing analogues of metallocenes, *e.g.* (59) and (60), now have a well established chemistry.[166]



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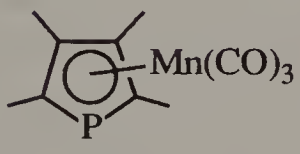

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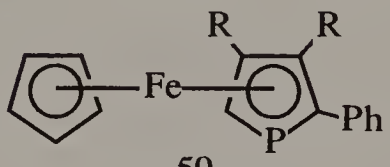

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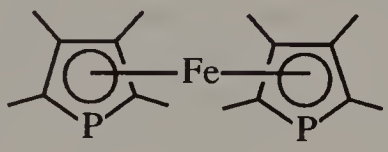


60

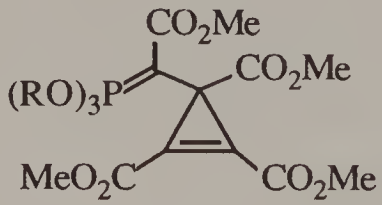
Most recent developments have concerned diphosphametallocenes related to (60). For example, studies of the complexation of diphosphaferrocenes with a variety of Lewis acids and both Cu(I) and Ag(I) salts have been reported.[180] A route to a diphosphazirconocene dichloride has been published together with its crystal structure.[181] Shortly after this, the same group attempted a synthesis,[182] this time from a 1-trimethylstannylphosphole, of a diphosphatitanocene dichloride but obtained only an η^5-phospholyltrichlorotitanium(IV) complex. However, a very recent attempt by a slightly modified route[183] was successful and a crystal structure was obtained for the product.

The field is very active and further development of this area of phospholyl anion chemistry can be expected.

IV. $\sigma^5\lambda^5$-Phosphole Derivatives

This rather brief section deals with phospholes singly-bound to five atoms (a $\sigma^5\lambda^5$-system) rather than three as in the $\sigma^3\lambda^3$-phospholes just discussed.

References to $\sigma^5\lambda^5$-phospholes have been in the literature for about 30 years[13] and, as will be seen in a later section, are almost certainly involved as transient intermediates in many reactions of phosphines and phospholes with acetylenic esters. However, until quite recently no such structure had been reliably characterized and, even now, few examples of the system are known. The first characterization was achieved[16,72] in reactions of trialkyl phosphites with dimethyl acetylenedicarboxylate at -50° which give (quantitatively) initially the unusual ylides (61) (R = Me, Et) which rearrange (also quantitatively) at -10° to give the $\sigma^5\lambda^5$-phospholes (62). Unlike their uncharacterized counterparts derived from triphenylphosphine,[184] these are stable for some hours at -10° but rearrange in a few minutes at 20° to give $\sigma^4\lambda^5$-phospholes in a manner similar to that outlined in Eqn. 21. Other reactions of (62) similar to those outlined in Eqn. 21 have also been studied.[16,73] Isolation of pure (62) (R = Me, Et) was not possible and characterizations were performed by ^{31}P, ^{1}H, and ^{13}C NMR spectroscopy which showed respectively that the P atom is five-coordinate (δ = -37.9 for R = Me), that all three alkoxy groups derived from the phosphite remain attached to P, and that the ring has the required symmetry of substitution (two doublets for ring carbon in the ^{13}C spectrum).



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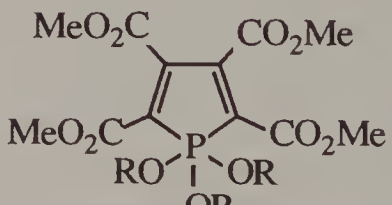


62

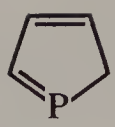
Reactions of the phosphites with the acetylenic ester at -10° lead directly to compounds of type (62)[73,185] and somewhat more stable bicyclic derivatives have been obtained [185] by related reactions at these temperatures.

Similar reactions have been carried out[73,74] using dialkylphosphonites. However, while it was still possible to characterize the $\sigma^5\lambda^5$-phosphole intermediates by ^{31}P NMR prior to rearrangement to the $\sigma^4\lambda^5$- product, these are considerably less stable than those derived from trialkyl phosphites. Thus, rearrangement to the corresponding $\sigma^4\lambda^5$-phosphole (Eqn. 21) is almost complete at -50° after only 45 minutes.

Further mention of transient $\sigma^5\lambda^5$-phospholes, this time with the P atom bonded to five carbon atoms, will be made in section VII.

V. $\sigma^2\lambda^3$-Phosphole Derivatives

Two types of $\sigma^2\lambda^3$-phosphole, the 2*H*- and 3*H*-systems (63) and (64), can be envisaged. They are cyclic analogues of the phosphaalkenes (65) and, like these, would be expected to be highly reactive unless kinetically stabilized by bulky substituents.[186] Since the chemistry of low-coordinate λ^3-phosphorus compounds was not at all well-developed in the early 1980s, it came as something of a surprise when, in 1981, clear evidence was presented[15] for the intermediacy of derivatives of (63) in a variety of reactions. Before commenting on this, however, it should be noted that there are now in the literature three synthetic routes which have proven effective for the generation of species of type (63). It is possible, though not certain, that structures of type (64) may also be derived from these in some reactions. The three routes are thermally-induced [1,5] reversible sigmatropic rearrangements of $\sigma^3\lambda^3$-phospholes (which is by far the most common approach to the system), cycloaddition reactions of acyclic $\sigma^2\lambda^3$- or $\sigma^1\lambda^3$-phosphorus compounds, and a photochemically induced rearrangement. In addition, only three stable $\sigma^2\lambda^3$-phosphole derivatives are known (only one of which is monocyclic) and one stable metal complex of the system has been reported. Since, in most instances, the formation of a $\sigma^2\lambda^3$-phosphole in a reaction is usually inferred from its subsequent reactions, syntheses and reactions will be treated together here.



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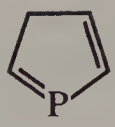
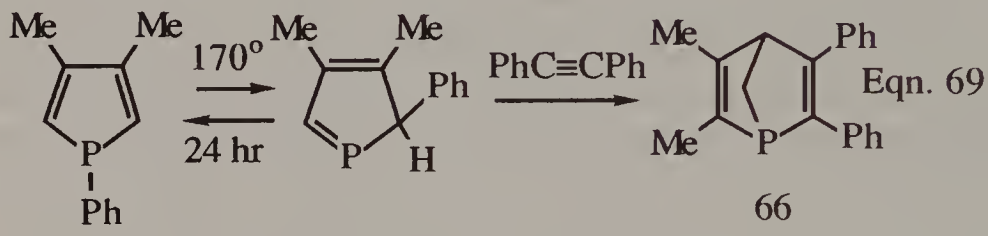


64

$RP{=}CR'_2$

65

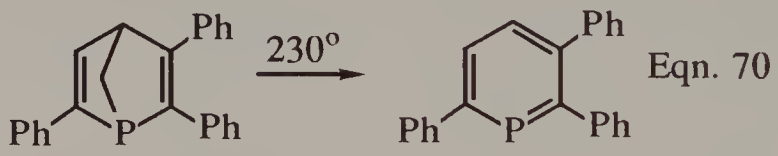
Considering first [1,5] sigmatropic rearrangements, it was observed[15] that both 3,4-dimethylphosphole and 1,2,5-triphenylphosphole enter into reactions of the type shown in Eqn. 69. The intermediate $\sigma^2\lambda^3$-phosphole could also be trapped with methanol (addition across the P=C bond), 2,3-dimethylbutadiene ([4+2] cycloaddition across the P=C bond), and $[CpFe(CO)_2]_2$ (to give a phosphaferrocene).



Eqn. 69

66

The corresponding reaction with 1,2,5-triphenylphosphole takes considerably longer and proceeds in lower yield. It was found also in this initial study[15] that, at still higher temperatures, the carbon bridge is eliminated from the 1-phosphanorbornadiene to give a λ^3-phosphinine as shown in Eqn. 70.



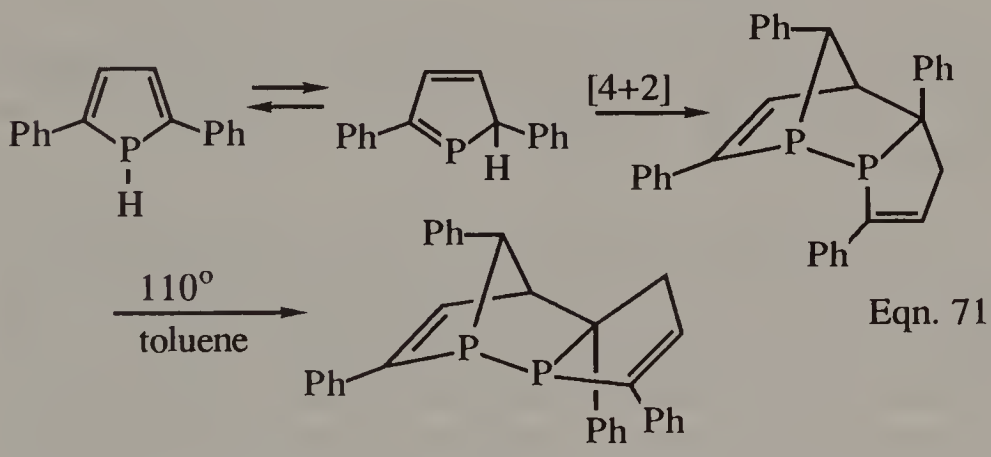
Eqn. 70

These reactions have received considerable further study. Thus, the synthesis of 1-phosphanorbornadienes has been explored further[187] as has an extension of the trapping reaction shown in Eqn. 69, using alkenes, to give phosphanorbornene derivatives.[188] In this last study a wide variety of (*E*)- and (*Z*)-alkenes was used and it was found that the former give predominantly α-*exo*-, β-*endo*- adducts. (*Z*)-Alkenes give the same products *via* an epimerization process. Regioselectivity is controlled by the steric effects in the phosphole moiety.

Other extensions to these studies include: i) the formation[140]

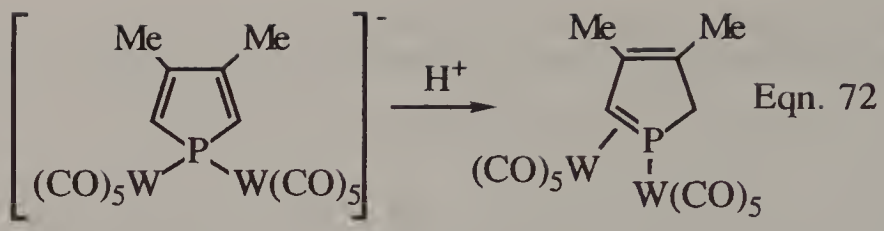
of the phosphine-substituted λ^3-phosphinine (46) by a series of reactions analogous to those outlined in Eqns. 69 and 70 (using the alkyne $Ph_2PC{\equiv}CPPh_2$, and ii) prolonged heating[79] of 1,2,5-triphenylphosphole in the *absence* of a trapping agent to give (Eqn. 25) a 1,1'-biphospholyl probably *via* structures of types (63) and (64) formed by consecutive [1,5] shifts. This is the only reference to structures of type (64) in the literature. The formation of tetrameric systems (Eqn. 26) presumably proceeds by a similar reaction sequence.

The [1,5] shifts noted above become significant only at temperatures around 170°. However, if the phenyl group on the P atom in the $\sigma^3\lambda^3$-phosphole precursor is replaced with a hydrogen atom (by protonation of a phospholyl anion), [1,5] proton shifts occur below room temperature.[64, 189] In certain instances[64] a [4+2] dimerization of the $\sigma^2\lambda^3$-phosphole so formed can occur (Eqn. 71) and the *endo* dimer so formed, a crystal structure of which has been obtained,[190] can rearrange to the more stable *exo* form on heating. An intramolecular [2+2] photocyclization of the *endo* dimer can also be made to occur.[64]



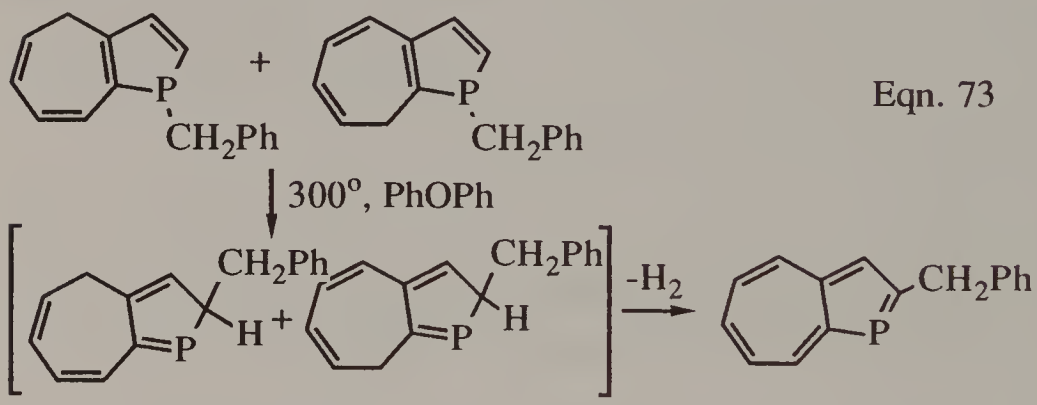
Eqn. 71

It is interesting to note also that if the protonation of the phospholyl grouping is performed[191] within the coordination sphere of a metal ion (Eqn. 72), a complexed $\sigma^2\lambda^3$-phosphole is obtained for which the crystal structure has been determined.[191]



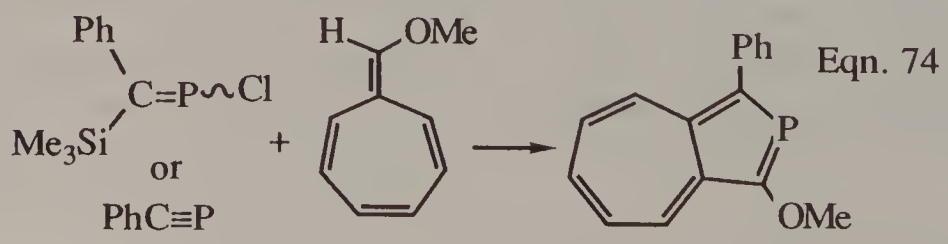
Eqn. 72

Another synthesis which involves a [1,5] sigmatropic shift, this time accompanied by loss of H_2, is one which leads[192] to the formation of a 1-phosphaazulene which may also be regarded as a cycloheptatrieno-$\sigma^2\lambda^3$-phosphole. The process is shown in Eqn. 73 and the starting $\sigma^3\lambda^3$-phosphole mixture is prepared by conventional methods discussed earlier in this survey (McCormack adduct dehydrogenation). The product is a stable blue-green oil which can be chromatographed.



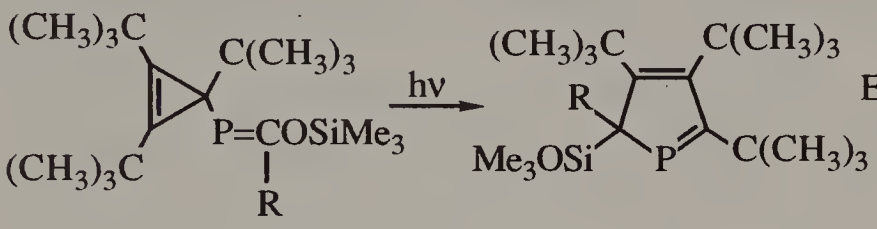
Eqn. 73

The 2-phosphaazulene system has been synthesized[193] using the second of the synthetic approaches mentioned at the beginning of this section. The reaction, of which there are two variants, is a one-step process outlined in Eqn. 74 and the cyclo-addition involving the chlorophosphaalkene is accompanied by the elimination of Me_3SiCl. The product is stable and is a red solid which gives a green solution in chloroform.



Eqn. 74

The remaining synthesis in the literature[194] of a $\sigma^2\lambda^3$-phosphole to be mentioned here, again of a stable species, is a photochemical process (Eqn. 75). The stability of the product arises from the very bulky substituents upon the system, a situation which is very common with the the wide range of similarly stabilized acyclic $\sigma^2\lambda^3$- and $\sigma^1\lambda^3$-phosphorus compounds (such as the starting materials in Eqns. 74 and 75) now known.[186] Some addition reaction chemistry of this phosphole has also been performed.[194]



Eqn. 75

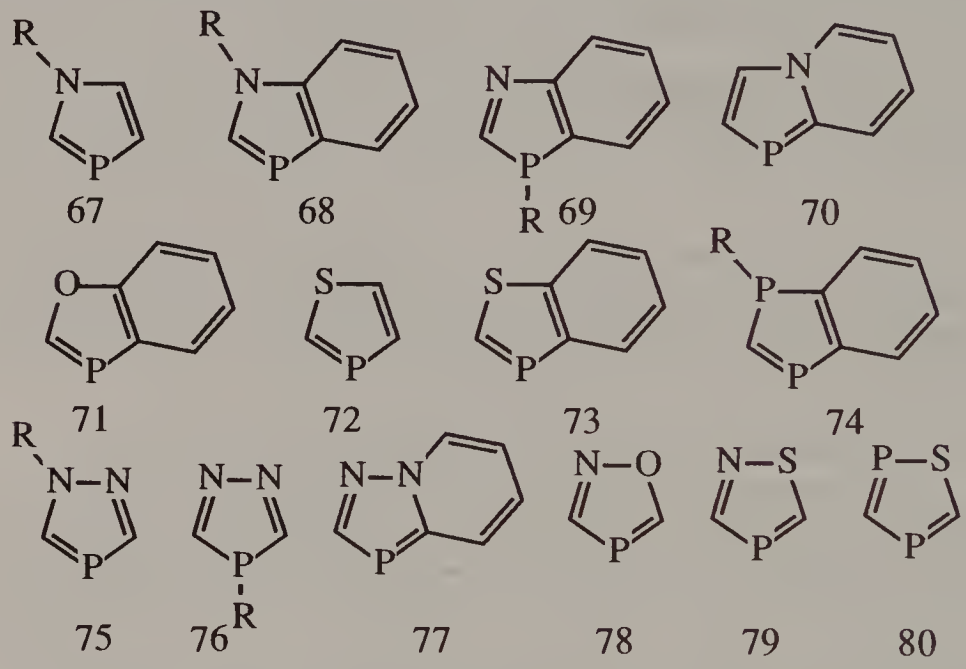
There are many other $\sigma^2\lambda^3$-phosphole derivatives in the literature. However, they all contain additional heteroatoms and. because of their somewhat different characteristics, will be surveyed briefly and separately in the next section.

VI. Phospholes Containing Additional Heteroatoms

As mentioned in the introduction to this Chapter, numerous phosphole derivatives are known[1] in which the P atom is bonded to another heteroatom in a fully unsaturated five-membered ring and it was stated that such systems are considered to be outside the scope of the survey. There are also, however, a great many related systems in which the P atom is bonded only to carbon with one or more heteroatoms in the 3- or 3,4-positions of the phosphole ring. Such systems are very closely related to the $\sigma^3\lambda^3$- and $\sigma^2\lambda^3$-phospholes already reviewed herein and some discussion of these heterophospholes is therefore in order. The topic has been reviewed very recently and very thoroughly[23] and details of the discussion, particularly regarding the synthetic routes employed, will not be presented again here. However, in summary, fourteen ring systems of this nature have been synthesized, mainly within the past ten years, and in some cases, several routes to a particular ring system have been developed.[23]

The vast majority of these heterocycles are analogues of the

$\sigma^2\lambda^3$-phospholes but a few analogues of $\sigma^3\lambda^3$-phospholes have been reported. The ring systems (and substituted derivatives thereof) covered in the aforementioned review[23] are the 1,3-azaphospholes (67), 1,3-benzazaphospholes containing σ^2- and σ^3-phosphorus, *i.e.* (68) and (69), pyridinophospholes (70), 1,3-benzoxaphospholes (71), 1,3-thiaphospholes (72), 1,3-benzthiaphospholes (73), 1,3-benzodiphospholes (74), 1,2,4-diazaphospholes (75) and (76), pyridinoazaphospholes (77), 1,2,4-oxazaphospholes (78), 1,2,4-thiazaphospholes (79), and 1,2,4-thisdiphospholes (80).

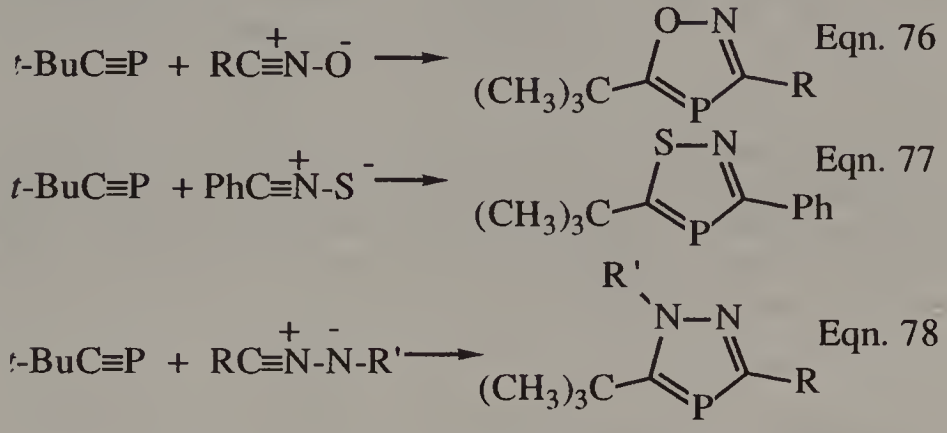


The routes to these systems are several and varied[23] and many of them involve 1,3-dipolar cycloadditions to phosphaalkenes or phosphaalkynes. The majority of the systems isolated are reasonably stable and, because of the low-coordinate nature of the P atom, they would be expected to have a very interesting chemistry which has not yet been explored.

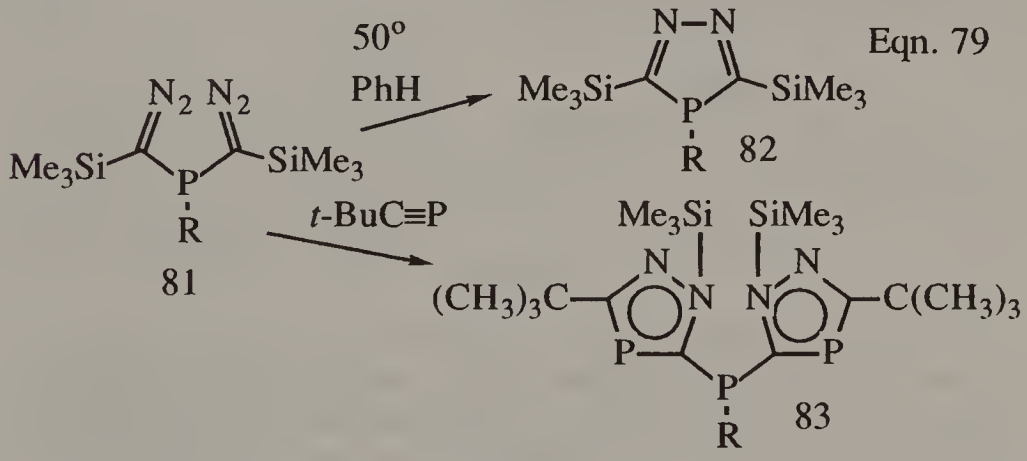
Several developments have taken place since the last review was prepared and these, in chronological order are outlined here.

Regitz, *et al.* have, in two recent papers,[195,196] developed routes to several heterophospholes. In the first of these,[195] which is an extension of some earlier work[197] by the same group, syntheses were reported for 1,2,4-oxazaphospholes (Eqn. 76), 1,2,4-thiazaphospholes (Eqn. 77), and 1*H*-1,2,4-diazaphospholes

(Eqn. 78) *via* cycloaddition reactions of *t*-BuC≡P with nitrile oxides, nitrile sulfides (generated *in situ*), and nitrile imines respectively. A high degree of regiospecificity was observed in many of the reactions.

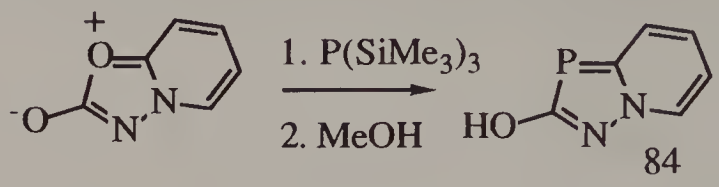


In the second paper,[196] an entirely different approach to ring construction was used. The starting point for heterophosphole formation in this process is the unusual phosphine (81) which can either eliminate nitrogen to give the 4*H*-1,2,4-diazaphosphole (82) (Eqn. 79) or react with *t*-BuC≡P to give a more complex 1,2,4-diazaphosphole(83) (Eqn. 79). Compound (83) can react further *via* the trimethylsilyl groups with a variety of reagents.



The remaining reports[198-200] of syntheses in this area come from Markl, *et al.* In the first of these[198] devoted mainly to arsenic heterocycles, the synthesis (Eqn. 80) of the unusual hydroxy-substituted 1,2,4-diazaphosphole derivative (84) is recorded. Spectroscopic examination of this product showed no sign of the presence

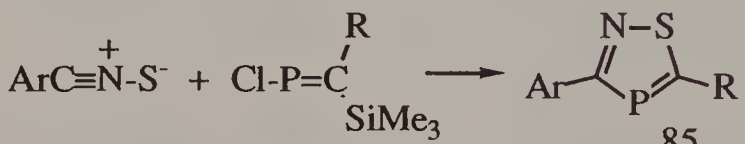
of the keto tautomer and this indicates a highly delocalized system.



Eqn. 80

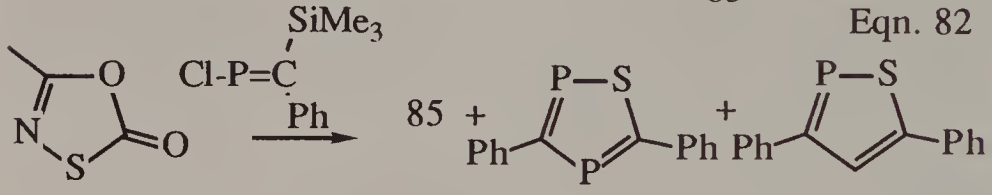
84

In the second of Markl's reports[199] routes to 1,2,4-thiazaphospholes of type (85) (Eqn. 81), and mixtures of 1,2,4-thiazaphospholes and 1,2-thiaphospholes were described. These reactions are quite similar to others reported by the same group and discussed in detail elsewhere.[23]



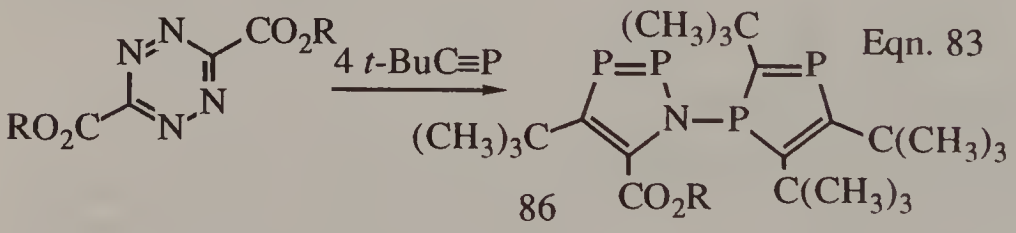
Eqn. 81

85



Eqn. 82

The third report from the Markl group records the synthesis (Eqn. 83) of the novel system (86).



Eqn. 83

86

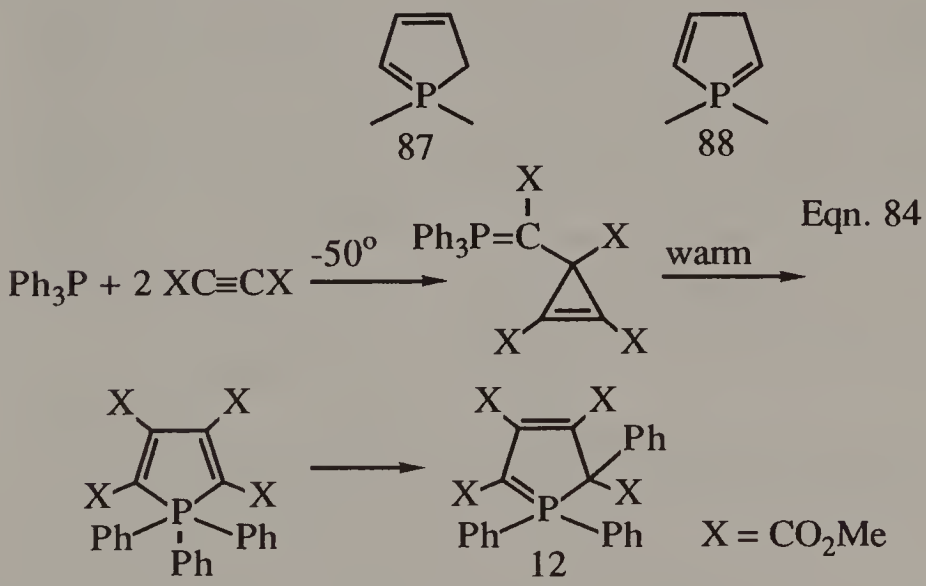
In concluding this section it should be mentioned that most of the work concerning heterophospholes containing two-coordinate phosphorus bonded only to carbon has been performed during the past five years and, clearly, significant further developments are expected.

VII. $\sigma^4\lambda^5$-Phosphole Derivatives

This aspect of phosphole chemistry has been fairly dormant for some years. However, for completeness in this survey a brief

review is in order. As with the $\sigma^2\lambda^3$-systems discussed earlier, two basic structures, (87) and (88), can be envisaged for the $\sigma^4\lambda^5$-systems. Also, as with the $\sigma^2\lambda^3$-phospholes, the 2*H*-structure (87) is more common than the 3*H*-structure (88).

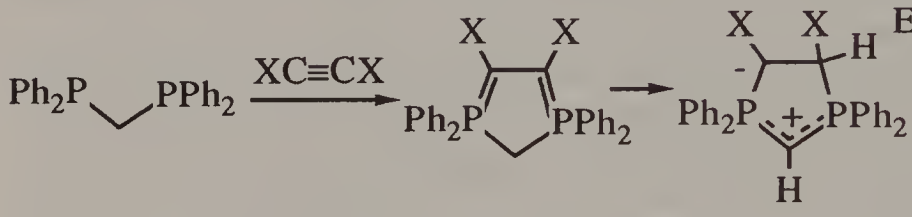
Considering first structures of type (87), these are prepared by variations on one basic synthetic route which is the reaction of a phosphine, a phosphite, a phosphonite, or a phosphole with an electrophilic alkyne. The alkyne most commonly used is dimethyl acetylenedicarboxylate and reactions between this electrophile and a variety of phosphines have been reviewed.[26] A condensed version of the reaction for triphenylphosphine[14,184] is shown in Eqn. 84 and it should be noted that the $\sigma^5\lambda^5$-phosphole intermediate is very short-lived even at quite low temperatures. Similar reactions occur for cyclopropyldiphenylphosphine[26] and certain phosphetanes.[201] That the phenyl-group migration illustrated in the last step of Eqn. 84 is intramolecular was shown[202] by experiments in which a mixture of triphenylphosphine and tri-*p*-tolylphosphine was treated with the ester. Only (12) (X = CO_2Me) or the tri-*p*-tolyl- equivalent was obtained and no scrambling of phenyl and *p*-tolyl groups was observed.



As mentioned earlier, this kind of reaction occurs also for trialkyl phosphites and dialkyl phosphonites (Eqn. 21, and Section IV) and the process therefore appears to be quite general. Indeed,

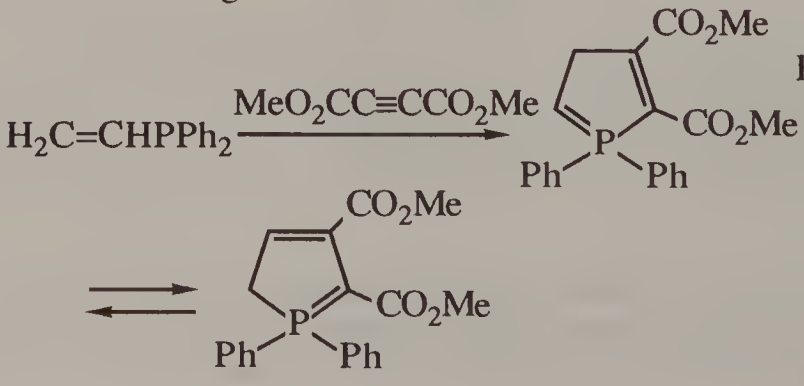
reactions of this type have been shown to occur within the coordination sphere of a metal. Thus, Ph_3PAuMe reacts[203] with $F_3CC{\equiv}CCF_3$ to give (12) (X = CF_3) while $CyRuH(PPh_3)_2$ reacts[204] with dimethyl acetylenedicarboxylate in benzene under reflux to give (12) (X = CO_2Me) in low yield.

In a related reaction, bis(diphenylphosphino)methane reacts[205] with dimethyl acetylenedicarboxylate (Eqn. 85) to give a $\sigma^4\lambda^5$-diphosphole derivative in which a tautomeric proton shift occurs.



Eqn. 85

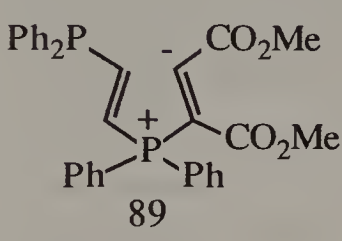
Several reactions of unsaturated phosphines, and of $\sigma^3\lambda^3$-phospholes, with alkynes leading to $\sigma^4\lambda^5$-phospholes have been performed. The reactions are frequently quite complex, the products are sometimes water-sensitive, and, in some instances, they have had to be characterized by trapping reactions. Mechanisms for the various reactions have been discussed thoroughly elsewhere[26] and only the broad conclusions will be summarized here. As will be seen shortly, the outcome of reactions in this general category are not easily predicted. In the first example, diphenylvinylphosphine reacts[206,207] with dimethyl acetylenedicarboxylate (Eqn. 86) to give initially a 3*H*- $\sigma^4\lambda^5$-system which rearranges to the 2*H*- isomer.



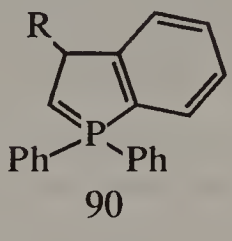
Eqn. 86

One might expect a similar reaction to occur between the vinylphosphine and benzyne, but a most unusual reaction occurs[207] in which the only identifiable product is 1,2-bis(diphenylphosphino)ethane. This result has not yet been explained.

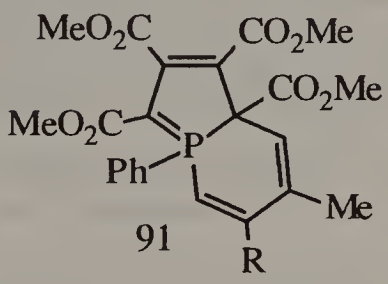
This type of investigation has been extended to reactions of *trans* $Ph_2PCH{=}CHPPh_2$ with alkynes and benzyne and it has been found[207] that while full cyclization to the $\sigma^4\lambda^5$-phosphole apparently does not occur with dimethyl acetylenedicarboxylate, the zwitterion (89) appears to be formed, a normal reaction occurs with benzyne to give the highly reactive 3*H*-system (90) (R = Ph_2P).



89



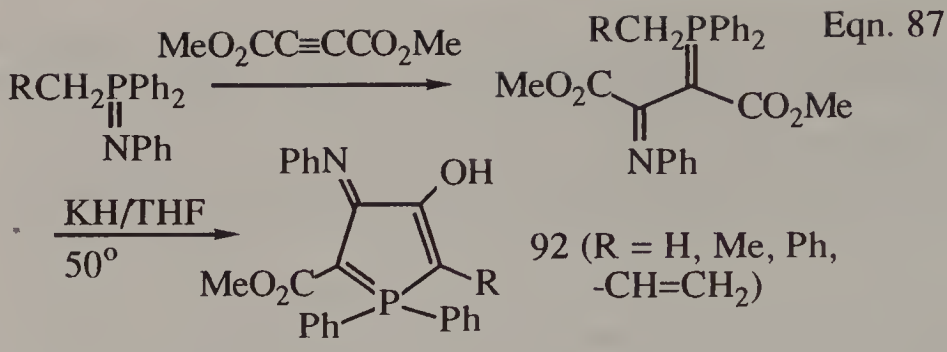
90



91

$\sigma^3\lambda^3$-Phospholes and phosphindoles also react with acetylenic esters to give a wide variety of very interesting products.[26] While for the most part these products are not $\sigma^4\lambda^5$-phospholes, such systems are formed in some instances. For example, 3-methyl- and 3,4-dimethyl-1-phenylphosphole react[208] with dimethyl acetylenedicarboxylate to give the bicyclic system (91) (R = H or Me) and it is probable[26] that in several other reactions of $\sigma^3\lambda^3$-phospholes and phosphindoles with the acetylenic ester, $\sigma^4\lambda^5$-phospholes are formed as transient intermediates.

Two other syntheses, both of 3*H*-systems, should be briefly mentioned. In the first of these Markl some time ago prepared[209] and characterized the first $\sigma^4\lambda^5$-phosphindole (90) (R = H) by a simple α-proton abstraction from the corresponding phosphindolinium salt. Much more recently Barluenga, *et al.*[210] have reported the synthesis in very high yield (90-95%) of the stable 3*H*- $\sigma^4\lambda^5$-phospholes (92) by the reaction of alkyldiphenyliminophosphoranes with dimethyl acetylenedicarboxylate as outlined in Eqn. 87.



VIII. Conclusion

As can be seen from the foregoing survey, phosphole chemistry has developed extremely rapidly over the past 30 years with most of the truly significant developments occurring during the past two decades. The three areas which show promise for continued rapid development are synthetic and reactivity studies regarding $\sigma^2\lambda^3$-phospholes, phospholes containing additional heteroatoms, and the chemistry and catalytic activity of metal complexes of both $\sigma^3\lambda^3$- and $\sigma^2\lambda^3$-phospholes and of phospholyl anions. However, phosphole chemistry has been rich in the unexpected and, no doubt, further surprises await us.

IX. Bibliography

1a. Schmidpeter, A. (1986). Synthetic routes to five-membered aromatic phosphorus heterocycles, *Phosphorus Sulfur*, *28*: 71.

1b. Arbuzov, B.A., and Dianova, E.N. (1986). Cycloaddition an Verbindungen mit $\lambda^3\sigma^2$-Phosphor- und $\lambda^3\sigma^2$-Arsen-Mehrfachbindungen, *Phosporus Sulfur*, *26*: 203.

2. Wittig, G., and Geissler, G. (1953). Course of reactions of pentaphenylphosphorus and certain derivatives, *Ann.*, *580*: 44.

3a. Leavitt, F.C., Manuel, T.A., and Johnson, F. (1959). Novel hetero cyclopentadienes, *J. Am. Chem. Soc.*, *81*: 3163.

3b. Leavitt, F.C., Manuel, T.A., Johnson, F., Matternas, L.U., and Lehman, D.S. (1960). Novel heterocyclopentadienes, *J. Am. Chem. Soc.*, *82*: 5099.

4a. Braye, E.H., and Hubel, W. (1959). Heterocyclic compounds from iron carbonyl complexes: Pentaphenylphosphole, *Chem. Ind. (London)*: 1250.

4b. Braye, E.H., Hubel, W., and Caplier, I. (1961). New unsat-

urated heterocyclic systems. I. *J. Am. Chem. Soc.*, *83*: 4406.

5. Quin, L.D., and Bryson, J.G. (1967). 1-Methylphosphole, *J. Am. Chem. Soc.*, *89*: 5984.
6. Mathey, F. (1969). New synthesis of phospholenes and phospholes, *C.R. Acad. Sci., Ser. C*, *269*: 1066.
7. Mathey, F., Mankowski-Favelier, R., and Maillet, R. (1970). Nouvelle preparation des phospholes. Complements experimentaux, donnees spectrales, *Bull. Soc. Chim. Fr.*: 4433.
8. Breque, A., Mathey, F., and Savignac, P. (1981). An improved one-pot synthesis of phospholes, *Synthesis*: 983.
9. Quin, L.D., Borleske, S.G., and Engel, J.F. (1973). Synthesis and spectral characterization of some C-alkylphospholes and phospholecarboxylates, *J. Org. Chem.*, *38*: 1858.

10a. Mathey, F. (1973). Metallation du sulfure de phenyl-1 dimethyl-3,4 phosphole. Application a la synthese de phospholes fonctionnels, *Tetrahedron Lett.*: 3255.

10b. Mathey, F. (1974). Preparation et proprietes de quelques sulfures de phospholes fonctionnels, *Tetrahedron*, *30*: 3127.

11. Braye, E.H., Caplier, I., and Saussez, R. (1971). Alkali aza-, phospha-, and arsacyclopentadienides and their chemical properties, *Tetrahedron*, *27*: 5523.
12. Charrier, C., and Mathey, F. (1987). Characterisation of the parent phosphole and phospholyl anion and some of their C-substituted derivatives by ^{1}H and ^{13}C NMR spectroscopy, *Tetrahedron Lett.*, *28*: 5025.
13. Johnson, A.W., and Tebby, J.C. (1961). The adducts from triphenylphosphine and dimethyl acetylenedicarboxylate, *J. Chem. Soc.*: 2126.
14. Waite, N.E., Tebby, J.C., Ward, R.S., and Williams, D.H. (1969). Reactions of phosphines with acetylenes. Part VII. Structure revision of a rearranged 1:2 adduct of triphenylphosphine and dimethyl acetylenedicarboxylate. A stable 2*H*-phosph(V)ole, *J. Chem. Soc.-C*: 1100.
15. Mathey, F., Mercier, F., Charrier, C., Fischer, J., and Mitschler, A. (1981). Dicoordinated 2*H*-phospholes as transient intermediates in the reactions of tervalent phospholes at high temperature. One-step synthesis of 1-phosphanorbornadienes and phosphorins from phospholes, *J. Am. Chem. Soc.*, *103*: 4595.

16. Tebby, J.C., Willetts, S.E., and Griffiths, D.V. (1981). Trapping of reactive intermediates from phosphites and dimethyl acetylenedicarboxylate. Diversion of reaction pathway towards stable phosphole derivatives, *J. Chem. Soc., Chem. Commun.*: 420.
17. Hughes, A.N., and Srivanavit, C. (1970). The chemistry of phosphole derivatives, *J. Heterocycl. Chem., 7*: 1.
18. Hughes, A.N., and Kleemola, D. (1976). Phospholes. The aromaticity problem, *J. Heterocycl. Chem., 13*: 1.
19. Hughes, A.N. (1979). Recent developments in phosphole and phosphindole chemistry, in *New Trends in Heterocyclic Chemistry*, (Mitra, R.B., Ayyangar, N.R., Gogte, V.N., Acheson, R.M., and Cromwell, N., eds.), Elsevier, Amsterdam, p. 216.
20. Mathey, F. (1980). Phosphole chemistry, *Top. Phosphorus Chem., 10*: 1.
21. Quin, L.D. (1981). *The Heterocyclic Chemistry of Phosphorus*, Wiley-Interscience, New York, Chapters 2,5,6,8.
22. Mathey, F. (1988). The organic chemistry of phospholes, *Chem. Rev., 88*: 429.
23. Quin, L.D., and Hughes, A.N. (1990). Cyclic phosphines, in *The Chemistry of Organophosphorus Compounds, Vol. 1*, (Hartley, F.R., ed.) Wiley, Chichester, p. 295.
24. Davies, M., and Hughes, A.N. (1972). Cyclic phosphonium ylides, *J. Heterocycl. Chem., 9*: 1.
25. Holah, D.G., Hughes, A.N., and Wright, K. (1975). Transition metal complexes of cyclic phosphines and their derivatives, *Coord. Chem. Rev., 15*: 239.
26. Hughes, A.N. (1981). Synthetic applications of dimethyl acetylenedicarboxylate in phosphorus heterocyclic chemistry, *Heterocycles, 15*: 637.
27. Mathey, F., Fischer, J., and Nelson, J.H. (1983). Complexing modes of the phosphole moiety, *Struct. Bonding, 55*: 153.
28a. McCormack, W.B. (1953). Substituted phosphacyclopentene *P,P*-dihalides, *U.S. Patent 2,663,736.*
28b. McCormack, W.B. (1953). Substituted phosphacyclopentene *P*-oxides, *U.S. Patent 2,663,737.*
29a. Campbell, I.G.M., Cookson, R.C., and Hocking, M.B. (1962). Synthesis of phospholes, *Chem. Ind. (London)*: 359.
29b. Campbell, I.G.M., Cookson, R.C., Hocking, M.B., and

Hughes, A.N. (1965). Synthesis and chemistry of phospholes, *J. Chem. Soc.*: 2184.

30. Lukas, B., Roberts, R.M.G., and Silver, J. (1983). Mossbauer studies on ferrocene complexes. IX. Phosphaferrocenes and their protonated derivatives, *J. Organomet. Chem.*, *256*: 103.
31. Freedman, L.D., Ezzell, B.R., Jenkins, R.N., and Harris, R.M. (1974). Some observations on the cleavage of *P*-substituted phospholes, *Phosphorus*, *4*: 199.
32. Cadogan, J.I.G., Scott, R.J., Gee, R.D., and Gosney, I. (1974). The reactivity of organophosphorus compounds. Part XXX. Iminophospholes and a new synthesis of benzofurans *via* intramolecular rearrangement of 1-*o*-nitroarylimino-1,2,5-triphenylphospholes, *J. Chem. Soc., Perkin Trans. I*: 1964.
33. Breque, A., Muller, G., Bonnard, H., Mathey, F., and Savignac, P. (1981). Phospholes and phospholes with functional substituents on the phosphorus, *Eur. Pat. 41,447.*
34. Isaacs, N.S., and El-Din, G.N. (1989). An improved synthesis of phospholes, *Synthesis*: 967.
35. Isaacs, N.S., and El-Din, G.N. (1989). Cycloadditions and other reactions of phospholes under high pressures, *Tetrahedron*, *45*: 7083.
36. Mathey, F., Lampin, J-P., and Thavard, D. (1976). Synthese de nouveaux phospholenes et phospholes avec substituants fonctionnels sur le phosphore, *Can. J. Chem.*, *54*: 2402.
37. Quin, L.D., Mesch, K.A., and Orton, W.L. (1982). Demonstration of C-protonation on phospholes and of δ-deshielding of ^{31}P using multicyclic phosphorus compounds, *Phosphorus Sulfur, 12*: 161.
38. Quin, L.D., Bryson, J.G., and Moreland, C.G. (1969). A study of 1-methylphosphole as a heteroaromatic substance, *J. Am. Chem. Soc.*, *91*: 3308.
39. Markl, G., and Potthast, R. (1968). 1-Phenylphosphol, *Tetrahedron Lett.*: 1755.

40a. Usher, D.A., and Westheimer, F.H. (1964). 1-Ethoxyphosphole 1-oxide, *J. Am. Chem. Soc.*, *86*: 4732.

40b. Chiu, Y.H., and Lipscomb, W.M. (1969). The molecular and crystal structure of $P_2O_4C_{12}H_{18}$, 1,8-diethoxy-3a,4,7,7a-tetrahydro-4,7-phosphinidinephosphindiole

1,8-dioxide, *J. Am. Chem. Soc.*, *91*: 4150.

41. Ashe, A.J., Mahmoud, S., Eisenbroich, C., and Wunsch, M. (1987). 1,1'-Diarsaferrocene, *Angew. Chem., Int. Ed. Eng.*, *26*: 229.

42. Markl, G., and Potthast, R. (1967). A simple synthesis of phospholes, *Angew. Chem., Int. Ed. Eng.*, *6*: 86.

43a. Egan, W., Tang, R., Zon, G., and Mislow, K. (1970). The low barrier to inversion in phospholes. A measure of aromaticity, *J. Am. Chem. Soc.*, *92*: 1442.

43b. Egan, W., Tang, R., Zon, G., and Mislow, K. (1971). Barriers to pyramidal inversion at phosphorus in phospholes, phosphindoles, and dibenzophospholes, *J. Am. Chem. Soc.*, *93*: 6205.

44. Marinetti, A., and Mathey, F. (1987). Insertion of terminal alkynes into the phosphirene ring, *Tetrahedron*, *28*: 5021.

45. Marinetti, A., Mathey, F., Fischer, J., and Mitschler, A. (1984). Synthesis and X-ray crystal structure of 1,2,3-triphenylphosphirene, *J. Chem. Soc., Chem. Commun.*: 45.

46. Braga, D., Caffyn, A.J.M., Jennings, M.C., Mays, M.J., Manojlovic-Muir, L., Raithby, P.R., Sabatino, P., and Woulfe, K.W. (1989). Co-ordinated phospholes from the coupling of alkynes with bridging phosphido ligands, *J. Chem. Soc., Chem. Commun.*: 1401.

47. Fongers, K.S., Hogeveen, H., and Kingma, R.F. (1983). Reaction of aluminum halide σ-complexes of cyclobutadienes with phosphonous dichlorides. Preparation of phospholium salts and phosphole oxides, *Tetrahedron Lett.*, *24*: 1423.

48a. Naumann, K., Zon, G., and Mislow, K. (1969). Perchloropolysilanes: Novel reducing agents for phosphine oxides and other organic oxides, *J. Am. Chem. Soc.*, *91*: 2788.

48b. Naumann, K., Zon, G., and Mislow, K. (1969). The use of hexachlorodisilane as a reducing agent. Stereospecific deoxygenation of acyclic phosphine oxides, *J. Am. Chem. Soc.*, *91*: 7012.

49a. Barrow, M.J., Davidson, J.L., Harrison, W., Sharp, D.W.A., Sim, G.A., and Wilson, F.B. (1973). Metal complexes of novel sulphur- and phosphorus-containing heterocycles. Preparation and structure of tricarbonyl-η^4-(1-pentafluorophenyl-2,3,4,5-tetrakistrifluoromethylthiophen)-manganese and π-cyclopentadienyl(1-hydroxy-2,3,4,5-tetra-

kistrifluoromethylphosphole 1-oxide)cobalt, *J. Chem. Soc., Chem. Commun.*: 583.

49b. Barrow, M.J., Freer, A.A., Harrison, W., Sim, G.A., Taylor, D.W., and Wilson, F.B. (1975). X-Ray crystallographic determination of the molecular structure of π-cyclopentadienyl-[1-hydroxy-2,3,4,5-tetrakis(trifluoromethyl)-phosphole 1-oxide]cobalt and tricarbonyl-η^4-[1-pentafluorophenyl-2,3,4,5-tetrakis(trifluoromethyl)thiophen]manganese, *J. Chem. Soc., Dalton Trans.*: 197.

50. Yasufuku, K., Hamada, A., Aoki, K., and Yamazaki, H. (1980). Cobalt metallacycles. 8. Preparative and kinetic studies on the reactivity of cobaltacyclopentadienes with phosphites, *J. Am. Chem. Soc., 102*: 4363.

51a. Lindner, E., Rau, A., and Hoehne, S. (1981). Preparation and properties of and reactions with metal-containing heterocycles. XX. Preparation, properties and crystal structure of λ^4-thia-λ^5-phospha-η^2-metallabicyclo[2.2.1]-heptadienes and their application to the synthesis of organometallic and organic compounds, *J. Organomet. Chem., 218*: 41.

51b. Lindner, E., Rau, A., and Hoehne, S. (1981). Syntheses with λ^4-thia-λ^5-phospha-η^2-manganabicyclo[2.2.1]heptadiene, *Angew. Chem., Int. Ed. Eng., 20*: 788.

52. Mathey, F., and Mankowski-Favelier, R. (1972). Resonance of phospholes. Reaction with *n*-butyllithium, *Org. Magn. Reson., 4*: 171.

53. Mathey, F. (1972). Reactions des phospholes avec le tertiobutyl lithium, l'acids trifluoroacetique et le chlorure de benzoyle, *Tetrahedron, 28*: 4171.

54a. Guimon, C., Pfister-Guillouzo, G., and Mathey, F. (1979). Electronic structure of phosphacymantrene by photoelectron spectroscopy (He I, He II) and E.H.T. calculations, *Nouv. J. Chim., 3*: 725.

54b. Kostic, N.M., and Fenske, R.F. (1983). Bonding in phosphaferrocenes and reactivity of the phospholyl ligand studied by molecular orbital calculations, *Organometallics, 2*: 1008.

55. Muller, G., Bonnard, H., and Mathey, F. (1981). Derives magnesiens et cadmiens du dimethyl-3,4-phospholyle: Synthese et utilisation pour la preparation de nouveaux phospholes avec substituants fonctionnels sur le phosphore,

Phosphorus Sulfur, 10: 175.
56. Alcaraz, J.-M., Deschamps, B., and Mathey, F. (1984). Donnees complementaires sur la conversion des phospholes en phosphorines, *Phosphorus Sulfur, 19*: 45.
57. Roberts, R.M.G., Silver, J., and Wells, A.S. (1986). Mossbauer and NMR spectroscopic syudies of diphosphaferrocene in trifluoromethanesulfonic (triflic) acid, *Inorg. Chim. Acta, 119*: 1.
58. Deschamps, B., and Mathey, F. (1985). Rearrangement of chloromethylphosphinidene into methylenechlorophosphine in the coordination sphere of tungsten. Stabilization of an unhindered P=C double bond without deactivation by π-complexation, *J. Chem. Soc., Chem. Commun.*: 1010.
59. Holand, S., and Mathey, F. (1981). New method for building carbon-phosphorus heterocycles, *J. Org. Chem., 46*: 4386.
60. Deschamps, B., and Mathey, F. (1985). Conversion directe des phospholes en dihydro-6,7 phosphepines dans la sphere de coordination de tungsten, *Tetrahedron Lett., 25*: 3461.
61. Charrier, C., Maigrot, N., and Mathey, F., (1987). Generation and chemical trapping of (1,2-ethanediphosphinidene)-tetracarbonyltungsten, *Organometallics, 6*: 586.
62. Holand, S., Mathey, F., Fischer, J., and Mitschler, A. (1983). Preparation of 3,3',4,4'-tetramethyl-1,1'-biphospholyl and its reactions with iron and cobalt carbonyls. Synthesis and X-ray crystal structure of a phospholyl complex with a chain of four cobalt atoms, *Organometallics, 2*: 1234.
63. Charrier, C., Bonnard, H., Mathey, F., and Neibecker, D. (1982). Synthese et proprietes d'un η^5-phospholyl-cobalt-dicarbonyle, *J. Organomet. Chem., 231*: 361.
64. Charrier, C. Bonnard, H., de Lauzon, G., and Mathey, F. (1983). Proton [1,5] shifts in *P*-unsubstituted 1*H*-phospholes. Synthesis and chemistry of 2*H*-phosphole dimers, *J. Am. Chem. Soc., 105*: 6871.
65. Santini, C.C., and Mathey, F. (1985). Direct Friedel-Crafts acylation of phosphole P-$M(CO)_5$ complexes. A simple access to functional phospholes, *J. Org. Chem., 50*: 467.
66. Deschamps, E., and Mathey, F. (1987). A la recherche des ferrocenylphospholes, *J. Organomet. Chem., 332*: 141.
67. Deschamps, E., and Mathey, F. (1990). Arylation and

heteroarylation of the phosphole ring, *J. Org. Chem.*, *55*: 2494.

68. Mathey, F. (1976). Derives α-carbonyles et "aromaticite" des phospholes trivalents, *Tetrahedron*, *32*: 2395.
69. Holah, D.G., Hughes, A.N., and Kleemola, D. (1977). A new route to the phosphindole system, *J. Heterocycl. Chem.*, *14*: 705, and references therein.
70. Knott, R.B., Honneger, H., Rae, A.D., Mathey, F., and de Lauzon, G. (1980). Methyl 3,4-dimethyl-1-phenyl-phosphole-2-carboxylate, *Cryst. Struct. Commun.*, *9*: 905.
71. Tan, W.H.-L.W., and Foucaud, A. (1988). 2-Amino-1-phenylphospholes from dichlorophenylphosphine and enamines, *Tetrahedron Lett.*, *29*: 4581.
72. Caesar, J.C., Griffiths, D.V., Tebby, J.C., and Willetts, S.E. (1984). Direct formation of λ^5-phospholes from trialkyl phosphites and dimethyl acetylenedicarboxylate. Alkoxyphosphonium ylides as reactive intermediates and stable products, *J. Chem. Soc., Perkin Trans. I*: 1627.
73. Caesar, J.C., Griffiths, D.V., and Tebby, J.C. (1987). Direct formation of λ^5-phospholes from dialkylphosphonites and dimethyl acetylenedicarboxylate, *Phosphorus Sulfur, 29*: 123.
74. Caesar, J.C., Griffiths, D.V., and Tebby, J.C. (1988). Oxophospholes from the alkoxyphosphonium ylides formed in the reaction of trialkyl phosphites or dialkyl phosphonites with dimethyl acetylenedicarboxylate, *J. Chem. Soc., Perkin Trans. I*: 175.
75. Charrier, C., Guilhem, J., and Mathey, F. (1981). Synthetic, structural, and chemical study of the 1,2-diphosphetene ring, *J. Org. Chem.*, *46*: 3.
76. Quin, L.D., Lloyd, J.R., and Caster, K.C. (1983). A new synthesis of *P*-methylphospholes by flash vacuum pyrolysis of the diphosphines derived from phosphole oxide dimers, *J. Chem. Soc., Chem. Commun.*: 1302.
77. Quin, L.D., and Caster, K.C. (1985). Thermal degradation of dimers of phospholes, *Phosphorus Sulfur, 25*: 117.
78. Markl, G., Hauptmann, H., and Lieb, F. (1974). Diphospha-dihydro-indazene: Zum 1,4-Diphosphacyclohexanring verbruckte phosphole, *Phosphorus*, *4*: 279.
79. Charrier, C., Bonnard, H., and Mathey, F. (1982). Synthesis of phosphorins by reaction of 1,2,5-triphenyl-

phosphole with alkynes, *J. Org. Chem.*, *47*: 2376.
80. Mathey, F., Mercier, F., Nief, F., Fischer, J., and Mitschler, A. (1982). Thermal tetramerization of 1-phenyl-3,4-dimethylphosphole. An access to 2,2'-biphospholes and to 2,2'-diphosphafulvalene complexes, *J. Am. Chem. Soc.*, *104*: 2077.
81. Fischer, J., Mitschler, A., Mathey, F., and Mercier, F. (1983). Crystal and molecular structure of a new eight-membered tetraphospha-macrocycle, *J. Chem. Soc., Dalton Trans.*: 841.
82. Mercier, F., Mathey, F., Fischer, J., and Nelson, J.H. (1984). Nickel-promoted thermal dimerization of 1-phenyl-3,4-dimethylphosphole: The first synthesis of a diphospholene, *J. Am. Chem. Soc.*, *106*: 425.
83. Mercier, F., Mathey, F., Fischer, J., and Nelson, J.H. (1985). Thermal dimerization of 1-phenyl-3,4-dimethylphosphole. An access to 2,2'-biphospholenes and complexes thereof, *Inorg. Chem.*, *24*: 4141.
84. Mercier, F., Holand, S., and Mathey, F. (1986). Synthesis and some reactions of a 2,2'-biphospholyl, *J. Organomet. Chem.*, *316*: 271.
85. Chan, T.H., and Wong, L.T.L. (1971). Benzo[*b*]phosphole and derivatives, *Can. J. Chem.*, *49*: 530.
86. Collins, D.J., Rowley, L.E., and Swan, J.M. (1974). Organophosphorus compounds. XII. A new synthesis of phosphindolines and phosphindoles, *Aust. J. Chem.*, *27*: 831.
87. Nief, F., Charrier, C., Mathey, F., and Simalty, M. (1982). On some chemical properties of 1-phenylphosphindole, *Phosphorus Sulfur*, *13*: 259.
88. Nief, F., Charrier, C., Mathey, F., and Simalty, M. (1981). New application of the phosphole-phosphorin ring expansion. Synthesis and complexing properties of 1-phenylisophosphinoline, *Nouv. J. Chim.*, *5*: 187.
89. Balthazor, T.M. (1980). Phosphindoline-3-one. A useful intermediate for phosphindole synthesis, *J. Org. Chem.*, *45*: 2519.
90. Rausch, M.D., and Klemann, L.P. (1967). Heterocyclic metalloindene systems, *J. Am. Chem. Soc.*, *89*: 5732.
91. Hughes, A.N., Amornraksa, K., Phisithkul, S., and Reutrakul, V. (1976). The reactions of 3-butyl-1,2-diphenylphosphindole with dimethyl acetylenedicarboxylate, *J. Heterocycl. Chem.*, *13*: 65.

92. Butters, T., and Winter, W. (1984). Synthese von Triphenylphosphan-en-inen und Phosphindolen sowie Rontgenstrukturanalyse von zwei Phosphindolen, *Ber.*, *117*: 990.
93. Winter, W. (1975). Photochemische Cyclisierung von *o,o'*-Bis(phenylathinyl)-triphenylphosphin zum Phosphindol-System, *Tetrahedron Lett.*: 3913.
94. Santini, C. Fischer, J., Mathey, F., and Mitschler, A. (1980). Phosphole [2+2] and [4+2] dimerizations around metal carbonyl moieties. Structure and chemistry of a new type of *exo* [4+2] dimers, *J. Am. Chem. Soc.*, *102*: 5809.
95. Baudler, M., and Simon, J. (1988). Existenz und Eigenschaften eines Phosphindendiphosphirans $(R^1P)_2C{=}PR^2$, *Ber.*, *121*: 281.
96. Chan, T.H., and Nwe, K.T. (1975). Isophosphindoline *P*-oxide. A reactive intermediate and its reaction as a Diels-Alder diene, *Tetrahedron*, *31*: 2537.
97. Quin, L.D., and Bernhardt, F.C. (1986). Carbon-carbon bond cleavage during silane reductions of the dimer of 2-phenylphosphindoline oxide, *J. Org. Chem.*, *51*: 3235.
98. Cornforth, J., Cornforth, R.H., and Gray, R.T. (1982). Synthesis of substituted dibenzophospholes. Part 1, *J. Chem. Soc., Perkin Trans. I*: 2289.
99. Affandi, S., Green, R.L., Hsieh, B.T., Holt, M.S., Nelson, J.H., and Alyea, E.C. (1987). Improved syntheses of tetraphenylphosphonium bromide and 1-phenyldibenzophosphole, *Synth. React. Inorg. Met.-Org. Chem.*, *17*: 307.
100. Allen, D.W., and Hutley, B.G. (1979). The chemistry of heteroarylphosphorus compounds. Part XIII. Some reactions of 5-(2-thienyl)dibenzophosphole and its quaternary salts, *Z. Naturforsch.*, *34b*: 1116.
101. Wittig, G., and Benz, E. (1959). The behavior of dehydrobenzene towards nucleophilic and electrophilic reagents, *Ber.*, *92*: 1999.
102. Zbiral, E. (1964). Arine als Electrophile Reagentien. II. (Umsetzung mit Phosphinen). Eine Verbesserte Darstellungweise von 9-Phospha-9-phenylfluorenen mit Arinen, *Tetrahedron Lett.*: 1649.
103. Campbell, I.G.M., and Way, J.K. (1961). Synthesis and stereochemistry of heterocyclic phosphorus compounds. Part II. Loss of optical activity in the reduction of (+)-2-carboxy-9-phenyl-9-phosphafluorene 9-oxide, *J. Chem. Soc.*: 2133.
104a. Freedman, L.D., and Doak, G.O. (1956). Phosphafluorinic

acid, *J. Org. Chem.*, *21*: 238.
104b. Freedman, L.D., and Doak, G.O. (1959). Preparation and ultraviolet absorption spectra of some derivatives of phosphafluorinic acid, *J. Org. Chem.*, *24*: 638.
105. Doak, G.O., Freedman, L.D., and Levy, J.B. (1964). The preparation of heterocyclic organophosphorus compounds by cyclodehydrohalogenation, *J. Org. Chem.*, *29*: 2382.
106. Allen, D.W., Millar, I.T., and Mann, F.G. (1967). Synthesis and reactions of 2,2'-biphenylylenebisdiethylphosphine. Formation of cyclic diquaternary dibromides with alkylene dibromides, and the nature and probable mechanism of their thermal decomposition, *J. Chem. Soc.-C*: 1869.
107. Cornforth, J., Ridley, D.D., Sierakowski, A.F., Uguen, D., and Wallace, T.W. (1982). Synthesis of substituted dibenzophospholes. Part 3. Synthesis of 4,6-diaryldibenzophospholes from *m*-quaterphenyls, *J. Chem. Soc., Perkin Trans. I*: 2317.
108. Bedford, A.F., Heineky, D.M., Millar, I.T., and Mortimer, C.T. (1962). Heats of formation and bond energies. Part VII. Pentaphenylphosphole, 9-phenyl-9-phosphafluorene, and their oxides, *J. Chem. Soc.*: 2932.
109a. Chuchman, R., Holah, D.G., Hughes, A.N., and Hui, B.C. (1971). The site of protonation in phosphole derivatives. 1*H*-Phospholium salts stabilized by complex transition metal ions, *J. Heterocycl. Chem.*, *8*: 877.
109b. Budd, D., Chuchman, R., Holah, D.G., Hughes, A.N., and Hui, B.C. (1972). Reactions of 1,2,5-triphenylphos- phole and its oxide, sulfide, and selenide with some trans- ition metal halides, *Can. J. Chem.*, *50*: 1008.
110. Quin, L.D., Belmont, S.E., Mathey, F., and Charrier, C. (1986). Reaction of phospholes with acids; [1,5] proton shifts in 1*H*-λ^5-phospholes, *J. Chem. Soc., Perkin Trans. II*: 629.
111a. Chiang, Y., and Whipple, E.B. (1963). The protonation of pyrroles, *J. Am. Chem. Soc.*, *85*: 2763.
111b. Houriet, R., Schwarz, H., Zummack, W., Andrade, J.-G., and Schleyer, P. von R. (1981). The α- *vs.* β-protonation of pyrrole, furan, thiophene and cyclopentadiene. Gas phase proton and hydrogen affinities. The bishomocyclopropenyl cation, *Nouv. J. Chim.*, *5*: 505.
112. Farnham, W.B., and Mislow, K. (1972). Kinetics of retro-

cyanoethylation of phosphonium salts and the question of phosphole aromaticity, *Chem. Commun.*: 469.
113. Coggon, P., Engel, J.F., McPhail, A.T., and Quin, L.D. (1970). Molecular structure of 1-benzylphosphole by X-ray analysis, *J. Am. Chem. Soc.*, *92*: 5779.
114. Coggon, P., and McPhail, A.T. (1973). Crystal and molecular structure of 1-benzylphosphole by X-ray analysis, *J. Chem. Soc., Dalton Trans.*: 1888.
115. Ozbirn, W.P., Jacobson, R.A., and Clardy, J.C. (1971). Crystal and molecular structure of 1,2,5-triphenylphosphole, *Chem. Commun.*: 1062.
116. Allen, D.W., Nowell, I.W., Oades, A.C., and Walker, P.E. (1978). Ring strain and the reactivity of dibenzophospholes and their quaternary salts, *J. Chem. Soc., Perkin Trans. I*: 98.
117. Winter, W. (1977). Eigenschaften und Kristall- bzw. Molekul-Struktur von 1,2-Diphenyl-3-[(2-phenylethinyl)-phenyl]-λ^3-phosphindol - ein Beitrag zur Problematik der Phosphol-Aromatizitat, *Ber.*, *110*: 2168.
118. Winter, W., and Butters, T. (1983). Notiz zur Problematik der Phosphindol-Aromatizitat. Verfeinerung der 1,2-Diphenyl-3-[2-(phenylethinyl)phenyl]-λ^3-phosphindol-Struktur, *Ber.*, *116*: 3271.
119. Schafer, W., Schweig, A., Markl, G., Hauptman, H., and Mathey, F. (1973). Direct proof of the non-aromaticity of phospholes and arsoles, *Angew. Chem., Int. Ed. Eng.*, *12*: 145.
120. Schafer, W., Schweig, A., and Mathey, F. (1976). Phospholes. Electronic structure, *J. Am. Chem. Soc.*, *98*: 407.
121. Lumbroso, H., Bertin, D.M., and Mathey, F. (1972). Electric moments of some phospholes, *C. R. Acad. Sci., Ser. C*, *274*: 100.
122. Bundgaard, T., and Jakobsen, H.J. (1972). On the aromaticity of phospholes as studied by ^{13}C NMR of 1-phenylphosphole, *Tetrahedron Lett.*: 3353.
123. Quin, L.D., Borleske, S.G., and Stocks, R.C. (1973). Position specificity for ^{13}C-^{31}P coupling constants for methyl substituents in phospholes and 2-phospholenes, *Org. Magn. Reson.*, *5*: 161.
124. Gray, G.A., and Nelson, J.H. (1980). ^{13}C Nuclear

magnetic resonance of organophosphorus compounds. XII. Phospholes and dibenzophospholes, *Org. Magn. Reson.*, *14*: 14.

125. Nelson, J.H., Affandi, S., Gray, G.A., and Alyea, E.C. (1987). ^{1}H And ^{13}C nuclear magnetic resonance of phenyldibenzophosphole and derivatives: Complete assignment using two-dimensional *J*-resolved and shift correlation methods, *Magn. Reson. Chem.*, *25*: 774.
126. Brown, D.A. (1962). The electronic structures of the cyclopentadiene analogues containing as ring member an element of group 5, *J. Chem. Soc.*: 929.
127. Rauk, A., Andose, J.D., Frick, W.G., Tang, R., and Mislow, K. (1971). Semiempirical calculation of barriers to pyramidal inversion for first and second-row elements, *J. Am. Chem. Soc.*, *93*: 6507.
128. Hase, H.L., Schweig, A., Hahn, H., and Radloff, J. (1973). Die Elektronstruktur des Phosphols und Arsoles, *Tetrahedron*, *29*: 469.
129. Andose, J.D., Rauk, A., and Mislow, K. (1974). Semiempirical calculations of barriers to pyramidal inversion. Extension to the third row of the periodic table, *J. Am. Chem. Soc.*, *96*: 6904.
130. Kaufmann, G., and Mathey, F. (1974). Etude theorique des phospholes: Controle angulaire et nature de l'aromaticite, *Phosphorus*, *4*: 231.
131. Palmer, M.H., Findlay, R.H., and Gaskell, A.J. (1974). Electronic charge distribution and moments of five- and six-membered heterocycles, *J. Chem. Soc., Perkin Trans. II*: 420.
132. Palmer, M.H., and Findlay, R.H. (1975). Non-empirical calculations of the electronic structure of some five-membered ring heterocycles containing sulphur and phosphorus: Thiophene and phosphole, *J. Chem. Soc., Perkin Trans. II*: 974.
133. von Niessen, W., Cederbaum, L.S., and Diercksen, G.H.F. (1976). The electronic structure of molecules by a many-body approach. IV. Ionization potentials and one-electron properties of pyrrole and phosphole, *J. Am. Chem. Soc.*, *98*: 2066.
134. Epiotis, N.D., and Cherry, W. (1976). On the aromaticity of phospholes and arsoles, *J. Am. Chem. Soc.*, *98*: 4365.
135. Hughes, A.N., and Edgecombe, K.E., unpublished results.

136. Trevor, D., and Theopold, K.H. (1989). Synthesis and X-ray crystal structure of a phospholyl anion, *Angew. Chem., Int. Ed. Eng., 28*: 1367.
137. Quin, L.D., and Orton, W.L. (1979). Evidence for delocalization in phosphole anions from their ^{31}P N.M.R. spectra, *J. Chem. Soc., Chem. Commun.*: 401.
138. Garrou, P.E. (1981). Δ_R ring contributions to ^{31}P NMR parameters of transition-metal-phosphorus chelate complexes, *Chem. Rev., 81*: 229.
139. Klebach, T.C. Lourens, R., and Bickelhaupt, F. (1978). Synthesis of *P*-mesityldiphenylmethylenephosphine: A stable compound with a localized P=C bond, *J. Am. Chem. Soc., 100*: 4886.
140. Holah, D.G., Hughes, A.N., Knudsen, K.L., and Perrier, R. (1988). The synthesis and some NMR properties of 2,3-bis(diphenylphosphino)-6-phenyl-λ^3-phosphinine, *J. Heterocycl. Chem., 25*: 155.
141. Mathey, F., and Mercier, F. (1981). Nouvelle voies d'acces aux phospha-7 norbornenes trivalents, *Tetrahedron Lett., 22*: 319.
142. Marinetti, A., Mathey, F., Fischer, J., and Mitschler, A. (1982). Stabilization of 7-phosphanorbornadienes by complexation: X-ray crystal structure of 2,3-bis(methoxycarbonyl)-5,6-dimethyl-7-phenyl-7-phosphanorbornadiene-(pentacarbonyl)chromium, *J. Chem. Soc., Chem. Commun.*: 667.
143. Marinetti, A., Mathey, F., Fischer, J., and Mitschler, A. (1982). Generation and trapping of terminal phosphinidene complexes. Synthesis and X-ray crystal structure of a stable phosphirene complex, *J. Am. Chem. Soc., 104*: 4484.
144. Mathey, F. (1987). The development of a carbene-like chemistry with terminal phosphinidene complexes, *Angew. Chem., Int. Ed. Eng., 26*: 275.
145. Svara, J., Marinetti, A., and Mathey, F. (1986). A preliminary chemical study of terminal allyl-, 3-butenyl-, and 4-pentenylphosphinidene complexes. Thermal rearrangement of 1-allylphosphinene complexes by insertion of the allylic C=C double bond into the phosphirene ring, *Organometallics, 5*: 1161.
146. Holt, N.S., Nelson, J.H., Savignac, P., and Alcock, W. (1985). Palladium-promoted Diels-Alder cycloadditions to 1-

phenyl-3,4-dimethylphosphole. Facile synthesis of a new class of chiral bidentate phosphines: 5-phosphino-7-phosphabicyclo[2.2.1]hept-2-enes, *J. Am. Chem. Soc.*, *107*: 6396.

147. Green. R.L., Nelson, J.H., and Fischer, J. (1987). Ruthenium(II)-promoted site selective intramolecular Diels-Alder syntheses of rigid chiral bidentate ligands from phospholes, *Organometallics*, *6*: 2256.
148. Vac, R., Nelson, J.H., Milosavljevic, E.B., Solujic, L., and Fischer, J. (1989). Ruthenium(II)-promoted site selective intramolecular Diels-Alder reactions, *Inorg. Chem.*, *28*: 4132.
149. Rahn, J.A., Holt, M.S., Gray, G.A., Alcock, N.W., and Nelson, J.H. (1989). Intramolecular [4+2] Diels-Alder cycloaddition reactions of phospholes promoted by palladium and platinum, *Inorg. Chem.*, *28*: 217.
150. Solujic, L., Milosavljevic, E.B., Nelson, J.H., Alcock, N.W., and Fischer, J. (1989). Intramolecular [4+2] Diels-Alder cycloaddition reactions of phospholes with vinylphosphines promoted by nickel, *Inorg. Chem.*, *28*: 3453.
151. Affandi, S., Nelson, J.H., and Fischer, J. (1989). Synthesis of unsymmetrical bidentate and tridentate phosphines by [4+2] Diels-Alder cycloadditions and Michael additions of (phosphole)- and (vinylphosphine)molybdenum carbonyl complexes, *Inorg. Chem.*, *28*: 4536.
152. Alcaraz, J.-M., Svara, J., and Mathey, F. (1986). A preliminary chemical study of a terminal methoxyphosphinidene tungstenpentacarbonyl complex, *Nouv. J. Chim.*, *10*: 321.
153. Mathey, F. (1973). Synthese et proprietes des (hydroxy-2) dihydro-1,2 phosphorines, *Tetrahedron*, *29*: 707.
154. Mathey, F., Thavard, D., and Bartet, B. (1975). Reactions du phenyl-1 dimethyl-3,4 phosphole avec divers chlorures d'acides aromatique, *Can. J. Chem.*, *53*: 855.
155. Mathey, F. (1979). Synthese de la phenyl-2 dimethyl-4,5 phosphorine a partir du benzyl-1 dimethyl-3,4 phosphole, *Tetrahedron Lett.*: 1753.
156. Alcaraz, J.-M., Breque, A., and Mathey, F. (1982). Acces aux [pyridyl-2']-2 phosphorines, *Tetrahedron Lett.*, *23*: 1565.
157. Hughes, A.N., Amornraksa, K., Phisithkul, S., and Reutrakul, V. (1976). Some ring expansion and related reactions of the phosphindole system, *J. Heterocycl. Chem.*,

13: 937.
158. Allen, D.W., and Oades, A.C. (1976). Reaction of dibenzophospholes with benzoyl chloride; ring expansions to dibenzo[*b,d*]phosphorins, *J. Chem. Soc., Perkin Trans. I*: 2050.
159. Hughes, A.N., and Srivanavit, C. (1971). Alkaline hydrolysis of 1-iodomethyl-1,2,5-triphenylphospholium iodide, a new route to the 4-phosphabicyclo[3.1.0]hex-2-ene system, *Can. J. Chem.*, *49*: 879.
160. Quin, L.D., Borleske, S.G., and Engel, J.F. (1973). Dimerization of phospholium ions, *J. Org. Chem.*, *38*: 1954.
161. Hughes, A.N., and Srivanavit, C. (1971). Thermal and photochemical ring expansion of some phosphole derivatives, *Can. J. Chem.*, *49*: 874.
162. Gilheany, D.G., Kennedy, D.A., Malone, J.F., and Walker, B.J. (1984). Fulvalene ylides. A Stevens rearrangement of 1-fluoren-9-ylidene-1,2,5-triphenyl-λ^5-phosphole, *J. Chem. Soc., Chem. Commun.*: 1217.
163. Gilheany, D.G., Kennedy, D.A., Malone, J.F., and Walker, B.J. (1985). A novel bicyclic phosphonium ylide from the reaction of a 1,2-dihydrophosphorin with dimethyl acetylenedicarboxylate, *Tetrahedron Lett.*, *26*: 531.
164. Barton, T.J., and Nelson, A.J. (1969). Heterocyclopentadiene photochemistry, *Tetrahedron Lett.*: 5037.
165. Mathey, F. (1975). Reaction des phospholes avec $Mn_2(CO)_{10}$. Identification du (dimethyl-3,4 phospholyl)-manganese tricarbonyl, *J. Organomet. Chem.*, *93*: 377.
166. Mathey, F. (1987). Aromatic phosphorus-carbon heterocycles as π-ligands in transition metal chemistry, *New. J. Chem.*, *11*: 585.
167. Wilkes, L.M., Nelson, J.H., McCusker, L.B., Seff, K., and Mathey, F. (1983). Ruthenium(II) complexes of 1-substituted 3,4-dimethylphospholes, *Inorg. Chem.*, *22*: 2476.
168. Vac, R., Nelson, J.H., Milosavlevic, E.B., and Solujic, L. (1989). Unique properties of ruthenium(II) phosphole complexes, *Inorg. Chem.*, *28*: 3831.
169. Bergounhou, C., Neibecker, D., and Reau, R. (1988). Unexpected non-influence of the phosphine/rhodium ratio on the activity and selectivity of rhodium-phosphine hydroformylation catalysts, *J. Chem. Soc., Chem. Commun.*: 1370.

170. Demay, C., and Bourgeois, C. (1983). Catalyst system and method for the hydroformylation of olefins, *Fr. Patent 2,544,713*.
171. Attar, S., Bearden, W.H., Alcock, N.W., Alyea, E.C., and Nelson, J.H. (1990). Phosphole complexes of gold(I) halides: Comparison of solution and solid state structures by a combination of solution and CP/MAS ^{31}P NMR spectroscopy and X-ray crystallography, *Inorg. Chem., 29*: 425.
172. Rahn, J.A., Baltusis, L., and Nelson, J.H. (1990). Solid-state structures of $(R_3P)_2PtX_2$ complexes as determined by a combination of $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ spectroscopy, *Inorg. Chem., 29*: 750.
173. Allen, D.W., and Hogarth, D. (1977). A comparison of the donor properties of 5-phenyldibenzophosphole and triphenylphosphine in tetrahedral nickel(II) complexes, *Phosphorus Sulfur, 3*: 381.
174. Affandi, S., Nelson, J.H., Alcock, N.W., Howarth, O.W., Alyea, E.C., and Sheldrick, G.M. (1988). Chromium, molybdenum, and tungsten carbonyl complexes of phenyl dibenzophosphole, *Organometallics, 7*: 1724.
175. Milosavljevic, E.B., Solujic, L., Affandi, S., and Nelson, J.H. (1988). Electrochemistry of 1-phenyl-dibenzophosphole complexes of group 6 metal carbonyls, *Organometallics, 7*: 1735.
176a. Budd, D.E., Holah, D.G., Hughes, A.N., and Hui, B.C. (1974). An efficient and selective monohydrido rhodium(I) homogenous hydrogenation catalyst containing a cyclic phosphine, *Can. J. Chem., 52*: 775.
176b. Holah, D.G., Hoodless, I.M., Hughes, A.N., Hui, B.C., and Martin, D. (1974). Further studies on the homogeneous hydrogenation of olefins catalyzed by a cyclic phosphine complex of rhodium(I) hydride, *Can. J. Chem., 52*: 3758.
177. Hayashi, T., Tanaka, M., and Ogata, I. (1979). Catalytic hydroformylation using dibenzophospholes as ligands, *J. Mol . Catal., 6*: 1.
178. Brown, J.M., Canning, L.R., Kent, A.G., and Sidebottom, P.J. (1982). Observation of dicarbonyldiphosphinerhodium hydrides and their olefin-trapping ability, *J. Chem. Soc., Chem. Commun.*: 721.
179a. Brown, J.M., and Kent, A.G. (1987). Structural characterisation in solution of intermediates in rhodium-catalyzed hydroformylation and their interconversion pathways, *J.*

Chem. Soc., Perkin Trans. II: 1597.

179b. Hjortkjaer, J., Dueholm, H., and De Mello, A. (1987). On the effect of dibenzophospholes on the catalytic activity of rhodium phosphine complexes, *J. Mol. Catal., 39*: 79.

180. Roberts, R.M.G., Silver, J., and Wells, A.S. (1986). Complexes of diphosphaferrocenes with Lewis acids and Cu(I), Ag(I) salts, *Inorg. Chim. Acta, 119*: 165.

181. Nief, F., Mathey, F., Ricard, L., and Robert, F. (1988). Coordination chemistry of the new 2,3,4,5-tetramethyl phospholyl (C_4Me_4P) π-ligand. Crystal and molecular structure of $(\eta^5\text{-}C_4Me_4P)_2ZrCl_2 \cdot 1/2C_{10}H_8$, *Organometallics, 7*: 921.

182. Nief, F., and Mathey, F. (1988). 1-Trimethylstannyl-phospholes as precursors of η^5-phospholyl complexes. Synthesis of (η^5-phospholyl)trichlorotitanium(IV) complexes, *J. Chem. Soc., Chem. Commun.*: 770.

183. Nief, F., Ricard, L., and Mathey, F. (1989). Synthesis of phospha- and diphosphatitanocene dichlorides. Crystal and molecular structure of bis (η^5-3,4-dimethylphospholyl)-dichlorotitanium(IV) and of (η^5-3,4-dimethylphospholyl)-trichlorotitanium(IV), *Organometallics, 8*: 1473.

184. Waite, N.E., Tebby, J.C., Ward, R.S., Shaw, M.A., and Williams, D.H. (1971). Reactions of phosphines and acetylenes. Part XIV. Isomeric 1:2 adducts from triaryl-phosphines and dimethyl acetylenedicarboxylate. A cyclo-pentadienylidene phosphorane, *J. Chem. Soc.-C*: 1620.

185. Burgada, R., Leroux, Y., and El Khoshnich, Y.O. (1981). Synthese et structure d'un trialcoxy-1,1,1 phospholeV. Premier modele pentacoordine contenant le cycle phosphole, *Tetrahedron Lett.*: 3533.

186. Markovski, L.N., and Romanenko, V.D. (1989). Phospha-alkynes and phosphaalkenes, *Tetrahedron, 45*: 6019.

187. Breque, A., Alcaraz, J.-M., Ricard, L., Mathey, F., Tambute, A., and Macaudiere, P. (1989). The use of 1-phosphanorbornadienes with chiral phosphorus at the bridge-head in catalytic asymmetric hydrogenation of dehydroamino acids, *New. J. Chem., 13*: 369.

188. Le Goff, P. Mathey, F., and Ricard, L. (1989). [4+2] Cycloadditions between 2*H*-phospholes and alkenes.

Synthesis and properties of 1-phosphanorbornenes, *J. Org. Chem.*, *54*: 4754.

189. de Lauzon, G., Charrier, C., Bonnard, H., and Mathey, F. (1982). Etude de la protonation des anions phosphoryles. Obtention de dimeres de phospholes -2*H*, *Tetrahedron Lett.*, *22*: 511.
190. de Lauzon, G., Charrier, C., Bonnard, H., Mathey, F., Fischer, J., and Mitschler, A. (1982). X-Ray crystal structure and Diels-Alder reactivity of the 3,4-dimethyl-2*H*-phosphole dimer, *J. Chem. Soc., Chem. Commun.*: 1272.
191. Holand, S., Charrier, C., Mathey, F., Fischer, J., and Mitschler, A. (1984). Stabilization of 2*H*-phospholes by complexation. A phosphorus-carbon double bond acting as a four-electron donor, *J. Am. Chem. Soc.*, *106*: 826.
192. Markl, G., and Seidl, E. (1983). 2-Benzyl-1-phosphaazulene, *Angew. Chem., Int. Ed. Eng.*, *22*: 57.
193. Markl, G., Seidl, E., and Trotsch, I. (1983). 1-Methoxy-3-phenyl-2-phosphaazulene - the first synthesis of 2-phosphaazulenes, *Angew. Chem., Int. Ed. Eng.*, *22*: 879.
194. Zurmuhlen, F., and Regitz, M. (1987). Phosphorus compounds with unusual coordination. XXV. Cyclopropenylphosphaalkenes, educts for the synthesis of stable 2*H*-phospholes, *J. Organomet. Chem.*, *332*: C1.
195. Rosch, W., and Regitz, M. (1987). Unusually coordinated phosphorus compounds; 22. Cycloaddition reactions of nitrilium betaines with a stable phosphaalkyne, *Synthesis*: 689.
196. Keller, H., and Regitz, M. (1988). Bis and tris(diazomethyl)phosphanes - new building blocks for the synthesis of phosphorus heterocycles, *Tetrahedron Lett.*, *29*: 925.
197. Rosch, W., Richter, H., and Regitz, M. (1987). Cycloaddition mesoionischer Verbindungen an ein stabiles Phosphaalkin - neue Moglichkeiten in der Synthese von Aza- und Thiaphospholen, *Ber.*, *120*: 1809.
198. Markl, G., and Pflaum, S. (1988). 4-Hydroxy-1,3λ^3-azaarsole - 3-Hydroxy-1,2,4λ^3-diazaphosphole - 3-Hydroxy-1,2,4λ^3-diazaarsole. Heterocyclische Phenole, *Tetrahedron Lett.*, *29*: 3387.
199. Markl, G., and Holzl, W. (1988). 1,2,4λ^3-Thiaazaphosphole, 1,2λ^3,4λ^3-Thiadiphosphole und 1,2λ^3-Thiaphos-

phole aus 1,3,4-Oxathiazol-2-onen und Phosphaalkenen, *Tetrahedron Lett.*, *29*: 4535.

200. Markl, G., Dietl, S., Ziegler, M.L., and Nuber, B. (1988). $1,2\lambda^3,3\lambda^3$-Azadiphosphole, ein aromatisches Ringsystem mit *cis*-P=P-Doppelbindung. $1\lambda^3\sigma^3,3\lambda^3\sigma^2$-Diphosphole, *Tetrahedron Lett.*, *29*: 5867.
201. Corfield, J.R., Harger, M.J.P., Shutt, J.R., and Trippett, S. (1970). Further ring openings and ring expansions of phosphetans, *J. Chem. Soc.-C*: 1855.
202. Waite, N.E., Allen, D.W., and Tebby, J.C. (1971). Reactions of phosphines with acetylenes. Part XV. The mechanism of the reaction of triphenylphosphine with excess dimethyl acetylenedicarboxylate, *Phosphorus*, *1*: 139.
203. Mitchell, C.M., and Stone, F.G.A. (1972). Reactions of low-valent metal complexes with fluorocarbons. Part XXII. Tertiary phosphine gold complexes, *J. Chem. Soc., Dalton Trans.*: 102.
204. Bruce, M.I., Catlow, A., Humphrey, M.G., Koutsantonis, G.A., Snow, M.R., and Tiekink, E.R.T. (1988). Cyclopentadienyl-ruthenium and -osmium chemistry. XXVIII. Reactions and isomerization of 1,2-bis(methoxycarbonyl)-ethenyl complexes, *J. Organomet. Chem.*, *338*: 59.
205. Shaw, M.A., Tebby, J.C., Ward, R.S., and Williams, D.H. (1970). Reactions of phosphines with acetylenes. Part XI. Formation of derivatives of 5*H*-diphos(V)ole and 1,4-diphos(V)orin, *J. Chem. Soc.-C*: 504.
206. Davies, M., and Hughes, A.N. (1969). Abnormal reaction of a phosphonium ylid with dimethyl acetylenedicarboxylate, *Chem. Ind. (London)*: 138.
207. Davies, M., Hughes, A.N., and Jafry, S.W.S. (1972). Cycloaddition and related reactions of some unsaturated phosphines with dimethyl acetylenedicarboxylate, *Can. J. Chem.*, *50*: 3625.
208. Holah, D.G., Hughes, A.N., and Kleemola, D. (1978). Reactions of simple phospholes with dimethyl acetylenedicarboxylate, *J. Heterocycl. Chem.*, *15*: 1319.
209. Markl, G. (1963). Intramolecular C-alkylation of phosphine methylenes to cyclic phosphonium salts and phosphorus ylides, *Z. Naturforsch.*, *18b*: 84.
210. Barluenga, J., Lopez, F., and Palacios, F. (1986). A simple synthesis of 3*H*-λ^5-phosphole derivatives from alkyldiphen-

ylphosphine imines and dimethyl acetylenedicarboxylate, *J. Chem. Soc., Chem. Commun.*: 1574.

CHAPTER 11

THE USE OF CARBON-PHOSPHORUS ANALOGUE COMPOUNDS IN THE REGULATION OF BIOLOGICAL PROCESSES

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I. Introduction

In the several years since our initial review of the use of phosphonic acids as analogues of natural phosphates for biological investigations,[1] numerous additional examples of this type of analogue use have been reported. Some of these have subsequently been reviewed.[2-5] In addition to continuing efforts in this direction, several other types of analogues of biological materials in which a carbon-phosphorus bond is present have received attention. In particular, compounds in which a phosphorus function is present in place of a carboxylic acid group or other carbon atom of the natural material have become of interest.

In the present discussion the status of efforts using carbon-phosphorus bond containing species as analogues of natural phosphate esters is updated. Included here are developments on the design of analogue species. Moreover, the further areas of phosphorus analogue use in biological systems is surveyed.

II. The Rationale for Using Compounds Containing Carbon-Phosphorus Bonds for Biological Regulation

A. Resistance to Normal Ester Cleavage Processes

A primary rationale for the use of compounds containing a carbon-phosphorus bond as regulators for normal biological processes lies in the fact that the carbon-phosphorus bond is normally resistant to hydrolysis under conditions which cleave ordinary phosphate ester linkages. Thus, introducing a phosphonic acid (or other carbon-phosphorus compound) of suitable structure to a biological system in place of a natural phosphate ester provides a potential means of regulating the normal processes of that system. For example, if phosphate ester hydrolysis is necessary to provide further metabolites for continued functioning of the system, the analogue could perturb that ester hydrolysis sufficiently to disrupt

normal functioning. Depending on the particular biological target and the experimental aim, such a disruption could serve to cease all biological function of the system, diminish the functioning of a particular normal process, or enhance a particular normal process.

Of course, in order for a carbon-phosphorus analogue to be of use in such a manner its structure must be properly designed. Ideally, all other structural and physico-chemical features will be identical in the natural phosphate and the analogue. In practice, this identity of other features can often be approximated quite well, but never absolutely attained. Fortunately, complete structural and physico-chemical correspondence aside from the modified linkage is often unnecessary for effective use of a substance.

Two features of the intended analogue for which correspondence with the natural material is desirable are size and shape, and acidity of the phosphorus acid functions.

For the first of these features, the design of the analogue needs to take into account the spatial relationships of the phosphorus acid site with all other functionalities in the molecule. For simple phosphate esters and their corresponding phosphonic acid analogues in which a methylene group has been introduced in place of the normal oxygen, the correspondence of size and shape is virtually *isosteric*. That is, in spite of small differences in bond distances and bond angles for the materials being compared,[6-8] the distances between the phosphorus acid site and distant sites are essentially the same for the compound pair. The natural phosphate ester and its methylene analogue are structurally superimposable.

With pyrophosphates and their methylene analogues, however, there are more significant spatial deviations. Replacement of the phosphoric anhydride oxygen of a P-O-P linkage by a methylene group (P-CH_2-P) results in an opening of the angle and a stretching of the distance between functionalities at the two ends of the linkage.[9] Thus, pyrophosphates and their methylenebisphosphonic acid analogues are only nominally isosteric.

With regard to the acidities of the phosphorus sites in the phosphate monoester and its isosteric methylene analogue, there is significant divergence. While the first pK_a for each represents a strong acid which would be completely dissociated at physiological pH, the second pK_a of a phosphonic acid is generally higher than that for the structurally related phosphate ester by 0.5-1.0 pK_a unit.[10-12] With this difference in the range of physiological pH (6-8), we might anticipate difficulties in the use of an analogue for

biochemical investigations owing to its being in a lower dissociative form than the natural phosphate.

An approach to overcoming this difficulty has been to develop carbon-phosphorus analogues which are *isopolar* with regard to the natural substance, in addition to being isosteric.[4,13] An analogue which is isopolar is one in which substituents are attached sufficiently close to the phosphonic acid site to decrease the second pK_a rendering its acidity closer to that of the natural phosphate monoester. These substituents must be sufficiently electron-withdrawing to increase the acidity of the acid function, and at the same time sufficiently small not to introduce new steric interactions. The use of fluorine substituents at the 1-position of a phosphonic acid has been demonstrated to provide the proper change in pK_a to better mimic the natural phosphate monoester, and possibly to serve as a better analogue.[13-17]

B. Modified Acid Linkages

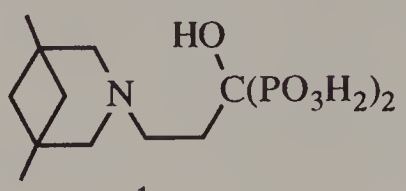
In recent years numerous investigations have been performed using analogues in which a normal carboxylic acid function has been replaced by another type of acidic linkage. This is done with the anticipation that changing the carboxylic acid linkage to another type of acid, of similar or different strength, might cause the analogue to serve as a false substrate for a normal metabolic process. Phosphorus-centered analogue acids can provide regulation of biological processes by several routes, including the introduction of a site of modified acidity, the formation of modified amide and ester linkages, and by resisting ordinary decarboxylation processes.

To this end a wide range of phosphorus-centered acid analoges of natural carboxylic acids have been synthesized and studied. In general, these involve replacement of a C-COOH linkage with a C-P(OH) linkage. The phosphorus-centered acid sites have included both dibasic linkages, which will exhibit very different acidic characteristics than the normal carboxylic acids, as well as monobasic linkages, expected to exhibit characteristics more closely corresponding to those of the natural materials.

III. Analogues of Pyrophosphate

The fundamentals of pyrophosphate analogue design and synthesis have been previously reviewed.[1,3,18] The use of phosphonic acid analogues of pyrophosphate in the treatment of

calcium deposition disorders has continued with the development of new materials substituted at the carbon of methylenebisphosphonic acid. Examples (1) and (2) of such materials bearing additional Lewis base binding sites in the substituents are shown.[19,20]



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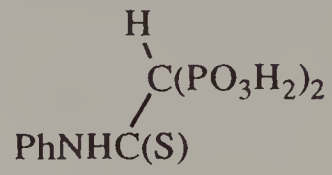

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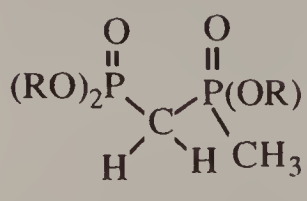
In addition, studies have been reported on the effect of derivatives of methylenebisphosphonic acid on the activity of RNA-polymerases. The analogues competed with pyrophosphate for incorporation into nucleoside triphosphates and served as enzyme inhibitors.[21,22]

With regard to the synthesis of new phosphonic acid analogues of pyrophosphate, a significant effort has been mounted for the incorporation of halogen at the position between the phosphorus sites. This effort has been made for the purpose of generating analogues which would be isopolar with the natural pyrophosphate.[14,23-26]

As the pyrophosphate linkage is an important component in numerous biological species, methylenebisphosphonate analogue design and synthesis has wider applications than simply as a replacement of inorganic pyrophosphate. These will be treated in the appropriate sections of this Chapter. There has been developed a general approach for the preparation of a range of pyrophosphate analogues applicable to all of these other areas.[27] This approach involves the generation of the phosphonate-phosphinate species (3) and its subsequent conversion to various derivatives through the dianion (4). Alkylation of (4) with alkyl halides at -78° occurs at the terminal anionic site to give species of general structure (5).



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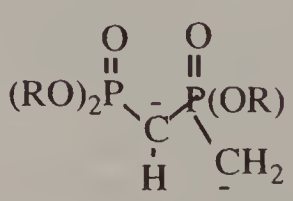

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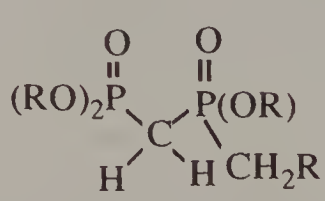

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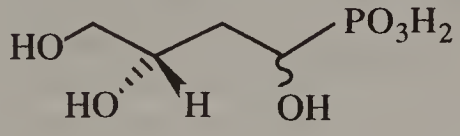
IV. Analogues of Glyerol Phosphate and Related Metabolites

A. Glycerol Phosphate and Phosphoglycerate

Since the prior reviews,[1,3] a report has been made of the synthesis of new isosteric phosphonic acid analogues of glycerol 3-phosphate in which a hydroxyl group is attached at the 1-carbon site.[28] These diastereoisomeric materials (6) are isopolar with the natural material and exhibit increased aqueous solubility compared to the simple isosteric methylene analogue (7). A new approach has been reported for the synthesis of isosteric and non-isosteric phosphonic acid analogues of glycerol 3-phosphate using osmium tetroxide oxidation of a precursor alkenylphosphonate.[29] In addition, an isosteric and isopolar analogue of glycerol 3-phosphate, the (±)-1,1-difluoro-3,4-dihydroxybutyl-1-phosphonate, has been synthesized and found to be a substrate for NADH linked glycerol 3-phosphate dehydrogenase.[30] Studies of the mode of action of (6) in *E. coli* have continued, determining the genetic source of resistance to its bacteriostatic effect in mutant strains.[31]



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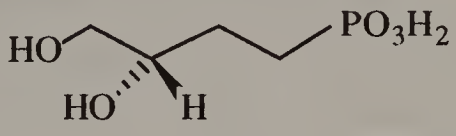

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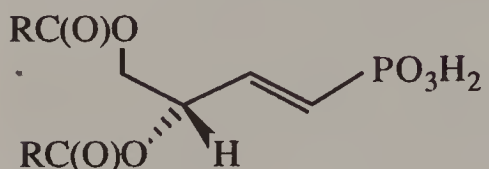
Syntheses of the isopolar and isosteric α-fluoromethylene analogues of 2-phospho- and 3-phospho-D-glyceric acid have been reported.[32,33] In other work the isosteric (methylene) phosphonic acid analogue of 3-phosphoglyceric acid has been found to be a potent inhibitor of phosphoglycerate mutases.[34] Moreover,this analogue was found to be an inhibitor of the photosynthetic activity of isolated spinach chloroplasts.[35]

B. Phosphonolipid Syntheses

1. Analogues of Phosphoglycerides

Two new nominally isosteric phosphonic acid analogues (8) and (9) of phosphatidic acid, PA, have been reported.[36,37] These materials contain a four-carbon backbone and chirality the same as that present in PA. The presence of the hydroxyl group at the 1-position in (9) renders it isopolar with PA as well as isosteric. A

route for the preparation of asymmetrically substituted phosphonolipids isosteric with and having the same chirality as natural PA has recently been reported.[38]



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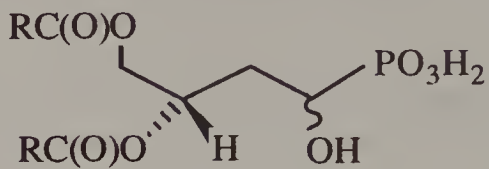

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The material (8) has also been esterified to yield an analogue of phosphatidylcholine, PC.[36] Other new isosteric analogues of PC and phosphatidylethanolamine, PE, have also been prepared which have carbon-phosphorus linkages in the head group portion of the molecule.[39,40] The synthesis of a non-isosteric diphosphonic acid analogue of cardiolipin has also been reported,[41] as well as that of an isosteric analogue of phosphatidylinositol bearing the carbon-phosphorus bond in the backbone portion.[42]

Continuing efforts have been made in the preparation of phosphonolipids related to the naturally occurring phosphonic acid, 2-aminoethylphosphonic acid, AEP. A synthesis of a phosphinic acid, having both the head group and backbone portion joined to phosphorus by carbon-phosphorus bonds, has been reported.[43] (This work includes a previously undecribed route for the formation of carbon-phosphorus bonds.) In addition, general approaches toward the synthesis of lipopolysaccharides incorporating the AEP unit,[44] and other substituted 2-aminoalkylphosphonic acids[45,46] have been developed.

Additional reports have also been made of the natural occurrence of AEP[47] and of its metabolism.[48,49]

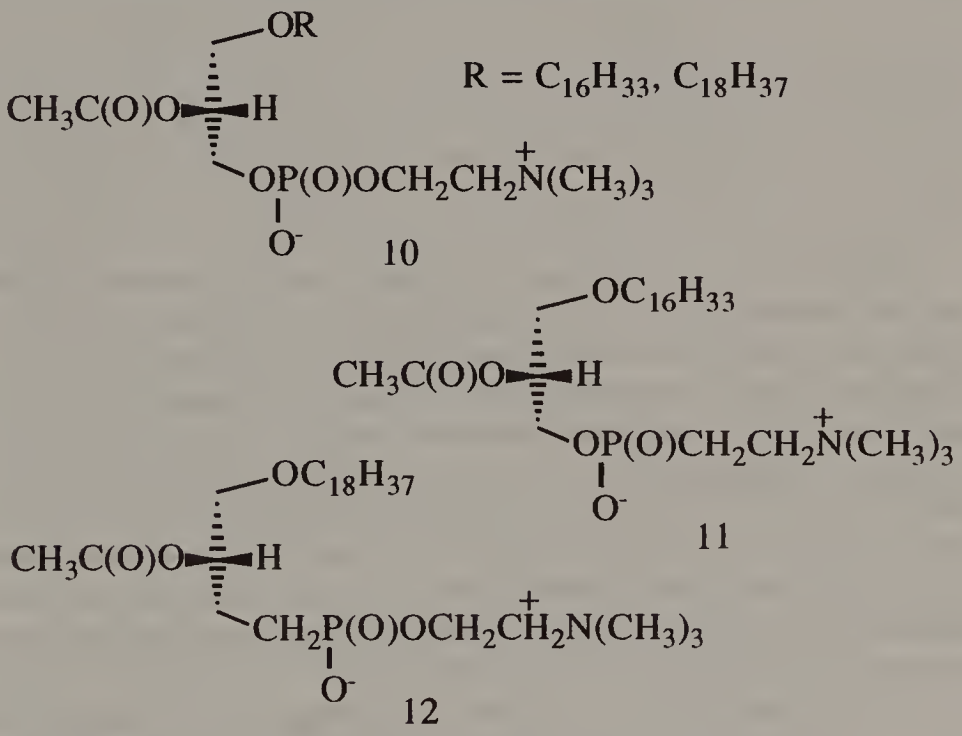
2. Analogues of Platelet Activating Factor (PAF)

The 1-*O*-alkyl-2-*O*-acetyl-*sn*-glycero-3-phosphocholine (10), known as platelet activating factor or PAF, has been found in recent years to have profound biological activity for several purposes. In response to the discoveries of the activity of PAF, numerous efforts have been undertaken to prepare analogues of PAF and thereby probe its mode of action in its various roles and to modify systematically its activity. To this end analogues of PAF have been synthesized in which a phosphate ester linkage has been replaced by a carbon-phosphorus linkage. With most of the analogues

prepared[50-56] the carbon-phosphorus linkage is in the choline head group rather than in the backbone, *i.e.* they are derivatives of AEP, an example of which is (11).[50]

Two reports have been made, however, in which a carbon-phosphorus bond is in the backbone portion of the material. In one of these[51] the compound has a three-carbon backbone and is thereby not isosteric with natural PAF. The other report is of the synthesis of an isosteric analogue (12).[56] Both of these latter analogues incorporate the same backbone stereochemistry as found in the natural PAF.

While the AEP derivative analogues of PAF have been demonstrated to elicit the biological responses of natural PAF,[50,53,54] no dramatic increases in potency have been achieved and some decreases on activity have been noted. The non-isosteric backbone phosphonate analogue[51] was found to be neither agonistic nor antagonistic relative to natural PAF.



3. Membrane Studies with Phosphonolipids

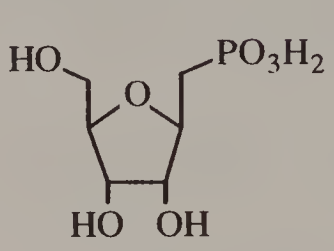
One of the driving forces for the synthesis and study of phosphonolipids has been the understanding of lipid behavior in membranes. Continuing efforts have been reported in the role undertaken by a variety of phosphonolipids when incorporated into

model membranes.[57-60]

V. Phosphorus-Carbon Analogues of Carbohydrates and Carbohydrate Phosphates

A. Analogues of Carbohydrate Phosphates

Earlier interest in the synthesis and biological study of phosphonic acid analogues of the natural carbohydrate phosphates has continued.[1,3] Several approaches to the preparation of isosteric[61,62] (13) and non-isosteric[63,64] analogues of ribose 1-phosphate have been reported. There has also been a report of the synthesis of an isosteric hydroxymethylene analogue (14) of ribose 5-phosphate in a protected form, deprotected immediately prior to use in biological studies.[65]



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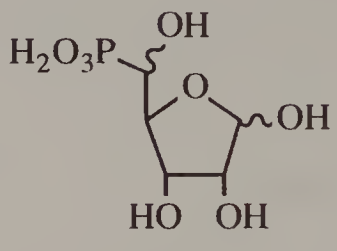

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Stereospecific syntheses of both α- and β- isomers of the isosteric phosphonic acid analogues of D-glucopyranose 1-phosphate has been reported.[66,67] Both syntheses use a Michaelis-Arbuzov reaction of the corresponding alkyl halide for introduction of the carbon-phosphorus bond. A similar approach has been used for the synthesis of isosteric analogues of the α- and β-isomers of D-mannopyranose.[68] There has also been reported a synthesis of the hydroxymethylene isosteric phosphonic acid analgoue of glucose 1-phosphate utilizing a phase-transfer catalyzed Abramov reaction.[69]

A synthesis of the non-isosteric (shortened) analogue of glucose 1-phosphate has also been reported.[70] In this latter work the analogue was coupled through a phosphorus anhydride linkage to UMP to produce a material with the intention of serving as an inhibitor of glycosyltransferase. The material exhibited slight antitumor activity. A related phosphonic acid species derived from methylenebisphosphonic acid coupled to the anomeric site of

α-D-glucopyranose and the 5'-oxygen of uridine exhibited slight inhibition of galactosyltransferase, but no antitumor activity.[71]

The synthesis of isosteric analogues of both arabinose 1-phosphate[72] and arabinose 1,5-diphosphate[73,74] have been reported. The latter of these bears the phosphonic acid linkage at the 1-position, with a normal phosphate ester linkage at the 5-position. A phosphonic acid analogue of Lipid X, a liposaccharide, has also been synthesized, along with related glycosylphosphonates of 2-amino-2-deoxyaldoses.[75]

In addition to the syntheses noted of analogues of aldose phosphates, several reports have been made of preparations of isosteric analogues of various ketose phosphates,[76-79] including a general approach to this class of compounds proceeding through 1-deoxy-1-nitrosugars.[80] Analogues of fructose 1,6-diphosphate have also been generated by the aldolase mediated reaction of several phosphonic acid analogues of 1,3-dihydroxyacetone phosphate and glyceraldehyde 3-phosphate.[81]

Analogues of D-erythrose 4-phosphate were prepared by oxidative cleavage of the corresponding phosphonic acid analogues of D-glucose 6-phosphate and investigated for activity as substrates of transaldolase and transketolase.[82] Other enzymatic studies with phosphonic acid analogues of carbohydrate phosphates included those with 3-dehydroquinate synthetase[83,84] and gluconate 6-phosphate dehydrogenase.[85]

In recent years significant interest has developed in the study of inositol phosphates and phosphatidylinositol owing to their role in second messenger processes. This biological role has spurred the synthesis of a wide range of structural analogues of these materials. We mentioned earlier[42] the synthesis of an isosteric phosphonic acid analogue of phosphatidylinositol. There has also been reported a synthesis of the racemic isosteric phosphonic acid analogue of inositol 1-phosphate using a Horner-Emmons approach.[86]

Finally, the synthesis of a phosphonosphingoglycolipid, found naturally in a marine organism, has been accomplished starting with D-galactose as the chiral precursor.[87]

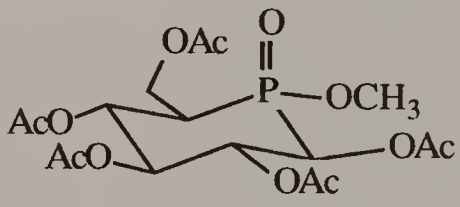
B. Analogues in which Phosphorus is Present in the Carbohydrate Ring

Several efforts have been directed toward the preparation of a different type of carbon-phosphorus bond containing carbohydrate analogue, that in which a phosphorus-centered functionality is

present in place of a normal atom in the ring of a carbohydrate pyranose or furanose ring.

Several reports have been made of analogues in which a phosphorus atom is present in place of the normal oxygen of the carbohydrate ring. These analogues have all been of the quinquevalent phosphorus type, containing a P=O linkage, and at least two carbon-phosphorus bonds. Phosphinate analogues of D-ribose[88] and D-glucose (15)[89] in this category have been prepared, as well as phosphine oxide analogues of D-xylose,[90] L-xylose,[91] D-glucose[90] and D-mannose (16).[92]

In addition, two reports have been made of the preparation of analogues of carbohydrates in which a phosphorus is present in place of the anomeric carbon atom. These analogues have been of the phosphonate (17)[93] and phosphinate (18)[94] types. Attempts to deprotect (18) to generate the parent carbohydrate analogue yielded ring-opened product.



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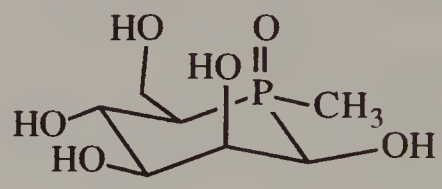

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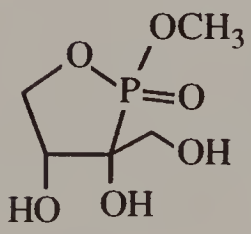

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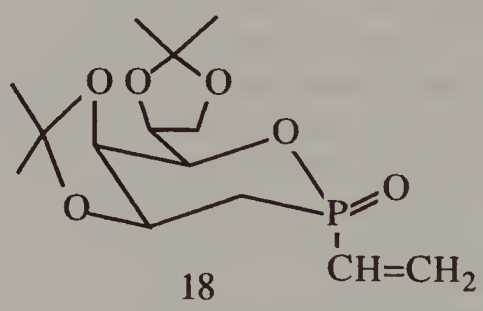


18

Analogues of inositol have been prepared in the phosphinate and phosphine oxide series in which phosphorus is contained as a member of the ring.[95]

C. Other Syntheses of Phosphorus-Containing Carbohydrate Analogues

A series of acetylenic phosphines and phosphonate derivatives of ribose and arabinose have been synthesized,[96] as well as phosphine derivatives of 3-deoxyribose.[97]

VI. Analogues of Nucleotides

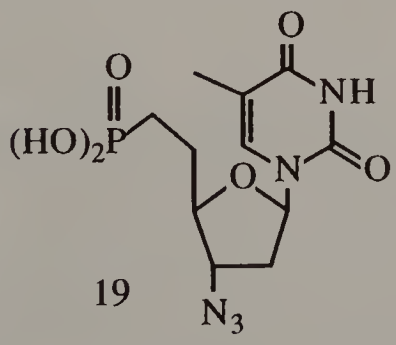
A. Analogues of Nucleoside Monophosphates

There has continued significant interest in the synthesis of isosteric and non-isosteric phosphonic acid analogues of natural nucleoside monophosphates. A general approach for the preparation of isosteric phosphonic acid analogues of nucleoside 3'-phosphates starting with D-glucose and the introduction of the carbon-phosphorus bond *via* a modified Wittig reaction has been noted.[98] The same general approach has been used for the preparation of the isosteric analogue of 2'-deoxyadenosine 3'-phosphate.[99] Another approach[100] to the analogue of adenosine 3'-phosphate also begins with D-glucose, but involves an alternative mode of functionalization and incorporation of the carbon-phosphorus bond *via* a Michaelis-Arbuzov reaction. In the latter instance the primary nucleotide analogue unit has been incorporated further into an analogue of an oligonucleotide.

The synthesis of isosteric analogues of 2'-deoxy-3'-nucleoside phosphates has been described.[101] Non-isosteric analogues of 2'-deoxy-dinucleoside phosphates bearing a carbon-phosphorus bond at the 3'-position of one of the nucleoside units with a thio-ester linkage at phosphorus have also been reported.[102]

A general approach involving incorporation of the phosphorus *via* a Michaelis-Arbuzov reaction has been described for the preparation of isosteric analogues of nucleoside 5'-phosphates.[103] A similar approach has also been used for the preparation of the non-isosteric analogue of adenosine 5'-phosphate.[104]

Two reports have been made of the preparation of the isosteric analogue (19) of AZT 5'-phosphate.[105,106]



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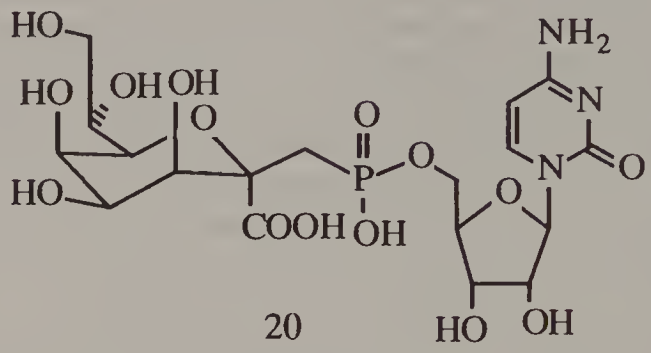
In addition, an isosteric phosphonic acid analogue (20) of CMP-KDO bearing the carbon-phosphorus bond to the KDO portion of the molecule has been synthesized.[107] This material has been found to be a modest inhibitor of CMP-KDO synthetase.



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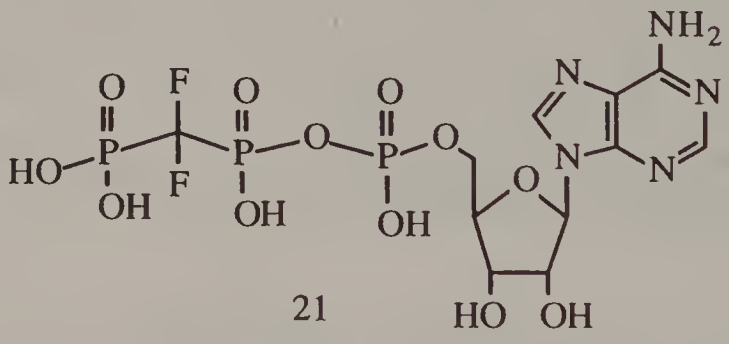
B. Analogues of Nucleoside Pyrophosphates

Analogues in which a phosphorus anhydride oxygen of a nucleoside polyphosphate was substituted by a methylene group were among the first phosphonate analogues used in mechanistic studies of biochemical action.[1,3] A particular concern in recent efforts has been the preparation of such analogues which are isopolar with the natural materials.[108-111] To this end the substitution of halogens for hydrogen at the bridging methylene group, such as in (21)[108] has been accomplished.



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The simple isosteric analogues of 2'-deoxythymidine 3'-diphosphate 5'-triphosphate (β,γ-methylene)[112], and of adenosine 5'-phosphosulfate[113] have also been reported.

Several examples of methylenebisphosphonate analogues of dinucleoside pyrophosphates have been prepared and investigated for their biochemical characteristics,[114,115] as well as analogues of an acylphosphonucleoside.[116,117] Several methylenebis-

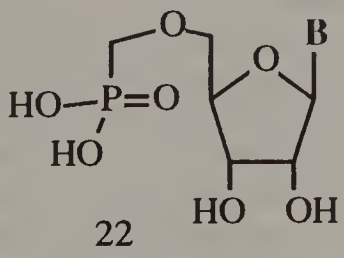
phosphonate analgoues of dinucleoside tetra-phosphates have also been prepared and investigated for their binding capabilites with metal ions and enzymes.[118,119]

A report has also been made of studies of the α,β-methylene analogues of ADP and ATP as substrates for creatine kinase. While serving as substrates, the rates of phosphoryl transfer are significantly lower with the analogues than with the natural materials.[120]

C. Alkylphosphonic Acid Analogues of Nucleotides

Analogues of nucleotides in which an alkyl group is present in place of a normal acidic hydroxyl group or oxide anion site represent species in which the normal esteric linkages remain present, but bear a different acidic nature at phosphorus. The chemistry and biology of phosphonomethyl analogues of nucleotides have recently been reviewed.[121] Several reports have been made recently of the preparation of the simple methylphosphonic acid analogues of nucleotides[122] and derived nucleic acids.[123] Enzymatic degradation of methylphosphonic acid analogues of oligodeoxynucleotides has been studied.[124] The synthesis of an analogue of 2'-deoxythymidine 3'-phosphate derived from methylthiophosphonic acid has also been reported.[125]

Hydroxymethylphosphonic acid has been used to generate nucleotide analogues (22) and (23) bearing phosphorus bound to the 5'-position of nucleosides respectively through phosphonate ester, and ether linkages.[126] Similar analogues of nucleoside 5'-diphosphates derived from hydroxymethylphosphonic acid have also been reported along with their activity toward polynucleotide phosphorylase.[127]



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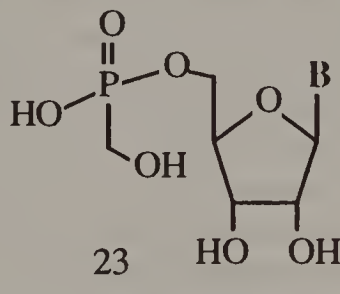

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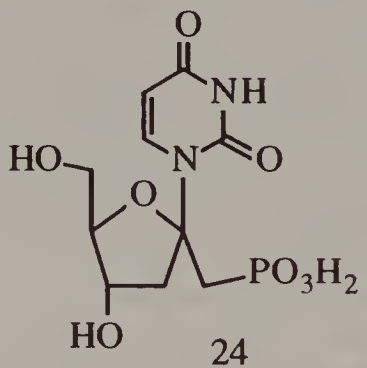
A series of difluoromethylphosphonic acid analogues of 2'-deoxynucleoside 3'-mono-, 5'-mono- and 3',5'-diphosphates has been prepared.[128] In addition, a difluoromethylphosphonic

acid analogue of a dinucleoside phosphate has been reported.[128] While nominally isosteric and isopolar with the natural material, this latter compound is not acidic at the phosphorus site. Similarly, an analogue of cyclic-UMP containing the thiophosphoryl group has been prepared from methylthiophosphonic acid,[129] and non-isosteric analogues of cyclic-2',3'-nucleoside monophosphates bearing ether linkages has been prepared from hydroxymethylphosphonic acid.[130] All of these materials lack the normal acidic functionality at phosphorus.

D. Nucleoside Derivatives Substituted at the 1'-Position

Arabino- and 2'-deoxyribo- series compounds have been synthesized bearing a phosphonomethylgroup at the 1'-position.[131-133] These materials, such as (24), are formally non-isosteric analogues of anhydro nucleosides substituted at the anomeric carbon and are of interest as transition state analogues of species in the biosynthetic pathway of pyrimidine nucleotides.



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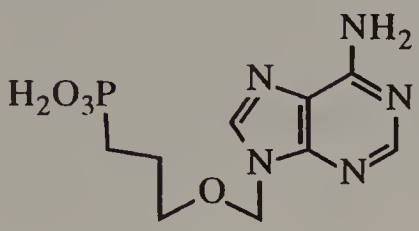
E. Phosphonic Acid Derivatives of Acyclic Nucleotides

The inhibition of purine nucleoside phosphorylase has been recognized as a target activity for antitumor and immunosuppressive agents.[134] To this end numerous materials have been synthesized incorporating critical structural components for such activity, which appear to include the presence of the heterocyclic base (normally a purine) and an acidic phosphate function distant from the heterocyclic base as in a normal nucleotide. The complete carbohydrate ring system is not present in such agents. Thus they constitute a type of *acyclic* nucleotide. As analogues of the acyclic phosphate nucleotides, phosphonic acid species have been prepared.

Several series of phosphonate acyclic nucleotide analogues have been reported. These include simple purines linked to

phosphonic acid functions *via* a saturated linear carbon chain,[134] as well as structurally more complex species which bear intervening oxygen ether linkages and attempt to duplicate the stereochemistry of a normal nucleotide bearing a complete carbohydrate ring system.[135-142] Examples of this latter type of structure are shown as (25)[137] and (26).[142]

Materials of this type have been demonstrated to have antiviral activity in a wide range of systems.



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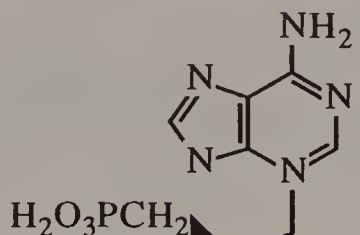

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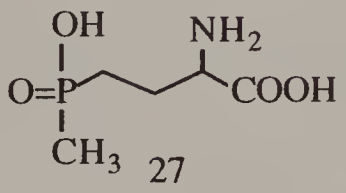
VII. Phosphorus Acid Functions as Replacements of Carboxylic Acid Groups

A. Amino Acids

1. Phosphinothricine and Related Materials

The isolation of the naturally occurring phosphinic acid phosphinothricin (27) from *Streptomyces viridochromogenes* and the subsequent discovery of its activity as an antibiotic, a fungicide, and a herbicide has stimulated major activity in the synthesis and study of analogues of naturally occurring amino acids in which an acidic phosphorus site is present in place of a normal carboxylic acid group.[143] As is evident from a brief consideration of its structure, phosphinothricin is an isosteric analogue of glutamic acid (28). In response to the discovery of the activity of (27), syntheses of phosphinothricin itself[144] and other carbon-phosphorus analogues of (28) have been synthesized, including the isosteric phosphonic acid analogue (29)[145] and cyclic phosphinamide forms, such as (30).[146] The cyclic phosphinamide form has been further introduced into a tripeptide analogue structure (being the amino terminus unit with alanylalanine) which possesses antitumor activity.[147]

Considering phosphinothricin and the structurally related carbon-phosphorus compounds as analogues of glutamic acid, it is the pendant carboxyl group which is replaced by a phosphorus acid function rather than that of the central α-amino acid linkage. Given the observable biological activity of phosphinothricin and its related compounds, the investigation of other carbon-phosphorus analogues of naturally occurring α-amino acids would appear to be a logical endeavour.



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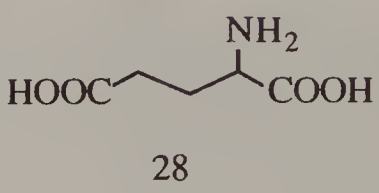

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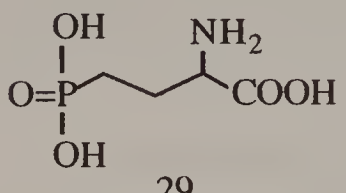

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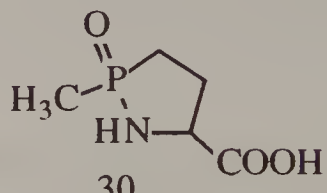

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2. Syntheses of Analogues of the Naturally Occurring α-Amino Acids

Several different general approaches have been used for the synthesis of phosphonic acid analogues of the natural α-amino acids in which the phosphorus acid site replaces the α-carboxylate group. That approach used most often involves the performance of an Abramov- or Pudovik-type reaction[148] of a phosphite or phosphorous acid on a Schiff base, preformed or generated *in situ*.[149-164] The corresponding reaction using hypophosphorous acid[165,166] or an alkyl phosphonite[167] has been used to prepare isosteric phosphonous and phosphinic acid analogues of α-amino acids. A related procedure involves the initial preparation of an imine of the general structure $R_2C{=}NCH_2P(O)(OR)_2$, itself an analogue of glycine, followed by alkylation and deprotection to yield analogues of the general structure $H_2NCHRPO_3H_2$.[168,169]

An alternative approach for the preparation of the phosphonic

acid analogues of α-amino acids involves the initial preparation of the appropriate 1-oxoalkylphosphonate *via* Michaelis-Arbuzov reaction of a phosphite with an acyl halide,[170] followed by imine formation with the carbonyl group and subsequent reduction of the imine.[171-174]

An interesting conversion of the natural α-amino acids into their phosphonic acid analogues has been reported.[175] This process involves the performance of a Hunsdiecker reaction on the *N*-carbobenzyloxy protected α-amino acid followed by a Michaelis-Becker reaction[170] to generate the carbon-phosphorus bond. A related approach involves the reaction of *N*-acetylated-1-substituted amines with a variety of phosphorus reagents to generate phosphonic[176,177] and phosphonous[178] acid analogues of the α-amino acids.

In addition to the *general* approaches to these analogues noted above, numerous syntheses of *specific* α-amino acid analogues have also been reported. The acidic amino acids, aspartic acid and glutamic acid have received the most attention with regards to analogue synthesis,[179-187] although there have been reported specific syntheses of carbon-phosphorus analogues of proline,[182,188,189] serine,[190] glycine,[191,192] alanine,[193,194] cysteine,[195] tryptophan,[196] arginine[197] and its metabolic precursor citrulline,[198] and the synthetic norvaline.[199]

Certain of these synthetic approaches are expected to be ameanable to the preparation of the α-amino acid analogues in optically active form *via* asymmetric induction when suitable pendant groups are present. This goal has been realized in a number of instances proceeding in the formation of up to 95% enantiomeric excess of of one stereoisomer.[200-205] A biochemical resolution approach using penicillin acylase has also yielded optically active analogue species.[206]

Peptide analogues, derived from natural α-amino acids and the phosphonic acid analogues, in which the phosphonic acid unit constitutes the acid terminus amino acid of the peptide, have been synthesized for several purposes. The most prominent application for such materials has been as antibacterial agents.[207-211] The use of these materials as hypotensive agents has also been claimed.[212,213] Phosphonic acid analogues of aspartame have

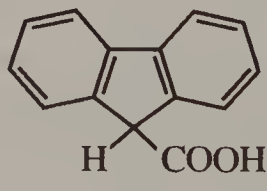
been synthesized, but none have been found to be sweet tasting.[214]

In addition to the those mentioned above, phosphorus-containing analogues of the α-amino acids and their derived peptides have been used in numerous biological investigations. Studies have been performed investigaing their activity as inhibitors of pyruvate kinase,[215] dihydrofolate reductase,[216] glutamine synthetase,[217] and angiotensin-converting enzyme,[218] as well as receptor antagonists of *N*-methyl-D-aspartate[219] and as a binding agent of divalent cations in biological systems.[220]

Finally, a protected isosteric phosphonic acid analogue (C-P in place of O-P) of *O*-phosphoserine has been synthesized with the intention of including it in peptides for replacement of natural phosphorylated serine peptides attached to human β-casein.[221]

B. Morphactin Analogues

Derivatives of fluorene-9-carboxylic acid (31), known as morphactines, are known to have profound activity as herbicides and plant growth regulators. In light of this fact, the synthesis and biological investigation of carbon-phosphorus analogues of 9-aminofluorene-9-carboxylic acid, such as the phosphonic acid analogue (32), has been undertaken. These materials have been prepared by the Pudovik-type reaction[148] of a fluorenoneimine with a dialkyl phosphite[222-224] and exhibit herbicidal activity similar to that of the parent carboxylic acid materials.



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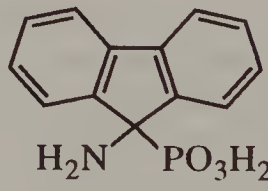

31

In further studies, the analogues of the type (31) have been coupled to natural α-amino acids *via* peptide linkages, the phosphorus component being the acid terminal unit.[225] These materials also exhibit significant herbicidal activity. Additionally, tertiary phosphine oxide analogues have been prepared, and exhibit herbicidal activity in the same range as do the phosphonic acid species.[226,227]

VIII. Miscellaneous Carbon-Phosphorus Systems Used in Biological Regulation

A. Prenyl Pyrophosphate Analogues

Interest has continued in the synthesis and use of phosphonic acid analogues of prenyl phosphates and pyrophosphates as regulators of isoprenoid biosynthesis. With this interest, analogues of geranyl pyrophosphate have been synthesized in which the normal anhydride oxygen has been replaced by a methylene or difluoromethylene group.[228] Both analogues have been found to serve as alternative substrates for a variety of isoprenoid enzymes.

Analogues of dimethylallyl pyrophosphate and isopentenyl pyrophosphate in which both the normal anhydride oxygen and the esteric oxygen atoms are replaced by methylene groups have been synthesized.[229] Both materials were found to be competitive inhibitors of the normal synthesis reaction involving isopentenyl pyrophosphate and geranyl pyrophosphate catalyzed by avian liver farnesyl diphosphate synthetase. There was isolated a material presumed to be the corresponding analogue of farnesyl pyrophosphate from these enzymatic reactions. The analogues (methylene or difluoromethylene groups replacing the anhydride oxygen, and those in which the esteric oxygen is also replaced by a methylene group) of farnesyl pyrophosphate have been synthesized and evaluated as inhibitors of squalene synthetase.[230,231]

The synthesis of a series of non-isosteric phosphonic acid analogues of prenyl pyrophosphates, lacking the normal esteric oxygen, have also been synthesized.[232,233]

B. Phosphoenolpyruvate Analogues

Earlier work on the synthesis and utilization of phosphonic acid analogues of phosphoenolpyruvate (PEP) has been reviewed.[1,3] Recently, new approaches for the preparation of these analogues have been reported.[234,235] The isosteric phosphonic acid analogue of PEP, along with other phosphonic acids, has been investigated as a potential herbicide through inhibition of PEP carboxylase.[235]

C. Derivatives of Antibiotics and Related Materials

Several reports have been made of the preparation and investigation of phosphonic and phosphinic acid analogues of antibiotics and their degradation products. In particular, phosphonic

and phosphinic acid analogues of penicillamine have been prepared,[236,237] as well as phosphonic acid derivatives of cephalosporins.[238,239] The latter exhibit significant antibacterial action.

D. Analogues of Acylphosphates

Two series of β-ketophosphonates have been synthesized as isosteric analogues of acylphosphonates, useful in enzyme inhibition studies.[240,241] The methylphosphonate analogues of acetyl phosphate, AMP, PEP, and ATP have also been prepared as substrate analogues for examination in phosphoryl transfer reactions.[242] The analogue of acetyl phosphate has been found to inhibit the reaction of acetyl phosphate with acetate kinase.[242]

IX. Bibliography

1. Engel, R. (1977). Phosphonates as analogues of natural phosphates, *Chem. Rev.*, *77*: 349.
2. Blackburn, G.M. (1981). Phosphonates as analogues of biological phosphates, *Chem. Ind. (London)*: 134.
3. Engel, R. (1983). Phosphonic acids and phosphonates as antimetabolites, *The role of phosphonates in living systems*, (Hilderbrand, R.L., ed.), CRC Press, Boca Raton, FL, p.79.
4. Blackburn, G.M., Taylor, G.E., Tattershall, R.H., Thatcher, G.R.J., and McLennan, A. (1986). Phosphonate analogues of biological phosphates, *Biophosphates and their analogues - Synthesis, structure, metabolism, and activity*, (Bruzik, K.S., and Stec, W.J., eds.), Elsevier Science Publishers B.V., Amsterdam, The Netherlands, p. 451.
5. Holy, A. (1987). Phosphonomethyl analogs of nucleotides and their derivatives: Chemistry and biology, *Nucleosid. Nucleotid.*, *6*: 147.
6. Kraut, J. (1961). Crystal structure of 2-aminoethyl phosphate, *Acta Crystallogr.*, *14*: 1146.
7. Ferrier, W.G., Lindsay, A.R., and Young, D.W. (1962). Confirmation of the crystal structure of 2-aminoethanol phosphate, *Acta Crystallogr.*, *20*: 1966.
8. Okaya, Y. (1966). Crystal structure of the stable modification of 2-aminoethylphosphonic acid, beta-ciliatine, *Acta Crystallogr.*, *20*: 712.
9. Larsen, M., Willet, R., and Yount, R.G. (1969). Imido-

diphosphate and pyrophosphate: possible biological significance of similar structures, *Science*, *166*: 1510.
10. Crofts, P.C., and Kosolapoff, G.M. (1953). Preparation and determination of apparent dissociation constants of some alkylphosphonic and dialkylphosphinic acids, *J. Am. Chem. Soc.*, *75*: 3379.
11. VanWazer, J.R. (1958). *Phosphorus and its compounds, Vol. 1*, Interscience, New York, pp. 364ff.
12. Rammler, D.H., Yengoyan, L., Paul, A.V., and Bax, P.C. (1967). Nucleoside phosphonic acids. II. The synthesis of 5'-deoxythymidine 5'-phosphonic acid and its pyrophosphate derivatives, *Biochemistry*, *6*: 1828.
13. Blackburn, G.M., Perree, T.D., Rashid, A., Bisbal, C., and Lebleu, B. (1986). Isosteric and isopolar analogues of nucleotides, *Chem. Scr.*, *26*: 21.
14. Blackburn, G.M., England, D.A., and Kolkmann, F. (1981). Monofluoro- and difluoro-methylenebisphosphonic acids: isopolar analogues of pyrophosphoric acid, *J. Chem. Soc., Chem. Commun.*: 930.
15. Blackburn, G.M., and Rashid, A. (1988). Stereoselective syntheses of the methylene- and α-fluoromethylene-phosphonate analogues of 2-phospho-D-glyceric acid, *J. Chem. Soc., Chem. Commun.*: 317.
16. Dessinges, A., and Vasella, A. (1988). Synthesis of a non-isosteric, isopolar monophosphate analog of β-D-fructose 2,6-bisphosphate, *Carbohydr. Res.*, *174*: 47.
17. Blackburn, G.M., and Rashid, A. (1989). Enantiospecific syntheses of the methylene- and α-fluoromethylene-phosphonate analogues of 3-phospho-D-glyceric acid, *J. Chem. Soc., Chem. Commun.*: 40.
18. Francis, M.D., and Martodam, R.R. (1983). Chemical, biochemical, and medicinal properties of the diphosphonates, *The role of phosphonates in living systems*, (Hilderbrand, R.L., ed.), CRC Press, Boca Raton, FL, p. 55ff.
19. Jaeggi, K.A. (1989). Preparation of azacycloalkylalkandiphosphonic acids for regulation of calcium metabolism, *Eur. Pat. Appl. 317,505*.
20. Oku, T., Todo, E., Kasahara, C., Nakamura, K., Kayakiri, H., and Hashimoto, M. (1987). Process for preparing diphosphonic acids and their use in treating bone disease, *Eur. Pat. Appl. 243,173*.

21. Komissarenko, S.V., Kolesnikov, I.N., and Fomovskaya, G.N. (1985). Effect of diphosphonic analogs of inorganic pyrophosphate on reactions catalyzed by DNA-dependent RNA-polymerase II, *Ukr. Biokhim. Zh.*, *57*: 62.
22. Komissarenko, S.V., Fomovskaya, G.N., Kolesnikova, I.N., Tarusova, N.B., Borisevich, A.N., and Lozinskii, M.O. (1985). Effect of diphosphonate analogs of inorganic pyrophosphate on the activity of RNA-polymerases from the calf thymus, *Ukr. Biokhim. Zh.*, *57*: 56.
23. Blackburn, G.M., and Kent, D.E. (1986). Method of introducing α-F for isopolar biological analogues of phosphates, *J. Chem. Soc., Perkin Trans. I*: 913.
24. Blackburn, G.M., Brown, D., Martin, S.J., and Parratt, M.J. (1987). Studies on selected transformations of some fluoromethanephosphonate esters, *J. Chem. Soc., Perkin Trans. I*: 181.
25. Blackburn, G.M., and Taylor, G.E. (1988). Syntheses of some fluorine-containing halomethanephosphonate and methylenebisphosphonate esters, *J. Organomet. Chem.*, *348*: 55.
26. McKenna, C.E., Khawli, L.A., Ahmad, W.-Y., Pham, P., and Bongartz, J.-P. (1988). Synthesis of α-halogenated methanediphosphonates, *Phosphorus Sulfur*, *37*: 1.
27. Stowell, M.H.B., Witte, J.F., and McClard, R.W. (1989). The phosphonylphosphinyldianion: a convenient synthon for the preparation of biologically interesting phosphonylphosphinyl(P-C-P-C) compounds, *Tetrahedron Lett.*, *30*: 411.
28. Lalinde, N., Tropp, B.E., and Engel, R. (1983). Isosteres of natural phosphates. 10. Synthesis of analogues related to glycerol 3-phosphate, *Tetrahedron*, *39*: 2369.
29. Pondaven-Raphalen, A., and Sturtz, G. (1987). Etude de la reaction de dihydroxylation de phosphonates α,β-, β,γ-, et γ,δ-ethyleniques a l'aide d'hydroperoxydes catalysee par le tetroxyde d'osmium: specificite d'action de l'hydroperoxyde de tertiobutyle, *Phosphorus Sulfur*, *29*: 329.
30. Chambers, R.D., Jaouhari, R., and O'Hagan, D. (1988). Synthesis of a difluoromethylenephosphonate analogue of glycerol-3-phosphate. A substrate for NADH linked glycerol-3-phosphate dehydrogenase, *J. Chem. Soc., Chem. Commun.*: 1169.
31. Hwang, Y.-W., Engel, R., and Tropp, B.E. (1984).

Correlation of 3,4-dihydroxybutyl 1-phosphonate resistance with a defect in cardiolipin synthesis in *Escherichia coli*, *J. Bacteriol.*, *157*: 846.

32. Blackburn, G.M., and Rashid, A. (1988). Stereoselective syntheses of the methylene- and α-fluoromethylene-phosphonate analogues of 2-phospho-D-glyceric acid, *J. Chem. Soc., Chem. Commun.*: 317.
33. Blackburn, G.M., and Rashid, A. (1989). Enantiospecific syntheses of the methylene and α-fluoromethylene-phosphonate analogues of 3-phospho-D-glyceric acid, *J. Chem. Soc., Chem. Commun.*: 40.
34. McAleese, S.M., Fothergill-Gilmore, L.A., and Dixon, H.B.F (1985). The phosphonomethyl analogue of 3-phosphoglycerate is a potent competitive inhibitor of phosphoglycerate mutases, *Biochem. J.*, *230*: 535.
35. Heuer, B., and Portis, A.R. (1987). Inhibition of the photosynthetic activities of isolated spinach chloroplasts by phosphonate compounds, *Plant Physiol.*, *84*: 649.
36. Schwatrz, P.W., Tropp, B.E., and Engel, R. (1988). Phosphonolipids. The synthesis of chiral vinylic phosphonolipid analogs of phosphatidic acid and phosphatidyl choline, *Chem. Phys. Lipids*, *49*: 1.
37. Schwartz, P.W., Tropp, B.E., and Engel, R. (1988). Phosphonolipids. 2. α-Hydroxyphosphonolipid analogs of phosphatidic acid, *Chem. Phys. Lipids*, *49*: 131.
38. Chu, T.-Y., Tropp, B.E., and Engel, R. (1990). The synthesis of chiral, asymmetrically substituted phosphonolipids, *Organic Paper #35, 199th National Meeting of the American Chemical Society*, April, 1990, Boston, MA.
39. Yamauchi, K., Une, F., Tabata, S., and Kinoshita, M. (1986), Synthesis of glycerophosphonolipids containing aminoalkylphosphonic acids, *J. Chem. Soc., Perkin Trans. I*: 765.
40. Wissner, A., Schaub, R.E., and Sum, P.E. (1987). Phosphocholine derivatives having antihypertensive action, *U.S. Patent 4,640,913*.
41. Moschidis, M.C. (1988). Synthesis of a phosphono analog of cardiolipin and study of its silicic acid column chromatography behavior, *Chem. Phys. Lipids*, *46*: 253.
42. Pratt, C., Tropp, B.E., and Engel, R. (1990). Synthesis of an isosteric analgue of phosphatidylinositol, *Organic Paper*

#1, 200th National Meeting of the American Chemical Society, August, 1990, Washington, DC.
43. Moschidis, M.C. (1985). Synthesis of 1,2-dipalmitoyloxy-propyl-3-(2-trimethylammoniummethyl)phosphinate, *Chem. Phys. Lipids*, *36*: 343.
44. Dreef, C.E., Valentijn, A.R.P.M., de Vroom, E., van der Marel, G.A., and van Boom, J.H. (1988). An approach towards the formation of an ester bond between the primary hydroxyl of a β-D-galactopyranoside and 2-aminoethylphosphonic acid and its *N*-methyl substituted derivatives, *Tetrahedron Lett.*, *29*: 1199.
45. Sauveur, F., Collignon, N., Guy, A., and Savignac, P. (1983). Acces a l'acide amino-2 propylphosphonique optiquement actif, *Phosphorus Sulfur*, *14*: 341.
46. Varlet, J.-M., Collignon, N., and Savignac, P. (1978). A new route to 2-aminoalkanephosphonic acids, *Syn. Commun.*, *8*: 335.
47. Miceli, M.V., Henderson, T.O., and Myers, T.C. (1987). Alkylphosphonic acid distribution in the planorbid snail *Helisoma sp.*, *Comp. Biochem. Physiol.*, *88B*: 603.
48. Olsen, D.B., Hepburn, T.W., Moos, M., Mariano, P.S., and Dunaway-Mariano, D. (1988). Investigation of the *Bacillus cereus* phosphonoacetaldehyde hydrolase. Evidence for a Schiff base mechanism and sequence analysis of an active-site peptide containing the catalytic lysine residue, *Biochemistry*, *27*: 2229.
49. Pipke, R., and Amrhein, N. (1988). Degradation of the phosphonate herbicide glyphosate by *Athrobacter atrocyaneus* ATCC 13752, *Appl. Envir.*, *54*: 1293.
50. Moschidis, M.C., Demopoulos, C.A., and Kritikou, L.C. (1983). Phosphono-platelet activating factor. I. Synthesis of 1-*O*-hexadecyl-2-*O*-acetyl-glyceryl-3-(2-trimethylammonium-methyl) phosphonate and its platelet activating potency, *Chem. Phys. Lipids*, *33*: 87.
51. Disselnkotter, H., Lieb, F., Oediger, H., and Wendisch, D. (1985). Synthesis of phosphono analogs of 2-*O*-acetyl-1-*O*-hexadecyl(octadecyl)-*sn*-3-glycerylphosphorylcholine (platelet activating factor), *Arch. Pharm.*, *318*: 695.
52. Moschidis, M.C., and Demopoulos, C.A. (1985). Phosphono-platelet activating factor. II. Synthesis of 2-acetamido-2-deoxy-1-*O*-octadecylglycerol-3-(2-trimethylammonium-ethyl) and (2-aminoethyl)phosphonates, *Chem. Phys.*

Lipids, *37*: 45.
53. Wissner, A., Kohler, C., and Goldstein, B.M. (1986). Analogs of platelet activating factor. 5. Multiple oxygen substitution of the alkoxy chain, *J. Med. Chem.*, *29*: 1315.
54. Anderson, R.C., Reitter, B.E., and Winslow, C.M. (1986). Platelet-activating factor analogs. II. Synthesis of the 1-*O*-(4-decyloxymethylphenyl)- and 1-*O*-(4-decyloxyphenylmethyl) analogs, *Chem. Phys. Lipids*, *39*: 73.
55. Ono, M., and Shiraiwa, M. (1988). Preparation of an acetylglycerophosphorylcholine derivative as an antihypertensive and a process for its preparation, *Jpn Patent 63 54,383*.
56. Liu, Y.-J., Tropp, B.E., and Engel, R. (1990). The synthesis of an isosteric phosphonic acid analogue of platelet activating factor, *Organic Paper #75, 200th National Meeting of the American Chemical Society*, August, 1990, Washington, DC.
57. Klose, G., Hentschel, M., Bayerl, T., and Strobel, U. (1984). The motional behavior of phosphonic acid dialkyl esters in model and microsomal membranes and their influence on the ion permeability, *Biophys. Membr. Transp.*: 185.
58. Bayerl, T., Klose, G., Ruckpaul, K., and Schwarze, W. (1985). Interaction of hexane phosphonic acid diethyl ester with phospholipids in hepatic microsomes and reconstituted liposomes as studied by ^{31}P-NMR, *Biochim. Biophys. Acta*, *812*: 437.
59. Bittman, R., Clejan, S., Fugler, L., and Rosenthal, A.F. (1986). The effect of cholesterol on glycerophosphono- and glycerophosphinocholines. Permeability measurements in lipid vesicles, *Biochim. Biophys. Acta*, *855*: 265.
60. Ostermayer, B., Albrecht, O., and Vogt, W. (1986). Polymerizable lipid analogues of diacetylenic phosphonic acids. Synthesis, spreading behaviour and polymerization at the gas-water interface, *Chem. Phys. Lipids*, *41*: 265.
61. Meyer, R.B., Stone, T.E., and Jesthi, P.K. (1984). 2,5-Anhydro-1-deoxy-1-phosphono-D-altritol, an isosteric analogue of α-D-ribofuranose 1-phosphate, *J. Med. Chem.*, *27*: 1095.
62. Nicotra, F., Panza, L., Ronchetti, F., and Toma, L. (1984). High stereoselective synthesis of diethyl (2,3-isopropylidene-5-trityl-α-D-ribofuranosyl)-methanephosphonate, a

precursor to the phosphono analog of α-D-ribose 1-phosphate, *Tetrahedron Lett.*, *25*: 5937.

63. Meuwly, R., and Vasella, A. (1985). Reactions of 1-*C*-nitroglycosyl halides and 1-*C*-nitroglycosyl sulfones with dialkyl-phosphite anions: nucleophilic attack *vs.* single-electron transfer, *Helv. Chim. Acta*, *68*: (1985).
64. Breuer, E., Melumad, D., Sarel, S., and Katz, E. (1983). Antiviral compounds. 3. The preparation of some diketo-phosphonates derived from sugars, *Eur. J. Med. Chem. - Chim. Ther.*, *18*: 487.
65. Mlotkowska, B., Tropp, B.E., and Engel, R. (1983). The preparation of methyl 5-deoxy-5-(dihydroxyphosphinoyl)-hydroxymethyl-2,3-*O*-isopropylidene-β-D-ribofuranoside, a precursor to a hydroxymethylene analog of D-ribose 5-phosphate, *Carbohydr. Res.*, *117*: 95.
66. Nicotra, F., Ronchetti, F., and Russo, G. (1982). Synthesis of the phosphono-analogue of α-D-glucose 1-phosphate, *J. Chem. Soc., Chem. Commun.*: 470.
67. Nicotra, F., Ronchetti, F., and Russo, G. (1982). Stereo-specific synthesis of the phosphono analogues of α- and β-D-glucose 1-phosphate, *J. Org. Chem.*, *47*: 4459.
68. Nicotra, F., Perego, R., Ronchetti, F., Russo, G., and Toma, L. (1984). Synthesis of the phosphono analogues of α- and β-D-mannopyranosyl phosphate, *Carbohydr. Res.*, *131*: 180.
69. Zhdanov, Y.A., Glebova, Z.I., and Uzlova, L.A. (1981). Interphase-catalyzed Abramov reaction in carbohydrate chemistry, *Zh. Obshch. Khim.*, *51*: 1675.
70. Vaghefi, M.M., Bernacki, R.J., Dalley, N.K., Wilson, B.E., and Robins, R.K. (1987). Synthesis of glycopyr-anosylphosphonate analogs of certain natural nucleoside diphosphate sugars as potential inhibitors of glycosyltrans-ferases, *J. Med. Chem.*, *30*: 1383.
71. Vaghefi, M.M., Bernacki, R.J., Hennen, W.J., and Robins, R.K. (1987). Synthesis of certain nucleoside methylenedi-phosphonate sugars as potential inhibitors of glycosyltrans-ferases, *J. Med. Chem.*, *30*: 1391.
72. Zhdanov, Y.A., Glebova, Z.I., Uzlova, L.A., and Vikrishchuk, N.I. (1983). Synthesis of isosteric

phosphonate analog of α-D-arabino-1-phosphate, *J. Gen. Chem. U.S.S.R., Engl. Transl., 53*: 2616.

73. Reitz, A.B., Nortey, S.O., and Maryanoff, B.E. (1985). Stereoselectivity in the electrophile-promoted cyclizations of a hydroxyolefin derived from arabinose. Synthesis of a phosphonate isostere of β-D-arabinose-1,5-diphosphate, *Tetrahedron Lett., 26*: 3915.
74. Maryanoff, B.E., Nortey, S.O., Inners, R.R., Campbell, S.A., Reitz, A.B., and Liotta, D. (1987). Synthesis of *C*-arabinofuranosyl compounds. Phosphonate and carboxylate isosteres of D-arabinose 1,5-bisphosphate, *Carbohydr. Res., 171*: 259.
75. Briner, K., and Vasella, A. (1987). Glycosylphosphonates of 2-amino-2-deoxy-aldoses. Synthesis of a phosphonate analogue of Lipid X, *Helv. Chim. Acta, 70*: 1341.
76. Le Marechal, P., Froussios, C., Level, M., and Azerad, R. (1981). Synthesis of phosphono analogs of 3-deoxy-D-arabino-hept-2-ulosonic acid 7-phosphate, *Carbohydr. Res., 94*: 1.
77. Roach, D.J.W., Harrison, R., Hall, C.R., and Inch, T.D. (1981). An improved synthesis of 6,7-dideoxy-α-D-*gluco*-heptose 7-phosphonic acid, *Biochem. J., 197*: 735.
78. Mirza, S., and Vasella, A. (1984). Deoxynitrosugars. 7th Communication. Synthesis of methyl shikimate and of diethyl phosphashikimate from D-ribose, *Helv. Chim. Acta, 67*: 1562.
79. Dessinges, A., and Vasella, A. (1988). Synthesis of a non-isosteric, isopolar monophosphate analog of β-D-fructose 2,6-bisphosphate, *Carbohydr. Res., 174*: 47.
80. Julina, R., and Vasella, A. (1985). Synthesis of isosteric phosphonate analogues of ulose-1-phosphates, *Helv. Chim. Acta, 68*: 819.
81. Bischofberger, N., Waldmann, H., Saito, T., Simon, E.S., Lees, W., Bednarski, M.D., and Whitesides, G.M. (1988). Synthesis of analogs of 1,3-dihydroxyacetone phosphate and glyceraldehyde 3-phosphate for use in studies of fructose-1,6-diphosphate aldolase, *J. Org. Chem., 53*: 3457.
82. Le Marechal, P., Froussios, C., Leval, M., and Azerad, R. (1980). Enzymic properties of phosphonic analogues of D-erythrose 4-phosphate, *Biochem. Biophys. Res.*

Commun., *92*: 1097.
83. Le Marechal, P., Froussios, C., Levev, M., and Azerad, R. (1980). The interaction of phosphonate and homophosphonate analogues of 3-deoxy-D-*arabino* heptulosonate 7-phosphate with 3-dehydroquinate synthetase from *Escherichia coli*, *Biochem. Biophys. Res. Commun.*, *92*: 1104.
84. Myrvold, S., Reimer, L.M., Pompliano, D.L., and Frost, J.W. (1989). Chemical inhibition of dehydroquinate synthase, *J. Am. Chem. Soc.*, *111*: 1861.
85. Roach, D.J.W., and Harrison, R. (1981). Dehydrogenation by gluconate 6-phosphate dehydrogenase of an isosteric phosphonate substrate analogue, *Biochem. J.*, *197*: 731.
86. Kulagowski, J.J. (1989). The synthesis of (±)*myo*-inositol-1-phosphonate, *Tetrahedron Lett.*, *30*: 3869.
87. Ohashi, K., Kosai, S., Arizuka, M., Watanabe, T., Fukunaga, M., Monden, K., Uchikoda, T., Yamagiwa, Y., and Kamikawa, T. (1988). Synthesis of a phosphonosphingoglycolipid found in the marine snail *Turbo cornutus*, *Tetrahedron Lett.*, *29*: 1189.
88. Hanaya, T., and Yamamoto, H. (1989). Synthesis and structural analysis of 4-deoxy-4-(hydroxyphosphinyl and phenylphosphinyl)-D-ribofuranoses, *Bull. Chem. Soc. Jpn.*, *62*: 2320.
89. Richter, T., Luger, P., Hanaya, T., and Yamamoto, H. (1989). An improved synthesis of the 5-deoxy-5-(hydroxyphosphinyl)-D-glucopyranoses, and crystal structures of 1,2,3,4,6-penta-*O*-acetyl-5-deoxy-5-[(*R*)-methoxyphosphinyl]-β-D-glucopyranose and its 5-[(*R*)-ethylphosphinyl] congener, *Carbohydr. Res.*, *193*: 9.
90. Yamamoto, H., Hanaya, T., Kawamoto, H., Inokawa, S., Yamashita, M., Armour, M.A., and Nakashima, T.T. (1985). Synthesis and structural analysis of 5-deoxy-5-*C*-(hydroxyphosphinyl)-D-xylo- and -glucopyranoses, *J. Org. Chem.*, *50*: 3516.
91. Yamamoto, H., Hanaya, T., Kawamoto, H., and Inokawa, S. (1988). Synthesis and structural analysis of 5-deoxy-5-[(*RS*)-ethylphosphinyl]-α,β-L-idopyranoses, *J. Org. Chem.*, *53*: 4790
92. Yamamoto, H., Hanaya, T., Ohmori, K., and Kawamoto, H. (1989). Synthesis of 5-deoxy-5-[(*R* and *S*)-methylphosphinyl]-α,β-D-mannopyranoses. The first phosphorus-in-

ring sugar analogs of D-mannose type, *Chem. Lett.*: 1471.
93. Wroblewski, A.E. (1986). Analogues of branched-chain tetrahydrofuranosides having phosphorus in the anomeric position, *Tetrahedron*, *42*: 3595.
94. Molin, H., Noren, J.O., and Claesson, A. (1989). Studies of the synthesis of sugar phosphonates related to 3-deoxy-D-manno-2-octulosonic acid (Kdo), *Carbohydr. Res.*, *194*: 209.
95. Inokawa, S. (1985). Phosphorus sugar compounds, *Jpn Patent 60,237,093*.
96. Tronchet, J.M.J., Bonenfant, A.P., Pallie, K.D., and Habashi, F. (1979). Phosphorus-containing sugars. III. Derivatives of enose- and ynosephosphonates and related compounds, *Helv. Chim. Acta*, *62*: 1622.
97. Saito, S.., Nakamura, Y., and Morita, Y. (1985). Syntheses of novel sugar phosphine derivatives, and homogeneous hydrogenation reactions with their rhodium complexes, *Chem. Pharm. Bull.*, *33*: 5284.
98. Albrecht, H.P., Jones, G.H., and Moffatt, J.G. (1984). Homonucleoside phosphonic acids-I. A general synthesis of isosteric phosphonate analogs of nucleoside 3'-phosphates, *Tetrahedron*, *40*: 79.
99. Morr, M., Ernst, L., and Grotjahn, L. (1983). 2',3'-Di-deoxy-3'-*C*-(phosphonomethyl)adenosine, the phosphonate analogue of 2'-deoxyadenosine 3'-phosphate, Z. *Naturforsch.*, *38b*: 1665.
100. Mazur, A., Tropp, B.E., and Engel, R. (1984). Isosteres of narural phosphates. 11. Synthesis of a phosphonic acid analogue of an oligonucleotide.
101. Morr, M., Kakoschke, C., and Fritz, H.J. (1984). 2'-Deoxy-3'-phosphonomethyl nucleosides, *Ger. Offen. 3,307,744*.
102. Hata, T., Sekine, M., Matsuzaki, J., and Hotada, H. (1986). *Jpn Patent 61,204,194*.
103. Padyukova, N.S., Karpeisky, M.Y., Kolobushkina, L.I., and Mikhailov, S.N. (1987). A new scheme for the synthesis of 5'-nucleotide phosphonate analogs, *Tetrahedron Lett.*, *28*: 3623.
104. Raju, N., Smee, D.F., Robins, R.K., and Vaghefi, M.M. (1989). Synthesis and biological properties of purine and pyrimidine 5'-deoxy-5'-(dihydroxyphosphinyl)-β-D-ribofuranosyl analogs of AMP, GMP, IMP, and CMP, *J. Med.*

Chem., *32*: 1307.
105. Tanaka, H., Fukui, M., Haraguchi, K., Masaki, M., and Miyasaka, T. (1989). Cleavage of a nucleoside oxetane with carbanions: synthesis of a highly promising candidate for anti-HIV agents. A phosphonate isostere of AZT 5'-phosphate, *Tetrahedron Lett.*, *30*: 2567.
106. Barton, D.H.R., Gero, S.D., Quiclet-Sire, B., and Samadi, M. (1989). Stereoselectivity in radical reactions of 2'-deoxynucleosides. A synthesis of an isostere of 3'-azido-3'-deoxythymidine-5'-monophosphate (azt-5' monophosphate), *Tetrahedron Lett.*, *30*: 4969.
107. Norbeck, D.W., Kramer, J.B., and Lartey, P.A. (1987). Synthesis of an isosteric phosphonate analogue of cytidine 5'-monophospho-3-deoxy-D-*manno*-2-octulosonic acid, *J. Org. Chem.*, *52*: 2174.
108. Blackburn, G.M., Kent, D.E., and Kolkmann, F. (1981). Three new β,γ-methylene analogues of adenosine triphosphate, *J. Chem. Soc., Chem. Commun.*: 1188.
109. Blackburn, G.M., Kent, D.E., and Kolkmann, F. (1984). The synthesis and metal binding characteristics of novel, isopolar phosphonate analogues of nucleotides, *J. Chem. Soc., Perkin Trans. I*: 1119.
110. Blackburn, G.M., Perree, T.D., Rashid, A., Bisbal, C., and Lebleu, B. (1986). Isosteric and isopolar analogs of nucleotides, *Chem. Scr.*, *26*: 21.
111. Blackburn, G.M., Eckstein, F., Kent, D.E., and Perree, T.D. (1985). Isopolar *vs.* isosteric phosphonate analogues of nucleotides, *Nucleosid. Nucleotid.*, *4*: 165.
112. Den Hertog, J.A.J., Lawson, M.P., De Jong, E.W.P., and Van Boom, J.H. (1981). Chemical synthesis of thymidine 3'-diphosphate 5'[(phosphonomethyl)phosphonyl phosphate]; an asymmetrically phosphorylated thymidine derivative, *J. R. Neth. Chem. Soc.*, *100*: 317.
113. Callahan, L., Ng, K., Geller, D.H., Agarwal, K., and Schwartz, N.B. (1989). Synthesis and properties of a nonhydrolyzable adenosine phosphosulfate analog, *Anal. Biochem.*, *177*: 67.
114. Marquez, V.E., Tseng, C.K.H., Gebeyehu, G., Cooney, D.A., Ahluwalia, G.S., Kelley, J.A., Dalal, M., Fuller, R.W., Wilson, Y.A., and Jones, D.G. (1986). Thiazole-4-carboxamide adenine dinucleotide (TAD). Analogues stable to phosphodiesterase hydrolysis, *J. Med. Chem.*, *29*: 1726.

115. Davies, L.C., Stock, J.A., Barrie, S.E., Orr, R.M., and Harrap, K.R. (1988). Dinucleotide analogues as inhibitors of thymidine kinase, thymidylate kinase, and ribonucleotide reductase, *J. Med. Chem.*, *31*: 1305.
116. Tarusova, N.B., Novikova, Z.S., Prishchenko, A.A., Yakovleva, G.M., and Khomutov, R.M. (1982). Organophosphorus analogs of biologically active compounds. 11. Synthesis of analogs of acylphosphates made of methylenediphosphorylated acid esters, *Izv. Akad. Nauk S.S.S.R., Ser. Khim.*: 402.
117. Tyrtysh, T.V., and Tarusova, N.B. (1986). Organophosphorus analogs of biologically active compounds. XV. Synthesis of *C*-acylphosphonate ATP analog and of *C*-substituted diphosphonates, the pyrophosphate analogs, *Bioorg. Khim.*, *12*: 1282.
118. Tarusova, N.B., Osipova, T.I., Tyrtysh, T.V., and Biryukov, A.I. (1987). Phosphonate analogs of P^1,P^4-bis-(5'-adenosyl)tetraphosphate (Ap_4A), *Bioact. Mol.*, *3*: 195.
119. Tarusova, N.B., Kondrat'eva, N.O., Tyrtysh, T.V., Timofeev, V.P., and Gnuchev, N.V. (1988). Organophosphorus analogs of biologically active compounds. XVI. Comparison of the optical properties of zinc(II) complexes of P^1,P^4-bis(5'-adenosyl)tetraphosphate and its phosphonate analogs, *Zh. Org. Khim.*, *24*: 1474.
120. Milner-White, J., and Rycroft, D.S. (1983). The αβ-methylene analogues of ADP and ATP act as substrates for creatine kinase, ΔG_o for this reaction and for the hydrolysis of the αβ-methylene analog of ATP, *Eur. J. Biochem.*, *133*: 169.
121. Holy, A. (1987). Phosphonomethyl analogs of nucleotides and their derivatives, *Nucleosid. Nucleotid.*, *6*: 147.
122. Katti, S.B., and Agarwal, K. (1986). Separation of diastereoisomers of methylphosphonate dinculeotides, *Tetrahedron Lett.*, *27*: 5327.
123. Marugg, J.E., DeVroom, E., Dreef, C.E., Tromp, M., Van der Marel, G.A., and Van Boom, J.H. (1986). Synthesis of nucleic acid methylphosphonates *via* the 1-hydroxybenzotriazole phosphotriester approach, *Nucleic Acids Res.*, *14*: 2171.
124. Agrawal, S., and Goodchild, J. (1987). Oligodeoxynucleoside methylphosphonates: synthesis and enzymic

degradation, *Tetrahedron Lett.*, *28*: 3539.
125. Niewiarowski, W., Lesnikowski, Z.J., Wilk, A., Guga, P., Okruszek, A., Uznanski, B., and Stec, W. (1987). Diastereoisomers of thymidine 3'-*O*-(methanephosphonothioate): synthesis, absolute configuration and reaction with 3'-methoxyacetylthymidine under reaction with 3'-methoxyacetylthymidine under conditions of triester approach to oligonucleotide synthesis, *Acta Biochim. Pol.*, *34*: 217.
126. Rosenberg, I., and Holy, A. (1987). Synthesis of phosphonomethyl analogs of diribonucleoside monophosphates containing modified internucleotide bond, *Collect. Czech. Chem. Commun.*, *52*: 2572.
127. Holy, A., Nishizawa, M., Rosenberg, I., and Votruba, I. (1987). The effect of phosphonoylmethyl analogs of ribonucleoside 5'-diphosphates on (*E. coli*) polynucleotide phosphorylase-catalyzed reactions, *Collect. Czech. Chem. Commun.*, *52*: 3042.
128. Bergstrom, D., Romo, E., and Shum, P. (1987). Fluorine substituted analogs of nucleosides and nucleotides, *Nucleosid. Nucleotid.*, *6*: 53.
129. Roelen, H.C.P.F., De Vroom, E., Van der Marel, G.A., and Van Boom, J.H. (1988). Synthesis of nucleic acid methylphosphonothioates, *Nucleic Acids Res.*, *16*: 7633.
130. Rosenberg, I., and Holy, A. (1985). Phosphonylmethyl analogs of ribonucleoside 2',3'-cyclic phosphates and 2'(3')-nucleotide methyl esters: synthesis and properties, *Collect. Czech. Chem. Commun.*, *50*: 1507.
131. Tatsuoka, T, Imao, and Suzuki, K. (1986). Phosphono nucleoside. 1. Synthesis of 2,3'-anhydro-1'-deoxy-1'-phosphono-1-β-D-fructofuranosyluracil, *Heterocycles*, *24*: 617.
132. Tatsuoka, T, Imao, K., and Suzuki, K. (1986). Phosphono nucleoside. 2. Synthesis of 1'-deoxy-1'-phosphono-1-β-D-fructofuranosyluracil and 1',3'-dideoxy-1'-phosphono-1-β-D-fructofuranosyluracil, *Heterocycles*, *24*: 2133.
133. Tatsuoka, T, Imao, and Suzuki, K. (1986). 1'-Deoxy-1'-phosphono-β-D-fructofuranosyluracils, *Jpn Patent 61,205,295*.
134. Nakamura, C.E., Chu, S.-H., Stoeckler, J.D., and Parks, R.E. (1986). Inhibition of purine nucleoside phosphorylase

by 9-(phosphonoalkyl)hypoxanthines, *Biochem. Pharm.*, *35*: 133.
135. Reist, E.J., Sturm, P.A., Pong, R.Y., and Sidwell, R.W. (1989). Synthesis of phosphonic acid analogs of acyclovir (ACV) and ganciclovir (DHPG), *Nucleosid. Nucleotid.*, *8*: 919.
136. Kim, C.U., Luh, B.Y., Misco, P.F., Bronson, J.J., Hitchcock, M.J.M., Ghazzouli, I., and Martin, J.C. (1989). Synthesis and biological activities of phosphonylalkylpurine derivatives, *Nucleosid. Nucleotid.*, *8*: 927.
137. Reist, E.J., and Sturm, P.A. (1984). Phosphonic acid analogs of natural and synthetic nucleoside phosphates, and their use as antiviral agents, *PCT Int. Appl. WO 84 04,748.*
138. Prisbe, E.J., Martin, J.C., McGee, D.P.C., Barker, M.F., Smee, D.F., Duke, A.E., Matthews, T.R., and Verheyden, J.P.H. (1986). Synthesis and antiherpes virus activity of phosphate and phosphonate derivatives of 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine, *J. Med. Chem.*, *29*: 671.
139. Rosenberg, I., and Holy, A. (1987). Acyclic nucleotide analogs. Part II. Synthesis of potential prodrugs and metabolites of 9-(*S*)-(3-hydroxy-2-phosphonylmethoxypropyl)adenine, *Collect. Czech. Chem. Commun.*, *52*: 2792.
140. Webb, R.R., and Martin, J.C. (1987). A convenient synthesis of S-HPMPA [(*S*)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine], *Tetrahedron Lett.*, *28*: 4963.
141. Holy, A. (1989). Acyclic nucleotide analogs. Part V. Synthesis of 3-amino- and 3-azido analogs of 9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine (HPMPA), *Collect. Czech. Chem. Commun.*, *54*: 446.
142. Webb, R.R. (1989). The bis-trityl route to (*S*)-HPMPA, *Nucleosid. Nucleotid.*, *8*: 619.
143. Bayer, E., Gugel, K.H., Haegele, K., Hagenmaier, H., Jessipow, S., Koenig, W.A., and Zaehner, H. (1972). Phosphinothricin und Phosphinothricyl-Alanyl-Alanin, *Helv. Chim. Acta*, *55*: 224.
144. Gruszecka, E., Soroka, M., and Mastalerz, P. (1979). Preparation of D,L-phosphinothricin by Strecker reaction, *Pol. J. Chem.*, *53*: 937.
145. Gruszecka, E., Mastalerz, P., and Soroka, M. (1975). New synthesis of phosphinothricin and analogues, *Roczn. Chem.*, *49*: 2127.
146. Nachev, I. (1989). Total synthesis and enzyme-substrate

interaction of D-, DL-, and L-phosphinothricin, 'bialaphos' (SF-1293) and its cyclic analogs, *J. Chem. Soc., Perkin Trans. I*: 125.

147. Nachev, I. (1988). Organophosphorus analogs and derivatives of the natural L-amino carboxylic acids and peptides. II. Synthesis, enzyme-substrate interactions of "bialaphos" (SF-1293) and its cyclic and phosphinic amide type analogs, *Bull. Chem. Soc. Jpn., 61*: 3705.
148. Engel, R. (1988). Phosphorus addition at sp^2 carbon, *Org. React., 36*: 175.
149. Maier, L. (1967). Organische Phosphorverbindungen XXIX. Eine neue Methode zur Darstellung von dialkylaminomethylsubstituierten Phosphonig- und Phosphinsauren der allgemeinen Formel $R_2NCH_2PH(O)OH$ und $(R_2NCH_2)_2P(O)OH$, *Helv. Chim. Acta, 50*: 1742.
150. Lukszo, J., and Tyka, R. (1977). New protective groups in the synthesis of 1-aminoalkanephosphonic acids and esters, *Synthesis*: 239.
151. Gancarz, R., and Wieczorek, J.S. (1977). A useful method for the preparation of 1-aminoalkanephosphonic acids, *Synthesis*: 625.
152. Tyka, R., and Lukszo, J. (1978). α-Aminophosphonic acids, *Poland Patent 99,012*.
153. Lukszo, J., Kowalik, J., and Mastalerz, P. (1978). Advantages of using di(*p*-methylbenzyl) hydrogen phosphite in the synthesis of aminophosphonates from aldimines, *Chemistry Letters*: 1103.
154. Lukszo, J., and Tyka, R. (1978). New synthesis of diethyl *N*-acyl-α-aminophosphonates, *Pol. J. Chem., 52*: 321.
155. Lukszo, J., and Tyka, R. (1978). An improved procedure for preparing 1-aminophosphonic esters and 1-aminonitriles by C-N bond cleavage in benzylic carbinamine derivatives, *Pol. J. Chem., 52*: 959.
156. Issleib, K., Doepfer, K.P., and Balszuweit, A. (1978). Contribution to the synthesis of α-aminoalkane phosphonic acid dialkyl esters, *Z. anorg. allg. Chem., 444*: 249.
157. Redmore, D. (1980). α-Amino phosphonic acids, *U.S. Patent 4,235,809*.
158. Oleksyszyn, J., and Gruszecka, E. (1981). Amidoalkylation of phosphorous acid, *Tetrahedron Lett., 22*: 3537.

159. Kudzin, Z.H. (1981). Phosphocysteine derivatives; thioureidoalkanephosphonates *via* acetals, *Synthesis*: 643.
160. Issleib, K., Doepfer, K.P., and Balszuweit, A. (1981). Synthesis of α-aminoalkane phosphonic acids *via* benzaldehydic Schiff bases, *Z. Naturforsch., B: anorg. Chem., org. Chem., 36B*: 1392.
161. Szewczyk, J., Lejczak, B., and Kafarski, P. (1982). Transesterification of diphenyl phosphonates using the potassium fluoride/crown ether/alcohol system; Part 1. Transesterification of diphenyl 1-(benzyloxycarbonylamino)-alkanephosphonates, *Synthesis*: 409.
162. Lejczak, B., Kafarski, P., and Szewczyk, J. (1982). Transesterification of diphenyl phosphonates using the potassium fluoride/crown ether/alcohol system; Part 2. The use of diphenyl 1-aminoalkanephosphonates in phosphono-peptide synthesis, *Synthesis*: 412.
163. Kudzin, Z.H., and Majchrzak, M.W. (1989). 1-Amino-alkanephosphonic acids. Addition of diethyl phosphite to *N*-diisobutylaluminoaldimines, *J. Organomet. Chem., 376*: 245.
164. Elhaddadi, M., Jacquier, R., Petrus, F., and Petrus, C. (1989). A new and convenient synthesis of 1-(benzyloxy-amino)alkanephosphonic acids from oximes, *Phosphorus Sulfur, 45*: 161.
165. Baylis, E.K., Campbell, C.D., Dingwall, J.G., and Pickles, W. (1981). α-Aminophosphonous acids: a new class of biologically active amino acid analogs, *ACS Symposium Series, 171*: 183.
166. Baylis, E.K., Campbell, C.D., and Dingwall, J.G. (1984). 1-Aminoalkylphosphonous acids. Part 1. Isosteres of the protein amino acids, *J. Chem. Soc., Perkin Trans. I*: 2845.
167. Wasielewski, C., Antczak, K., and Rachon, J. (1979). Phosphoranaloge von Aminosaure und Peptiden; Eine einfache Methode zur Darstellung der α-Aminobenzylphos-phinsauren, *Z. Chem., 19*: 253.
168. Genet, J.P., Uziel, J., and Juge, S. (1988). Synthesis of α-aminophosphonic acids by palladium(0) alkylation of diethyl aminomethylphosphonic Schiff bases, *Tetrahedron Lett., 29*: 4559.
169. Genet, J.P., Uziel, J., Touzin, A.M., and Juge, S. (1990).

Synthesis of diethyl (1-aminoalkyl)phosphonates under solid-liquid phase-transfer catalysis conditions, *Synthesis*: 41.

170. Engel, R. (1988). *Synthesis of carbon-phosphorus bonds*, CRC Press, Boca Raton, FL.
171. Asano, S., Kitahara, T., Ogawa, T., and Matsui, M. (1973). The synthesis of α-amino phosphonic acids, *Agr. Biol. Chem.*, *37*: 1193.
172. Khomutov, R.M., Osipova, T.I., Zhukov, Y.N., and Gandurina, I.A. (1979). Organophosphorus analogs of biologically active substances. Communication 5. Synthesis of α-aminophosphonic acids and some of their derivatives, *Izv. Akad. Nauk S.S.S.R., Ser. Khim.*: 2118.
173. Kowalik, J., Kupczyk-Subotkowska, L., and Mastalerz, P. (1981). Preparation of dialkyl 1-aminoalkanephosphonates by reduction of dialkyl 1-hydroxyiminoalkanephosphonates with zinc in formic acid, *Synthesis*: 57.
174. Krzyzanowska, B., and Pilichowska, S. (1988). Synthesis of *O,O*-dialkyl 1-aminoalkanephosphonate *via N*-phosphinylated imines and enamines, *Pol. J. Chem.*, *62*: 165.
175. Osapay, G., Szilagyi, I., and Seres, J. (1987). Conversion of amino acids and dipeptides into their phosphonic analogs. Aminoalkylphosphonic acids and peptides. II, *Tetrahedron*, *43*: 2977.
176. Ku, B., and Oh, D.Y. (1988). Facile synthesis of α-phosphorylated α-amino acids, *Tetrahedron Lett.*, *29*: 4465.
177. Soroka, M. (1990). The synthesis of 1-aminoalkylphosphonic acids. A revised mechanism of the reaction of phosphorus trichloride, amides, and aldehydes or ketones in acetic acid (Oleksyszyn reaction), *Liebig's Ann. Chem.*: 331.
178. Tyka, R., and Haegele, G. (1989). Synthesis of aminobenzylphosphonous acids *via* direct amidoalkylation of hypophosphorous acid, *Phosphorus Sulfur*, *44*: 103.
179. Soroka, M., and Mastalerz, P. (1976). The synthesis of phosphonic and phosphinic analogs of aspartic acid and asparagine, *Roczn. Chem.*, *50*: 661.
180. Gruszecka, E., Soroka, M., and Mastalerz, P. (1979). Phosphonic analogs of α-methylaspartic and α-methylglutamic acids, *Pol. J. Chem.*, *53*: 2327.
181. Parsons, J.L., and Dubicki, H. (1979). *N*-(Phosphono-

acetyl)-L-aspartic acid, *U.S. 4,154,759*.
182. Starks, F.W., and Schulz, R.J. (1979). *N*-(Phosphonoacetyl)-±L-aspartic acid derivatives, *Ger. Offen. 2,849,396*.
183. Oleksyszyn, J., Gruszecka, E., Kafarski, P., and Mastalerz, P. (1982). New phosphonic analogs of aspartic and glutamic acid by aminoalkylation of trivalent phosphorus chlorides with ethyl acetyloacetate or ethyl levulinate and benzyl carbamate, *Monatsh. Chem., 113*: 59.
184. Sturtz, G., and Guillamot, G. (1984). Analogues phosphonoglutamiques d'amethopterine (methotrexate). Partie I. - Synthese, *Eur. J. Med. Chem.*: 267.
185. Kafarski, P., Lejczak, B., Mastalerz, P., Dus, D., and Radzikowski, C. (1985). *N*-(Phosphonoacetyl)amino phosphonates. Phosphonate analogs of *N*-(phosphonoacetyl)-L-aspartic acid (PALA), *J. Med. Chem., 28*: 1555.
186. Crooks, S.L., Robinson, M.B., Koerner, J.F., and Johnson, R.L. (1986). Cyclic analogs of 2-amino-4-phosphonobutanoic acid (APB) and their inhibition of hippocampal excitatory transmission and displacement of [^{3}H]APB binding, *J. Med. Chem., 29*: 1988.
187. Farrington, G.K., Kumar, A., and Wedler, F.C. (1985). Design and synthesis of new transition-state analogue inhibitors of aspartate transcarbamylase, *J. Med. Chem., 28*: 1668.
188. Subotkowski, W., Tyka, R., and Mastalerz, P. (1980). Phosphonic analogs of proline, *Pol. J. Chem., 54*: 503.
189. Pagani Zecchini, G., Paglialunga Paradisi, M., Torrini, I., and Lucente, G. (1989). A convenient route to pyrrolidine-2-phosphonic acid dipeptides, *Int. J. Pept. Protein Res., 34*: 33.
190. Lejczak, B., Kafarski, P., Soroka, M., and Mastalerz, P. (1984). Synthesis of the phosphonic acid analog of proline, *Synthesis*: 577.
191. Oleksyszyn, J., and Subotkowska, L. (1980). Aminomethanephosphonic acid and its diphenyl ester, *Synthesis*: 906.
192. Pulwer, M.J., and Balthazor, T.M. (1986). A convenient synthesis of aminomethylphosphonic acid, *Synth. Commun., 16*: 733.
193. Isbell, A.F., Berry, J.P., and Tansey, L.W. (1972). Amino phosphonic acids. III. The synthesis and properties of 2-aminomethylphosphonic and 3-aminomethylphosphonic acids, *J. Org. Chem., 37*: 3399.

194. Flynn, G.A., Beight, D.W., Bohme, E.H.W., and Metcalf, B.W. (1985). The synthesis of fluorinated aminophosphonic acid inhibitors of alanine racemase, *Tetrahedron Lett.*, *26*: 285.
195. Kowalik, J., Zygmunt, J., and Mastalerz, P. (1981). 1-Amino-2-mercaptoethanephosphonic acid, the phosphonic analog of cysteine, *Pol. J. Chem.*, *55*: 713.
196. Subotkowski, W., Kowalik, J., Tyka, R., and Mastalerz, P. (1981). The phosphonic analog of tryptophan, *Pol. J. Chem.*, *55*: 853.
197. Lacoste, A.-M., Cassaigne, A., and Neuzil, E. (1972). Synthese et proprietes de l'analogue phosphonique de l'arginine, *C. R. Acad. Sci. Paris, Ser. D*, *275*: 3009.
198. Lacoste, A.-M., Cassaigne, A., and Neuzil, E. (1972). Synthese et proprietes de l'analogue phosphonique de la citrulline, *C. R. Acad. Sci. Paris, Ser D*, *274*: 1418.
199. Nachev, I. (1988). Organophosphorus analogs and derivatives of the natural L-amino carboxylic acids and peptides. III. Synthesis and enzyme-substrate interactions of D-, DL-, and L-5-dihydroxyphosphinyl-3,4-didehydro-norvaline and their cyclic analogs and derivatives, *Bull. Chem. Soc. Jpn.*, *61*: 3711.
200. Glowiak, T., Sawka-Dobrowolska, W., Kowalik, J., Mastalerz, P., Soroka, M., and Zon, J. (1977). Absolute configuration of optically active aminophosphonic acids, *Tetrahedron Lett.*: 3965.
201. Huber, J.W., and Gilmore, W.F. (1979). Optically active α-aminophosphonic acids from ureidophosphonates, *Tetrahedron Lett.*: 3049.
202. Kowalik, J., Zygmunt, J., and Mastalerz, P. (1983). Determination of absolute configuarion of optically active 1-aminoalkanephosphonic acids by chemical correlations, *Phosphorus Sulfur*, *18*: 393.
203. Villanueva, J.M., Collignon, N., Guy, A., and Savignac, P. (1983). Preparation d'acides aminocarboxy-alkylphosphoniques optiquement actifs, *Tetrahedron*, *39*: 1299.
204. Schoellkopf, U., and Schuetze, R. (1987). Asymmetric synthesis of α-aminophosphonic acids. III. Asymmetric synthesis of diethyl (*S*)-(1-aminoalkyl)phosphonates using (+)-camphor as chiral auxiliary agent, *Liebig's Ann. Chem.*: 45.

205. Bartlett, P.A., and McLaren, K.L. (1987). Diastereoselectivity in the alkylation of chiral 2-aminomethyl-1,3,2-dioxaphosphorinane 2-oxides, *Phosphorus Sulfur*, *33*: 1.
206. Svedas, V., Solodenko, V.A., Kozlova, E.V., Kasheva, T.N., and Kukhar, V.P. (1990). Preparation of chiral (1-aminoalkyl)phosphonic acids *via* kinetic resolution of [1-(phenylacetylamino)alkyl]phosphonic acids using penicillin acylase, *U.S.S.R. Patent 1,544,775*.
207. Atherton, F.R., Hall, M.J., Hassall, C.H., Ringrose, P.S., and Lambert, R.W. (1977). Peptide derivatives of phosphonic and phosphinic acids and intermediates therefor, *U.S. Patent 4,016,148*.
208. Atherton, F.R., Hall, M.J., Hassall, C.H., Lambert, R.W., and Ringrose, P.S. (1979). Peptide derivatives, *Ger. Offen. 2,855,786*.
209. Allen, J.G., Havas, L., Leicht, E., Lenox-Smith, I., and Nisbet, L.J. (1979). Phosphonopeptides as antibacterial agents: metabolism and pharmacokinetics of alafosfalin in animals and humans, *Antimicrob. Agents Chemothr.*, *16*: 306.
210. Szewczyk, J., Lejczak, B., and Kafarski, P. (1982). A simple method for the preparation of diastereoisomeric phosphonodipeptides, *Experientia*, *38*: 983.
211. Issleib, K., Dopfer, K.P., and Balszuweit, A. (1987). Phospha-pharmaca - antibacterial and virucidic compounds, *Phosphorus Sulfur*, *30*: 633.
212. Teranishi, M., Takahashi, M., Muragata, T., Kase, H., and Kubo, K. (1986). Phosphorus-containing peptides, *Jpn. Patent 61 37,800*.
213. Teranishi, M., Takahashi, M., and Kase, H. (1986). Phosphorus-containing peptide derivatives, *Jpn. Patent 61 37,790*.
214. Nelson, V., and Mastalerz, P. (1984). Phosphorus-containing analogs of aspartame, *J. Pharm. Sci.*, *73*: 1844.
215. Izbicka-Dimitrijevic, E., Mastalerz, P., and Kochman, M. (1981). Dual effects of phenylalanine analogs on rabbit-muscle pyruvate kinase activity, *Eur. J. Biochem.*, *114*: 565.
216. Sturtz, G., Guillamot, G., Bordeaux, M., and Chauvet, M. (1984). Analogues phosphonoglutamiques d'amethopterine (methotrexate) Partie II. - Inhibition de la dihydrofolate reductase, *Eur. J. Med. Chem.*: 274.
217. Lejczak, B., Starzemska, H., and Mastalerz, P. (1981).

Inhibition of rat liver glutamine synthetase by phosphonic analogues of glutamic acid, *Experientia*, *37*: 461.
218. Flynn, G.A., and Giroux, E.L. The synthesis of an aminophosphonic acid converting enzyme inhibitor, *Tetrahedron Lett.*, *27*: 1757.
219. Ornstein, P.L., Schaus, J.M., Chambers, J.W., Huser, D.L., Leander, J.D., Wong, D.T., Paschal, J.W., Jones, N.D., and Deeter, J.B. (1989). Synthesis and pharmacology of a series of 3- and 4-(phosphonoalkyl)pyridine- and -piperidine-2-carboxylic acids. Potent *N*-methyl-D-aspartate receptor antagonists, *J. Med. Chem.*, *32*: 827.
220. Swiatek, J., and Tatarowski, T. (1987). NMR studies on the interaction of calcium and magnesium with phosphorus analogs of aspartic acid, *Pol. J. Chem.*, *61*: 699.
221. Valerio, R.M., Alewood, P.F., and Johns, R.B. (1988). Synthesis of optically active 2-(*tert*-butyloxycarbonylamino)-4-dialkoxyphosphorylbutanoate protected isosteres of *O*-phosphonoserine for peptide synthesis, *Synthesis*: 786.
222. Gancarz, R., and Wieczorek, J.S. (1980). Synthesis of phosphonic analogs of morphactins, *J. prakt. Chem.*, *322*: 213.
223. Wieczorek, J.S., and Gancarz, R. (1980). α-Aminophosphonic acid esters, *Poland Patent 105,252*.
224. Gancarz, R., Kafarski, P., Lejczak, B., Mastalerz, P., Wieczorek, J.S., Przybylka, E., and Czerwinski, W. (1983). Phosphonic analogues of morphactines, *Phosphorus Sulfur*, *18*: 373.
225. Lejczak, B., Kafarski, P., Gancarz, R., Jaskulska, E., Mastalerz, P., Wieczorek, J.S., and Krol, M. (1985). Phosphonic analogues of morphactins. Part III: peptides containing *P*-terminal 9-aminofluorene-9-ylphosphonic acid, *Pestic. Sci.*, *16*: 227.
226. Gancarz, R., Wielkopolski, W., Jaskulska, E., Kafarski, P., Lejczak, B., Mastalerz, P., and Wieczorek, J.S. (1985). Phosphonic analogues of morphactins. Part IV: 9-aminofluoren-9-ylphosphine oxides, *Pestic. Sci.*, *16*: 234.
227. Kafarski, P., Lejczak, B., Gancarz, R., Jaskulska, E., Mastalerz, P., Wieczorek, J.S., and Zbyryt, I. (1985). Phosphonic analogues of morphactins. Part V: peptides containing 9-aminofluoren-9-ylphosphine oxides, *Pestic. Sci.*, *16*: 239.
228. Stremler, K.E., and Poulter, C.D. (1987). Methane- and

difluoromethanediphosphonate analogues of geranyl diphosphate: hydrolysis-inert alternate substrates, *J. Am. Chem. Soc.*, *109*: 5542.

229. McClard, R.W., Fujita, T.S., Stremler, K.E., and Poulter, C.D. (1987). Novel phosphonylphosphinyl (P-C-P-C) analogues of biochemically interesting diphosphates. Synthesis and properties of P-C-P-C- analogues of isopentenyl diphosphate and dimethylallyl diphosphate, *J. Am. Chem. Soc.*, *109*: 5544.
230. Biller, S.A., Forster, C., Gordon, E.M., Harrity, T., Scott, W.A., and Ciosek, C.P. (1988). Isoprenoid (phosphinylmethyl)phosphonates as inhibitors of squalene synthetase, *J. Med. Chem.*, *31*: 1869.
231. Biller, S.A. (1989). Preparation of alkenylphosphinylmethylphosphonates as squalene synthetase inhibitors, *Eur. Patent Appl. 324,421*.
232. Kolodyazhnyi, O.I., Yakovlev, V.I., Grishkun, E.V., Kovalenko, A.B., and Kukhar, V.P. (1987). Carbon-phosphorus analogs of natural prenylpyrophosphates, *Dopov. Akad. Nauk Ukr. RSR, Ser. B: Geol. Khim. Biol. Nauki*: 51.
233. Kolodyazhnyi, O.I., Yakovlev, V.I., Grishkun, E.V., Kovalenko, A.B., and Kukhar, V.P. (1987). Carbon-phosphorus analogs of natural prenylpyrophosphates, *Dopov. Akad. Nauk Ukr. RSR, Ser. B: Geol. Khim. Biol. Nauki*: 52.
234. Sekine, M., Fatatsugi, T., Yamada, K., and Hata, T. (1982). Silyl phosphites. Part 20. A facile synthesis of phosphoenolpyruvate and its analogue utilizing *in situ* generated trimethylsilyl bromide, *J. Chem. Soc., Perkin Trans. I*: 2509.
235. McFadden, H.G., Harris, R.L.N., and Jenkins, L.D. (1987). Potential inhibitors of phospho*enol*pyruvate (PEP) carboxylase: phosphonic acid substrate analogues derived from Stobbe-type condensations of ethyl 3-(diethoxyphosphinoyl)propanoate, *Aust. J. Chem.*, *40*: 1619.
236. Hoppe, I., Schoellkopf, U., Nieger, M.,, and Egert, E. (1985). Asymmetric synthesis of α-aminophosphonic acids. 2. Asymmetric addition of a chiral cyclic phosphite to a cyclic imine. Synthesis of the phosphonic acid analogs of D- and L-penicillamine, *Angew. Chem.*, *97*: 1066.
237. Drauz, K., Koban, H.G., Martens, J., and Schwarze, W.

(1985). Phosphonic and phosphinic acid analogs of penicillamine, *Liebig's Ann. Chem.*: 448.

238. Denzel, T., Breuer, H., Treuner, U.D., Cimarusti, C.M., Koster, W.H., and Sykes, R.B. (1981). Phosphonic acid derivatives of 7-[(2-amino-4-thiazolyl)oximino]cephalosporins, *Brit. UK Pat. Appl. 2,071,664*.
239. Tsunemoto, D., Nishide, K., Yamamura, M., Kobori, T., and Sato, K. (1989). Preparation of 3-(phosphinylmethyl)-cephalosporins as antibiotic agents, *Jpn. Patent 01 93,595*.
240. Zygmunt, J., Kafarski, P., and Mastalerz, P. (1978). Preparation of oxoalkanephosphonic acids, *Synthesis*: 609.
241. Tang, K.-C., and Coward, J.K. (1983). Synthesis of acyl phosphonate analogues of biologically important acyl phosphates: *N*-(2-amino-10-methylpteroyl)-5-amino-2-oxopentanephosphonic acid, *J. Org. Chem.*, *48*: 5001.
242. Lazarus, R.A., Benkovic, P.A., and Benkovic, S.J. (1979). The synthesis and properties in enzymic reactions of substrate analogs containing the methylphosphonyl group, *Arch, Biochem. Biophys.*, *197*: 218.

CHAPTER 12

GLYCEROPHOSPHOLIPIDS: SOME RELIABLE AND RECENT SYNTHESES

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I. Introduction

Phospholipids are major cell components which have an important role in determining membrane composition and function. Chemically, they are phosphoesters or -diesters derived from: a) a hydrophobic alcohol, in most cases glycerol esterified with fatty acyl functions, *i.e.* a 1,2-diacyl-*sn*-glycerol derivative, or an *N*-acylsphingosine, and b) a hydrophilic alcohol, particularly an aminoalcohol or a polyol.

In biological membranes glycerophospholipids (GPL) contain usually a saturated fatty acyl (FA) group in the 1-position and an unsaturated FA group at the 2-position. There is a stereogenic site at the 2-position of the GPL, the naturally occurring 1,2-diacyl-*sn*-glycerol-3-phospholipid existing with the (*R*) configuration.

Naturally occurring phospholipids have provided useful models for biochemical and membrane research, but the need for well defined chemical structures for biochemical and biophysical studies can be satisfied only by chemical synthesis. Synthetic methods fall into two categories: a) semisynthesis in which an inexpensive natural phospholipid is cleaved enzymatically followed by chemical replacement of the cleaved substituent, a method limited to small quantities and still may not generate chemically defined phospholipids owing to the heterogeneity of the source material, and b) total synthesis which often involves assembly of a 1,2-diradylglycerol followed by phosphorylation.

The chemical syntheses of GPL and their analogues bound to a variety of groups have proven to be useful in physical studies of model and biological membranes. The physical, chemical, and biochemical properties differ markedly between enantiomers of a chiral GPL, and also with the racemic mixture. To study the behavior of natural GPL, it is necessary to synthesize it in its

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natural form. The synthesis of the unnatural enantiomer is also useful for the study of the role of binding to receptors in the action of GPL on cellular processes.

In addition to their well-known membrane structural-based properties, there are also GPL with important functional properties in cells. Because of their low natural abundance, new chemical approaches have been developed to synthesize them.

The synthesis of non-hydrolyzable, acylamino, and phosphorothioate analogs of GPL has been useful for structure and dynamic studies of biomembranes, membrane-bound enzymes, and analysis of biological activity as well as for liposome studies. Liponucleotides have been synthesized as prodrugs of nucleoside derivatives.

This review is concerned with reliable and recent total syntheses of some important GPL. There exist numerous prior reviews which should be consulted for a complete view of the subject.[1-7]

II. Acyl GPL and Intermediates

The classical approach to chiral diacyl GPL preparation was developed by Fischer and Baer starting from the readily available D-mannitol.[8,9] The bisacetonide of D-mannitol was prepared by reaction with acetone in the presence of zinc chloride and the resultant diol was cleaved with lead tetraacetate. Catalytic reduction produced (*S*)-glycerol acetonide which was further converted to *sn*-glycerol 3-phosphate and 1,2-distearoyl-*sn*-glycerol 3-phosphate.[10,11] Improvements have been made on this approach in recent years[12-20] resulting in higher yields (62%) with simpler work-up procedures. Notable improvements include the use of periodate[21-23] along with potassium carbonate[24,25] in the cleavage of the D-mannitol diacetonide, and sodium borohydride for the reduction of the intermediate aldehyde.[23,26] A one-pot approach has also been described.[20] Other protecting groups for the hydroxyl functions of the D-mannitol have also been studied.[27,28]

Symmetric-chain phosphatidyl cholines (PC) have been prepared by the acylation of *sn*-glycerol 3-phosphocholine.[29-37] The acylating species is usually the fatty-acid anhydride, and the procedures are performed in the presence of a molar excess of catalysts such as DMAP. Without catalyst the acylation requires higher temperatures and long reaction times resulting in extensive acyl and phosphoryl migration.[38] An efficient diacylation has been

reported in >90% yield in 3 hr at room temperature using 2.5 equivalents of the fatty acyl anhydride and 2.1 equivalents of DMAP with DMF as the solvent.[39,40] More recently ultrasound assisted acylation has been accomplished.[41]

In a two-step procedure asymmetric diacyl glycerophosphocholines have been synthesized from commercially available *sn*-glycerol 3-phosphocholine.[42] This procedure accomplishes the differential acylation in high yield (88%) with <3% acyl migration.

The synthesis of mixed-acid phosphatidylcholines with widely different chain lengths has been reported by acylation of lysophosphatidylcholines with a ten-fold excess of fatty acid anhydrides in the presence of 4-pyrrolidinopyridine as a catalyst.[43] While the reaction proceeds in yields of >90% with <1% acyl migration, the reaction requires a large quantity of the rather expensive fatty acid anhydride. Decreasing the amount of anhydride requires higher temperatures to achieve the acylation at which further acyl migration occurs. There has recently been reported a stereoselective acylation procedure *via* lipase-catalyzed reaction using vinyl or isopropenyl esters of carboxylic acids as activated acylating reagents.[44,45]

There are disadvantages to the early reported approaches[8,9] to GPL synthesis. These include the multiple steps required (nine from D-mannitol to GPL for symmetrically substituted products, and fourteen for asymmetrically substituted products), the fact that the D-mannitol diacetonide is unstable on storage,[1] and 1,2-isopropylidene-*sn*-glycerol undergoes partial racemization during storage,[3,46] and complete racemization in the presence of traces of acid.[26] However, configurational stability is retained for several months in the presence of small amounts of sodium hydroxide when stored at 0-5°[47] or if the material is worked-up at pH 7.2 and sodium bicarbonate is added prior to distillation.[48] In spite of these disadvantages, the approach starting with D-mannitol remains the basis for much of the phospholipid synthesis preformed today.

In addition to D-mannitol, other natural products have been used as chiral precursors for the synthesis of natural and unnatural GPL. In contrast to the (*R*)-glyceraldehyde acetonide and (*S*)-glycerol acetonide, the enantiomeric starting materials are not readily available. They can be prepared from L-mannitol, an unnatural material which is synthesized from L-arabinose through a lengthy series of reactions.[49]

A simplified procedure for the preparation of 2,3-*O*-isoprop-

ylidene-*sn*-glycerol starting from L-arabinose has been reported.[50] This procedure has been improved and used to obtain 1-acyl-*sn*-glycerol.[51] As the acyl chain length is increased, the cleavage of the ketal linkage becomes more difficult and the harsh conditions required result in isomerization. However, the ketal can be removed under mild conditions and without isomerization using dimethylboron bromide.

The 2,3-*O*-isopropylidene-*sn*-glycerol has been used to prepare the configurationally unnatural *sn*-glycerol-1-phosphocholine.[52]

L-Ascorbic acid has been used as an inexpensive chiral starting material for the preparation of (*R*)-glycerol acetonide.[53] The saturated diol function of ascorbic acid was easily protected as the acetonide by dissolution in an excess of acetone containing a catalytic amount of acetyl chloride. Subsequent treatment with sodium borohydride, basic hydrolysis, lead tetraacetate cleavage, and final sodium borohydride reduction gave the (*R*)-glycerol acetonide in 50-60% yield. This procedure has been modified and adapted to large scale synthesis.[54,55]

Alternative syntheses of (*S*)-glyceraldehyde and (*R*)-glycerol acetonides include oxidative α-diol cleavages of D-sorbitol,[56] L-galactono-1,4-lactone,[57] L-arabinose,[58] (*2R,3R*)-dimethyl tartrate,[59] and a route from L-erythrulose.[60]

Derivatives in both the (*R*)- and (*S*)-glyceraldehyde and glycerol series have been prepared by selective cleavage of a suitable protected chiral (*2R,3S*)-butane-1,2,3,4-tetrol derivative.[61] Moreover, chiral glycerides and optically active glycidol have been prepared from commercially available L- and D-serine. Both enantiomeric series can be produced by the same reaction sequence.[62]

Racemic glycidol has been used to obtain the asymmetrically substituted (1-saturated-2-unsaturated) diacylglycerol using the levulinoyl protecting group, removable with hydrazine hydrate.[63] This protecting group has also been used in the synthesis of monoacylglycerides[64] and dithioester analogs of PC.

Asymmetric epoxidation of allyl alcohol[65] produces optically active glycidol, and recent modifications of the procedure[66] provide a very attractive synthon for the preparation of chiral GPL.[67] Titanium-assisted nucleophilic opening of the optically active glycidol has been used to obtain the 1-acyl-*sn*-glycerol without significant loss of starting enantiomeric excess.[68-69] The

opening was performed with carboxylate ion at 0° with no formation of the regioisomer. The 1-acyl-*sn*-glycerol obtained was used as an intermediate for a new synthesis of chiral GPL.[69] The limiting factor of this approach was the low-yielding (<50%) titanium-assisted opening of the glycidol.

When an alcohol was used as the nucleophilic reagent and the reaction was performed at 70-75° without solvent, 1-alkoxy-2,3-propanediol was obtained (45-59%) with formation of ~5% of the 2-alkoxy isomer.[70]

Higher yields were obtained using a Lewis-acid catalyzed (BF_3 etherate) opening of the ring of (*R*)- and (*S*)-glycidyl arenesulfonates with fatty acid anhydrides to produce symmetrically substituted diacyl-*sn*-glycerols and the corresponding GPL.[71] The arenesulfonate group protects the *sn*-3-position from acyl migrations, and phosphorylation is performed after later conversion to the iodide. Direct phosphorylation of the tosylate resulted in partial racemization. The method can be applied to the synthesis of the configurationally unnatural 2,3-diacyl-*sn*-glycero-1-phosphocholine, can be modified to accommodate a different phosphorus-containing head-group, can be used to generate a chiral (or achiral) triglyceride, but it could not be used for unsaturated acyl phosphocholines.

Using benzyl alcohol as a nucleophilic reagent in the presence of BF_3 etherate produced 1-*O*-benzyl-*sn*-glycerol-3-*O*-arenesulfonate.[72] The subsequent sequence of alkylation, debenzylation (hydrogenolysis), acylation, and phosphorylation gives 1-acyl-2-*O*-alkyl-3-*sn*-glycerophosphocholine in high yield and with high (93-96%) enantiomeric excess.

A convenient synthesis of mixed-acid glycerophosphocholine has been reported starting from 1-*O*-acyl-2-*O*-benzylglycerol-3-*O*-(β,β,β-trichloroethyl) carbonate.[73] This method requires no chromatographic purification until the final step. The Zn/acetic acid removal of the trichloroethoxycarbonyl group allows the synthesis of labile or functionalized glycerophosphocholines with no acyl migration. The method is applicable to *sn*-glycerol derivatives by using 1-*O*-acyl-2-*O*-benzyl-*sn*-glycerol as starting material.

Diacyl and mixed acid diacyl glycerols have been prepared (85-95% yield) from 3-allyl protected 1,2-glycerol and fatty acids in the presence of DCC/DMAP.[74] Removal of the allyl ether group was accomplished by isomerization to the enol ether derivative followed by cleavage under neutral conditions with NBS/THF.

Subsequent phosphorylation by acid catalyzed coupling with a dialkyl phosphoramidite followed by a one-step deprotection-substitution reaction gave the GPL in 65% overall yield. This procedure avoids the risk of base catalyzed acyl migration and permits easy purification of the non-ionic intermediates.

The first synthesis of a diacylglycerophosphocholine hydroperoxide was reported using a combination of lipoxygenase catalyzed peroxidation, lipase-catalyzed stearoylation, and DCC mediated esterification.[75] Linoleic acid was converted to its hydroperoxide *via* lipoxygenase-catalyzed peroxidation, and then to its methyl ester, followed by perketal protection of the hydroperoxy group and hydrolysis to the perketal acid. Lipase-catalyzed enantiotopic group-specific stearoylation of 2-*O*-benzyl glycerol with vinyl stearate produced an alcohol which was phosphorylated with phosphorus oxychloride and choline tosylate, and debenzylated by hydrogenolysis to yield 1-stearoyl-*sn*-glycero-3-phosphocholine. Esterification of this material with the previously noted perketal in the presence of DCC followed by purification and mild acidic hydrolysis gave the asymmetric diacylglycerophosphocholine hydroperoxide. The toxicity of this material toward human endothelial cells is being examined.

A stereospecific synthesis of 2-amidophosphatidylcholines starting from L-serine has been reported.[76] This approach follows an earlier report that replacement of the 2-ester function by an amide group abolishes the susceptibility of the material to enzymatic hydrolysis.[77] The 2-amido analogue of PC was found to be a potent inhibitor of phospholipase A_2,[78] as well as fluoroketone GPL analogues.[79]

In an attempt to prepare more stable and functional liposomes, the synthesis of 1,2-dimyristoyl-1,2-deoxyphosphatidylcholines has ben reported.[80] Two routes were reported for the preparation of the key intermediate, 1,2-dimyristoylamidopropan-3-ol. These include starting from 2,3-dibromopropionic acid, and from L-asparagine. The phosphocholine group was introduced by standard methods.

The synthesis of several acylaminophospholipids have been reported as possible inhibitors of phospholipase A_2.[81] Routes for the syntheses of these materials begin with 1-aminopropanediol and from 2-aminopropanediol. The unnatural 3-dodecanoyl-2-dodecanoylamino-2-deoxy-*sn*-glycero-1-phosphocholine has also been prepared starting from L-serine.

III. Ether Phospholipids

Since the discovery of platelet activating factor (PAF) as the first bioactive phospholipid,[82-84] a great number of synthetic schemes have been reported for homologs and analogues of PAF.[4,27,85-88] The purposes of these efforts have been to find the structural requirements for activity (measured as ability to stimulate platelet aggregation, the enhancement of the desirable biological actions (development of a "magic bullet" for anti-hypertensive activity) with minimization of untoward effects, and to develop an antagonist of PAF.

The first reliable method for the synthesis of 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphorylcholine (PAF) was reported starting from 1-*O*-alkyl-*sn*-glycerol.[89] The major disadvantage of this approach was the early attachment of the 2-acetyl group which allowed undesirable acyl migration to occur. This approach is still used with certain modifications, *e.g.* use of methoxytrityl as a protecting group. To avoid acyl migration, 2-chlorophenyl *O,O*-bis(1-benzotriazolyl) phosphate has been used in a very mild phosphorylation procedure.[90]

Recently, this general approach has been used to prepare a photoreactive, radioactive, aggregating analogue of PAF starting from racemic isopropylidene glycerol.[91] The procedure involved the introduction of a phthalimidoundecyl group as the ether function using the mesylate ester of the alcohol. The photoreactive and radioactive functionality was introduced in the last step by converting the phthalimido group into a photoreactive azide and radioiodination with $Na^{125}I$. The analogue thus produced has been used to identify PAF binding sites in rabbit platelet membranes.[92,93]

The original approach has also been modified to avoid acyl migration by introducing the phosphorylcholine function at the 3-position of the glycerol backbone prior to acetylation of the 2-position.[27,94,95] The starting material for this approach was D-mannitol, yielding the 1-*O*-alkyl-*sn*-glycerol in eight steps.

Unsaturated PAF species have been obtained by protecting the 2-hydroxyl group with a benzoyl function (rather than a benzyl group), removable by alkaline hydrolysis.[96] The intermediate 1-*O*-alkyl-*sn*-glycerol was prepared from L-serine.[62]

Several unsaturated PAF analogues have been prepared using the methoxyethoxymethyl (MEM) group for the protection of the

2-position hydroxyl function.[97] A standard method[98] was used for the preparation of 2-*O*-[(methoxyethoxy)methyl]-1,3-benzylidene glycerol and removal of the benzylidene group[99] prior to phosphorylation with phosphorus oxychloride and choline tosylate. After removal of the protecting MEM group, the racemic PAF analogues were obtained by acetylation of the intermediate lyso material using acetic anhydride with DMAP. The *sn*-1-unsaturated-alkyl lyso compound was later used to obtain radioactively labelled PAF upon reduction with tritium gas.[100]

The *sn*-1-saturated alkyl lyso intermediate species was used for the preparation of a racemic 2-*O*-methylcarbamyl analogue of PAF.[101] Other 2-carbamyl analogues of PAF were synthesized in a similar manner to provide lipids which were used to prepare liposomes which were more stable hydrolytically.[102]

Numerous analogues of PAF have been prepared using the fundamental approach described by Godfroid, *et al.*[89] These include PAF labelled with tritium in the alkyl chain,[103] labelled in the choline moiety,[104] labelled with an azido group,[105] and labelled with a fluorescent 9-anthranylmethyl group.[106] All of the materials thus prepared exhibit biological activity comparable to that of PAF and are of great value in the stimulation of binding sites and development of receptor antagonist toward PAF.[107-108]

There has recently been described the synthesis of potential PAF-hapten starting from commercially available 2,3-*O*-isopropylidene L-glycerol.[109] The terminal methyl of an unsaturated alkyl group at the *sn*-1-position was replaced by a carboxyl group, and its conjugation with amino groups of proteins was expected to raise the production of specific antibodies against PAF. The unsaturated alkyl chain in this species was introduced by the reaction of the 2,3-*O*-isopropylidene L-glycerol with 16-mesyloxy-(*E*)-8-hexadecanoic acid. The unsaturated modified PAF could be tritiated to generate a radioactively labelled PAF analogue.

In a similar manner an aldehydic (*sn*-1-alkyl chain) analogue of PAF was synthesized for the generation of hapten-protein conjugates and the production of specific PAF antibodies.[110] The reactive aldehyde function at the chain terminus was generated by ozonolysis of an olefinic linkage in the final step of the synthesis. The PAF-analogue was conjugated to thyroglobulin *via* reductive amination for production of PAF specific antibodies. The purified antibodies bind stereospecifically to tritiated PAF and the solid phase thus developed is anticipated to be applicable to the

quantitation of PAF in biological systems.

A spin-labelled derivative of PAF has been prepared[111] starting from 2,3-*O*-isopropylidene L-glycerol using a previously described approach.[112] The spin-labelled group was introduced at the 2-*O*-position using 4-doxylpentanoic acid in the presence of DCC as described by Patel, *et al.*[113] This spin-labelled analogue was shown to be as potent as ET-18-OCH_3 in antitumor activity. The ESR spectrum demonstrated the material to have a more restricted mobility in a membrane than its ester-linked counterparts, a finding that may be of importance in elucidating the mechanism by which the antitumor ether-linked phospholipids perturb the structure of cellular membranes.

A trideuterated-*O*-alkyl PAF derivative has been prepared from racemic isopropylidene glycerol for use as an internal standard in quantitative mass spectrometric studies.[114] The tritium label was introduced at the methyl terminus of the alkyl chain at an early stage of the overall synthesis *via* tosylate displacement using tritiated methyl magnesium iodide. Subsequent deprotection and functionalization was accomplished using a previously developed method.[115]

The total synthesis of lyso platelet activating factor (lysoPAF; 1-*O*-alkyl-*sn*-glycero-3-phosphocholine) and its enantiomer has been reported starting from commercially available racemic isopropylidene glycerol.[116] Following initial alkylation to generate the racemic 1-*O*-alkylglycerol, the material was converted into racemic PAF using standard procedures. This material was then treated with snake venom phospholipase A_2 to give the lysoPAF of the natural configuration in optically pure form. The unnatural enantiomer, not susceptible to the action of the enzyme, was converted to the lysoPAF by deacylation with methanolic NaOH. This approach is also applicable to the preparation of unsaturated lysoPAF (natural and unnatural enantiomers).

Cyclic tin intermediates have also been used for the synthesis of PAF analogues.[117] Starting with 2-*O*-benzylglycerol, initial treatment with dibutyltin oxide gave an intermediate which could be converted to racemic PAF using standard methods.[94]

The synthesis of 1-*O*-hexadecyl-2,3-di-*O*-acetyl-4-phosphorylcholine, a homologous analogue of PAF, has been reported starting with diacetone glucose.[118] The material has been shown to be a weak antagonist of PAF.

The D- and L-tartaric acids have also been utilized to prepare

stereospecifically the natural 1-*O*-hexadecyl-2-*O*-acetyl-*sn*-glycero-3-phosphocholine (C16-PAF) and its unnatural enantiomer. In eleven steps, C16-PAF was produced in 21% overall yield utilizing the C-2 stereogenic site of the tartaric acid for the stereogenic site of the target material.[119] With modifications of the method, the 2-*O*-methyl analogue as well as the *N*-methylpiperidine and *N*-methylpyrrolidine analogues were prepared. These materials were found to possess 10-fold higher activity in the aggregation assay and 3-fold greater activity in the anti-hypertension assay than the natural C16-PAF.[46] As the route involves a deprotection *via* hydrogenolysis, it can not be applied to unsaturated PAF analogues.

(*S*)-(-)-Malic acid has also been used as a starting materials for the preparation of natural C16-PAF.[120] The C16-PAF was obtained in a nine-step synthesis in 50% overall yield.

Serine served as the starting material for a stereospecific synthesis of the amide analogue of PAF and related derivatives.[121,122] Phosphorylation in this procedure was accomplished using 2-chloro-2-oxo-1,3,2-dioxaphospholane followed by incorporation of a choline function by treatment with trimethylamine. The 1-*O*-octadecyl-2-*N*-acetamidoaminodeoxy-*sn*-glycerol-3-phosphorylcholine exhibited potent platelet activation. Racemic 3-octadecanamido-2-ethoxypropylphosphocholine was found to inhibit a late step in HIV replication.[122a]

An noted, numerous naturally occurring chiral starting materials have been used for the preparation of PAF and analogues thereof. However, these routes are generally quite long. A shorter and more efficient route which is independent of the availability of naturally occurring chiral starting materials has been described for the synthesis of PAF and its analogues of either enantiomeric form and with saturated or unsaturated alkyl chains.[123] This approach begins with the commercially available chiral glycidol arenesulfonates. The key feature of the approach is the excellent regio- and stereospecific opening of the glycidyl ring with long-chain alcohols (saturated or unsaturated) in the presence of BF_3 etherate. Among the advantages of using this approach compared to the titanium(IV) alkoxides are improved yields, higher enantiomeric excess of the desired material, the absence of competitive ring opening processes involving other nucleophilic species, and easier work-up procedures.

A naphthyvinyl-labelled ether-ester analogue of phosphatidylcholine (NVPC) has been synthesized and used to assay

phospholipase A_2 using HPLC with fluorescent detection of NVPC and lyso-NVPC.[124] The naphthylvinyl group was prepared by a Wittig reaction, and, after deprotection and activation, was introduced into the *sn*-1-position of 2,3-*O*-isopropylidene-*sn*-glycerol prepared from L-serine.[62]

Several GPL covalently labeled with the 7-nitrobenz-2-oxa-1,3-diazol-4-yl (NBD) group have been synthesized and used as fluorescent probes of biological and model membranes.[125]

Diether analogues of the natural GPL are important molecules bearing biological activity, acting on cytoplasmic targets. *O*-Alkyl-GPL with C-16 or C-18 alkyl chains at the *sn*-1-position and an *O*-methyl group at the *sn*-2-position have been noted to exhibit antimicrobial activity,[126] immunomodulatory properties,[127,128] and potent cytotoxic activity toward various tumor cells.[129]

Different explanations regarding the mechanism of cytotoxic activity have been proposed, including membrane interactions and protein kinase C inhibition.[130] However, the biological investigations have in the main used racemic mixtures of 1-*O*-alkyl-2-*O*-methyl-GPL; the availability of the separate enantiomeric forms should provide better tools for understanding the process.

The glycidyl tosylate method previously noted for the preparation of PAF analogues has been applied to the preparation of diether-PC species.[131] Using this approach a variety of alkyl groups can be introduced at the 2-*O*-position. This approach allows the preparation of both enantiomeric forms of the materials with high optical purities.

L-Methylglycerate has also been used as a chiral starting material for the preparation of diether-PC materials.[132,133] This approach involved trityl protection of the ultimate *sn*-3-position followed by methylation of the *sn*-2-position prior to reduction of the carboxylate function and introduction of the alkyl group. Detritylation and phosphorylation using 2-chloro-2-oxo-1,3,2-dioxaphospholane and ring opening with trimethylamine completed the synthesis.

The preparation of deuterium and carbon-13 labelled 1,2-di-*O*-hexadecyl-*sn*-glycero-3-phosphorylethanolamine and -choline has been accomplished starting with commercially available 3-*O*-benzyl-*sn*-glycerol.[134] Alkylation was facilitated with the use of a phase-transfer catalyst and a strong base. No monoalkylation

product was detected in this procedure. Phosphorylation was performed by a previously explored method.[135] The labelled compounds were characterized by FAB mass spectrometry. Subsequent work resulted in a convenient chirospecific synthesis of deuterium and carbon-13 labelled 1-*O*-alkyl-2-*O*-alkyl-*sn*-glycero-3-phosphorylethanolamine and -choline starting from commercially available 2,3-*O*-isopropylidene-*sn*-glycerol.[136] The key step in this approach was the lithium aluminum hydride reduction of 2,3-*O*-benzylidene-1-*O*-hexadecyl-*sn*-glycerol to provide as a major product the 3-*O*-benzyl-1-*O*-hexadecyl-*sn*-glycerol.

The synthesis of a conformationally restricted 1,2-dialkyl ether phospholipid having a C-2 methyl group and the 2-*O*-methyl linkage has been reported starting from 2-methylprop-2-en-1-ol.[137] Subsequently the 1,2-di-*O*-hexadecyl compound bearing a C-2 methyl group was prepared using a variation of the same technique.[138] The racemic modification was prepared in both instances. The replacement of the normal C-2 hydrogen of the glycerol backbone by a methyl group results in restricted conformational freedom at the interface region of PC bilayers, similar to those GPL whose backbone carbon atoms have been incorporated into a ring.[139-145] This class of synthetic GPL is useful for understanding the role of flexibility of bond rotation in the backbone and conformational changes at the interface in interactions with proteins and other lipids, as well as for understanding the conformational preference of phospholipase A_2 for substrate phospholipids.[142,146] Conformationally restricted chiral cyclic PAF analogues derived from 2-deoxy-D-erythro-pentose have been synthesized.[147] These analogues were poor antagonists and agonists of PAF.

The antitumor and antimetastic activities of the ether GPL have been explained by the direct accumulation of the GPL analogues within tumor cells which disrupts the normal GPL metabolism and leads to cell death. The synthesis of a radioiodinated ether GPL expected to concentrate within the neoplastic cell and thereby allow visualization *via* scintigraphic imaging has been reported.[148] In this instance phosphorylation was performed according to a previously reported method[149] using 2-bromoethyl dichlorophosphate

IV. Thio-glycerophospholipids

Acylthioester and alkylthioether glycerophospholipids have

been synthesized as structural analogues of GPL intended to help elucidate the mechanisms of GPL biological activity. Such materials have also been used as substrates for spectrophotometric assays of phospholipases.

A chiral synthesis of a di-thioester analogue of phosphatidylcholine, 1,2-bis(heptanoylthio)-1,2-dideoxy-*sn*-glycero-3-phosphorylcholine has been reported starting from 1-trityl-*sn*-glycerol.[150] The thio ester functionalities were introduced with the proper stereochemistry *via* a series of reactions including tosylation of the *sn*-3-position, cyclic trithiocarbonate formation by reaction with potassium methyl xanthate, reduction, and acylation. The starting material was prepared from D-mannitol, and the choline functionality introduced using previously reported procedures.[151,152] A similar synthesis of racemic material was reported starting with glycidol.[153] More recently the glycidol approach was applied to the synthesis of chiral thio ether GPL analogues starting with allyl alcohol which was converted to the chiral glycidol (optical purity >98%) *via* asymmetric epoxidation using optically active diisopropyl tartrate as the chiral adjunct.[154] The epoxide ring was opened by treatment with a long-chain alkyl mercaptan in the presence of traces of butyl lithium, and the intermediate subsequently converted to a thio analogue of PAF using a previously reported approach.[150]

Methyl L-glycerate was used as the chiral starting material in the preparation of 1-thioether-2-*O*-methyl-*sn*-glycero-3-phosphocholines.[134] The procedure involved introduction of the sulfur by displacement of a substituted sulfonate function from the *sn*-1-position using potassium thioacetate, followed by reduction to the thiol and subsequent alkylation. Direct displacement of the sulfonate function by alkyl sulfide was quite inefficient.

A general synthetic route to thioether choline phospholipids has been described starting from diethyl malonate or glycerol.[155] This approach has been used to prepare 3-hexadecylmercapto-2-methoxymethylglycero-1-phosphorylcholine (Ilmofosine), one of the most potent antineoplastic thioether analogues reported thus far.

The thio-PAF analogue, 1-deoxy-1-octadecylthio-2-*O*-acetyl-*sn*-glycero-3-phosphocholine, has been synthesized starting from (*S*)-1-mercaptopropane-2,3-diol.[156] The corresponding 2-deoxy-2-thioacetyl analogue has also been reported using 1,2-isopropylidene-*sn*-glycerol as the chiral starting material.[157] Both syntheses utilized classical protection/deprotection methods.

A further stereospecific synthesis of the biologically active

2-thio-PAF analogue has been reported using the commercially available D-α,β-isopropylideneglycerol-γ-tosylate as the source of chirality.[158,159] Migration of the thioacetyl group and loss of chirality was prevented through the use of Sephadex LH-20 for purifications. The stereochemical integrity of the product was established by enzymatic assay. This material has been demonstrated to be a potent antihypertensive phospholipid. Intermediates in this approach were utilized for the preparation of additional analogues of PAF, those bearing thiomethyl or long-chain thioacyl functions at the 2-position. Both the simple 2-thio-PAF analogue and the long-chain thioacyl analogues are completely hydrolyzed by phospholipase A_2 and thus are useful mechanistic probes for kinetic studies.

There has also been reported the stereospecific synthesis of 2-thiophosphatidylcholines using methyl D-glycerate as the chiral source.[160] The thioacyl function was introduced at the 2-position of the trityl-protected methyl D-glycerate by displacement of a substituted arenesulfonate ester group with inversion of configuration. The phosphodiester moiety was introduced using a bromoethyl dichlorophosphate/trimethylamine sequence.[115]

Racemic cysteine has been used as the chiral starting material for the preparation of a 2-aza-1-thia-1,2-deoxy-3-glycerophosphorylcholine analogue of PAF.[161] S-Alkylation of the free cysteine was accomplished with 1-bromooctadecane in the presence of KOH and ethanol, followed by acetylation of the free amino function. The optically active analogue was prepared starting with commercially available (*S*)-*N*-acetylcysteine using an analogous approach.

D-Serine has also been used to provide the stereogenic center in a synthesis of a PAF analogue, 1,2-deoxy-1-thiohexadecyl-2-*N*-acylamino-*sn*-glycero-3-phosphorylcholine.[162]

Recently there has been reported the synthesis of azathia-PAF analogues with oxygen- and sulfur-containing side-chains starting from 1-acetylthio-3-hydroxy-2-propylamine hydrochloride.[163,164] Phosphorylation was accomplished using 2-chloro-2-oxo-1,3,2-dioxaphospholane with ring opening upon treatment with trimethylamine to generate the choline portion of the analogue. A series of azathia-PAF analogues containing a methioninol were also synthesized starting with methionine.[165] This series included sulfides, sulfoxides, and sulfones.

Analogues of GPL in which sulfur is present in place of

phosphate esteric oxygen have also been reported. Racemic diacylthiophosphatidylcholines have been synthesized using procedures reported earlier for related structures.[166,167] Overall yields in this synthesis were low owing to significant by-products being generated from an intermediate thiol. The characteristics of the material are quite dependent on the chain length. While the dioctanoyl system was easily dispersed and rapidly hydrolyzed to produce a free thiol group in the presence of phospholipase C, the didecanoyl system was not. When 5,5'-dithiobis-(2-nitrobenzoic acid) was included as a thiol reactive chromogenic agent, the dioctanoyl species served as a useful substrate for continuous spectrophotometric assay for phospholipase C.

Recently thiophosphoric acid esters with a C-S-P linkage (phosphorothiolates) have been prepared by a Michaelis-Arbuzov reaction between *S*-substituted thioimides and trimethyl or tris(trimethylsilyl) phosphite.[168] This approach is anticipated to allow the synthesis of thiophosphatidylserine and new thio-PAF analogues.

Racemic thionophospholipids (P=S) have been prepared by the reaction of diacylglycerol with $P(S)Cl_3$ in the presence of choline tosylate.[169,170] These materials have been used in ^{31}P-NMR studies of lipid polymorphism. Chiral species in this series have been synthesized starting with D-mannitol.[171] The diastereo- isomeric thiono compounds (stereogenic at both C-2 and P) were distinguished by the stereospecific action of phospholipases A_2 and C. These thiono analogues of phosphatidylcholine, along with the corresponding analogues of phosphatidylglycerol and phosphatidylethanolamine, have also been synthesized starting with 1,2-diacyl-*sn*-glycerol.[172]

Using the phosphoramidite approach of Bruzik, Salamonczyk, and Stec,[172] a thionophosphono analogue of PAF has been prepared.[173] In other work the stereoisomers differing in configuration at phosphorus have been prepared and investigated.[174] This approach used chemical techniques previously described[172,175,176] along with the stereospecific action of bee venom phospholipase A_2 to effect separation of the stereoisomers. The activities of the two diastereoisomers in platelet aggregation and serotonin secretion were compared with that of 1-*O*-hexadecyl-2-*O*-acetyl-*sn*-3-glycerophosphocholine. The (S_P) diastereoisomer only exhibited the same activity as the natural

material, suggesting that the phosphate group is likely involved in interaction with the receptor.

In further efforts, the diastereoisomers of 1,2-dipalmitoyl-*sn*-glycero-3-thiophospho-1-inositol have been prepared and separated.[177,178] The procedure involved phosphitylation of protected inositol using $ClP(OCH_3)N(i\text{-}Pr)_2$. The phosphorothioate analogues, differing in their configuration about phosphorus, of phosphatidylserine have been synthesized from 1,2-dipalmitoyl-*sn*-glycerol and *N*-trityl-L-serine methoxymethyl ester using this same phosphitylating agent.[179] Again, the diastereoisomers were differentiated using phospholipase A_2. The chiral thiophospholipds have proved to be useful analogues for the study of the mechanism of enzyme reactions involving GPL and in probing the role of the phosphate head group of GPL in various membrane functions.

Finally, a 2-*O*-thiophosphonate-substituted analogue of PAF has been reported.[180]

V. Phosphatidylinositols

Phosphatidylinositol (PI), one of a number of phospholipids found in the membranes of animal cells, is a key intermediate for the production of the intracellular second messengers D-*myo*-inositol 1,4,5-triphosphate (IP3) and diacylglycerol.[181,182,182a] Initially, PI is phosphorylated by a kinase to produce phosphatidylinositol 4-phosphate (PIP), followed by further kinase-catalyzed phosphorylation producing phosphatidylinositol 4,5-diphosphate (PIP2) which is cleaved by a receptor-coupled phospholipase C on stimulation by a range of neurotransmitters, hormones, and growth factors. The IP3 released by hydrolysis controls the liberation of calcium ion from an intracellular store into the cytosol.

In order to understand the relative importance of the several enzymes involved, supplies of pure, chemically and stereochemically well defined PI analogues were required. The synthesis of PI analogues has been treated in several reviews.[183,185]

A mild and convenient procedure for the synthesis of *myo*-inositol phosphates has been reported.[186] Partially protected *myo*-inositol, prepared by standard procedures, was phosphitylated using *N,N*-diisopropyl dibenzyl phosphoramidite/tetrazole in near quantitative yield. Oxidation of the phosphite with MCPBA followed by cleavage of the protecting groups provided the free IP3

without the need of ion-exchange chromatography for purification. Numerous other syntheses of IP3 and IP4 have also been reported.[187-198]

Recently the enantiomeric forms of *myo*-inositol 1,3,4,5-tetraphosphate (IP4) have been synthesized by the phosphitylation of dibenzylated *myo*-inositol.[199] Oxidation with MCPBA followed by hydrogenolysis produced the IP4 species in 76% yield. The *myo*-inositol 1,4,5-triphosphate and 1,4,5-tris(thiophosphates) have also been prepared using 2-diethylamino-1,3,2-benzodioxaphosphepane as a phosphitylating agent followed by oxidation and deprotection by hydrogenolysis (or the use of sodium naphthalide/THF in the instance of the thiophosphate).[200]

The *myo*-inositol 1-phosphorothioate 4,5-bisphosphate has been prepared and attached to a fluorescent reporter group at the 1-position. This material is used in probing the interactions of the second messenger species with proteins.[201,202]

Other types of analogues of the natural phosphatidylinositol phosphates have also received attention. Resolved *trans*-cyclohex-3,5-dien-1,2-diol, produced from benzene, has been used for the synthesis of *chiro*-inositol 2,3,5-trisphosphate and 1,2,4,5-tetrakisphosphate.[203]

Phosphonate analogues of *myo*-inositol phosphate have been reported.[204] The 5-methylenephosphonate analogue of D-*myo*-inositol 1,4,5-trisphosphate was synthesized and shown to be a long-lived agonist of calcium mobilization.[205]

Diastereoisomers of an analogue of phosphatidylinositol 4,5-bisphosphate were synthesized by a non-regioselective phosphorylation of racemic 3,6-di-*O*-benzyl-4,5-bis-*O*-(dianilino phosphoryl)-*myo*-inositol with racemic 1,2-di-*O*-stearoylglycero 3-phosphate in the presence of 2,4,6-triisopropylbenzenesulfonyl chloride, followed by deprotection.[206,207] More recently has been synthesized 1-*O*-(1,2-di-*O*-palmitoyl-*sn*-glycero-3-phosphoryl)-D-*myo*-inositol 4,5-bisphosphate by phosphitylation of 1,2-di-*O*-palmitoyl-*sn*-glycerol with optically active and suitably protected D-*myo*-inositol.[208] In a similar manner, using a chiral suitably protected maninositase having a free hydroxyl at the 1-position of the D-*myo*-inositol portion, has been prepared 1-*O*-(1,2-di-*O*-palmitoyl-*sn*-glycero-3-phosphoryl)-2-*O*-D-mannopyranosyl-D-*myo*-inositol, a fragment of mycobacterium phospholipids.[209]

The thiophosphono analogues of phosphatidyl inositol in

both the (R_P) and (S_P) stereoisomeric forms have been synthesized by phosphitylation of a suitably protected inositol using an enzymatic approach to separate the stereoisomeric forms.[177] A similar approach was used in other work in which the diasteroeisomeric forms were separated by silica gel chromatography.[178] These diastereoisomers are of interest for testing the stereoselectivity of phosphatidylinositol-specific phospholipase C and for use as possible antimetabolites in inositol phosphate metabolism. Both reports noted that the stereoisomer that is hydrolyzed by phospholipase C has the same configuration at phosphorus as that of the thiono-analogue of phosphatidylcholine which is hydrolyzed by phospholipase A_2.

1,2-Di-*O*-palmitoyl-*sn*-glycer-3-yl-D-*myo*-inositol 1-phosphate has been synthesized in a convenient manner.[210] Resolution of the starting protected inositol was accomplished using camphanic acid chloride. The method was later improved by a selective phosphorylation of (+)-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol.[210a]

The syntheses of 1-fluoro-1-deoxy-*scyllo*-inositol and 2-fluoro-2-deoxy-1-phosphatidyl-*scyllo*-inositol were reported as the first examples of fluorinated analogues of inositol and phosphatidylinositol.[211]

A convenient method for the synthesis of the four stereoisomers of dihexadecanoyl phosphatidylinositol has been reported.[212] Acid labile pentaprotected *myo*-inositols, resolved using camphanic acid chloride, were coupled with chiral phenyl dihexadecanoylglyceryl phosphates, followed by deprotection, to yield the desired materials. The product diastereoisomers have been used to study the stereoselectivity of a partially purified phosphatidylinositol 4-kinase derived from human erythrocyte membranes. The results indicate that the chirality of the inositol ring is crucial for efficient phosphorylation, whereas the chirality of the glycerol moiety is relatively unimportant. The similarities in phosphorylation rates of the naturally occurring phosphatidylinositol and its synthetic stereochemical counterparts suggest that the enzyme is relatively tolerant to variations in the fatty acid composition.

The synthesis of ether-linked analogues of phosphatidylinositol has been reported.[213] This work has in common with that previously noted the requirement for suitable distinguishing protection of the inositol ring hydroxyls with removal under mild conditions and the capability for resolution of the inositol system. A

racemic isosteric phosphonate analogue of phosphatidyl-*myo*-inositol was prepared by trichloroacetonitrile mediated condensation of a protected *myo*-inositol with 3,4-dipalmitoyloxy-butyl-1-phosphonic acid followed by removal of all protecting groups.[213a] The optically active phosphonate analogues were synthesized by alkylation of the α-lithio anion of a properyl protected *myo*-inositol-1-(methylphosphonate) diester with 1,2-isopropylidene-*sn*-glycerol-3-trifluoromethanesulfonate, followed by protective group manipulation.[231b] In another approach, phosphatidylinositol isolated from yeast was used.[214] This material was subjected to selective protection of hydroxyl groups, phosphorylation, and deprotection to generate phosphatidylinositol 4-phosphate of the proper stereochemistry, as well as the unnatural phosphatidylinositol 6-phosphate.

VI. Liponucleotides

Synthetic and naturally occurring nucleosides have been found to possess potent cytotoxic activity in cell culture and in tumor-bearing animals. However, the lack of preferential uptake by tumor cells, due in part to the poor lipid solubilities of the nucleosides, together with their rapid catabolism *via* deaminase enzymes and their toxicity have limited their use as chemotherapeutic agents.

One approach to overcome these drawbacks has been to attach the drug (nucleoside) to a non-toxic carrier molecule that protects the molecule from degradation, carries it to the cell, and then releases it by enzymatic or chemical action. Several liponucleotide pro-drugs have been prepared in which the nucleoside has been covalently attached to a phospholipid.[215-218]

The methodology most often used to prepare liponucleotides has involved the condensation of a phosphatidic acid with a suitably protected nucleoside in the presence of TPS or DCC for the monophosphate species,[216] or with an activated nucleoside monophosphomorpholidate for the diphosphate species.[219]

A recent application of this approach has combined the antineoplastic properties of ether and thioether analogues of PAF with the favorable activity of Ara-C-phospholipid conjugates.[217,220-222] The rationale for this effort is that the conjugates, upon enzymatic action, will release two cytotoxic agents, Ara-C and an ether or thioether lipid, to attack two targets, nucleic acid synthesis and membranes, of neoplastic cells.

Treatment of AIDS patients with azidothymidine (AZT, Zidovudine) prolongs life and reduces morbidity, but fails to reduce isolation rates of HIV virus from peripheral blood mononuclear cells. This may be due to inadequate inhibition of virus production by macrophages, a major reservoir of HIV. Several phospholipids having AZT or a dideoxynucleoside as the polar head group, with the object to deliver larger proportions of antiretroviral nucleosides into macrophages as liposomal liponucleotides, have been synthesized.[223] Inhibitors of the reverse transcriptase of HIV were coupled with phosphatidic acid in the presence of TPA or *via* nucleoside-monophosphate morpholidate. These liposomal liponucleotides demonstrated antiretroviral activity in HIV injected U937 and CEM cells. Amidoalkyl, oxyalkyl, and thioalkyl ether lipids have been chemically linked to anti-HIV-1 nucleosides (AZT, DDi) through phosphate and phosphonate linkages. These conjugates have shown promising *in vitro* anti-HIV-1 activity.[223a]

The cyclic enediol phosphoryl (CEP) method of activation has been used for the preparation of phosphatidyl-3'-nucleosides.[224] The approach involved the successive couplings of two alcohols, the protected nucleoside and the diacylglycerol, using the CEP-O-CEP reagent followed by removal protective groups. For the preparation of the isomeric phosphatidyl-5'-nucleoside the order of couplings was reversed. Another difunctional phosphorylating agent,[225] as well as the hydrogen phosphonate method,[226] has used for the preparation of nucleoside-phospholipid conjugates. The latter approach has also been modified for the preparation of nucleoside-3'-hydrogen-phosphonothioate species.[227]

Cytidine diphosphate diacylglycerols (CDP-diacylglycerol) are metabolic liponucleotides, substrates for the biosynthesis of several classes of GPL. They serve as activated intermediate donors of the phosphatidyl function to alcohols to form the corresponding GPL. Several CDP-diacylglycerol species have been synthesized,[228] but phosphonate analogues, where the C-P bond makes them resistant to hydrolytic enzymes, and thereby potential inhibitors of GPL biosynthesis, have been reported for very few of them. Two phosphonic analogs of CDP-diacylglycerol still containing the central pyrophosphate moiety have been synthesized[229] following a reported procedure.[230] The synthesis of a CDP-diacylglycerol analogue containing a non-transferable phosphatidyl group has been described[231] by the reaction of a novel ylid reagent[232] with a previously reported diether aldehyde.[233] The CDP-diacylglycerol analogue was found to be a

very powerful inhibitor of platelet PI synthetase.[234] A silyl reagent with potential use in the synthesis of polyphosphate analogs has also been reported.[235] The preparation of phosphonolipids and phosphinolipids will be considered in more detail in the following section.

VII. Phosphono and Phosphino Analogues of GPL

The replacement of one of the P-O bonds in the phosphate diester moiety of GPL by the less reactive P-C bond (phosphonate) or both P-O bonds by P-C bonds (phosphinate) results in analogues that are resistant to hydrolytic enzymes, resistance to phospholipase C if the P-C bond is on the "glycerol side", to phospholipase D if the P-C bond is on the "head-group side", or resistance to both in the phosphinate analogues. The analogues are of interest as potential enzyme inhibitors and as specific antimetabolites able to inhibit or perturb a given normal metabolic process.

Numerous phosphono and phosphino analogues of GPL have been synthesized following the independent pioneering work of Baer and Rosenthal. This subject has been extensively reviewed.[1,236-239]

The synthesis of natural phosphonolipids (derivatives of aminoethylphosphonic acid) has been accompanied by the coupling of a diacylglycerol to a 2-substitutedethylphosphonic acid derivative.[20,240,241] Phosphono analogues of PAF bearing a shortened chain in the choline portion have been prepared in a similar manner.[242,243] This type of PAF analogue was found to have neither agonist nor antagonist activity relative to the natural PAF. The corresponding isosteric (3-substitutedpropylphosphonic acid derivative) of PAF was synthesized in a similar manner and was found to be significantly less potent (1/3000) compared to the natural PAF.[244] The syntheses of other related analogues of PAF have also been reported.[245] Of particular interest are the analogues having the C-P bond in the backbone portion, both isosteric[244] and "shortened" non-isosteric[243] species.

Reports of synthetic phosphono analogues of GPL (phosphonolipids) have been the subject of numerous reports. These syntheses involved the formation of the P-C bond using an Arbuzov or Becker reaction performed on a backbone-related alkyl halide.[246] The development of silyl esters of trivalent phosphorus acids and ester cleavage processes utilizing silyl halides has

facilitated these synthetic efforts.[236,247-256]

Recently the first phosphonate analogues of phosphatidylinositol were prepared using long-chain-alkylphosphonic acids and ω-carboalkoxyalkylphosphonic acids in coupling reactions with suitably protected *myo*-inositol.[204]

The synthesis of phosphonic acid analogues of cardiolipin have been reported recently[257] using an Arbuzov reaction for the generation of the C-P bond. A similar reaction sequence has been used for the preparation of an analogue of cardiolipin in which two phosphorus centers are present (and two C-P bonds).[258,259]

The use of phosphonates as analogues of natural phosphates has been successful for the regulation of metabolic processes in a number of instances.[236] While there has been a special interest in the use of isosteric analogues, in some situations the isosteric phosphonate was incapable of substituting for the natural phosphate in enzymatic processes.[260-263] Blackburn has noted[238] two main points of differences which could cause this inability to serve in place of the natural materials: the second pK_a of the phosphonic acid shows it to be a less acidic species than the natural phosphate, and the lack of non-bonded electrons at the site adjacent to the phosphorus in the analogue. In order to provide a region of high electron density near the phosphoryl center, analogues have been synthesized bearing an olefinic linkage[256] or a hydroxyl group[264,265] adjacent to it.

Phosphonic acid analogues of phospholipids have also been prepared which incorporate amide or thioamide linkages into the acyl functions along the backbone.[180] The synthesis used serine as a source of stereogenic carbon, following a previously developed method.[122]

Completely non-hydrolyzable, optically active, isosteric and non-isosteric phosphinate analogues of GPL have been prepared.[233] In addition to the replacement of normal ester linkages at phosphorus with C-P linkages, the normal acyl linkages of GPL were replaced by ether functions, giving an inert character to the analogue without disturbing their normal physical properties. The original approaches were improved[266] through the use of phase transfer processes previously described.[267]

The synthesis of a diester phosphinate analogue of phosphatidylcholine has been reported involving an unusual C-P bond forming reaction,[268,269] and an amination following a

previously reported method.[270] Using a similar approach, the synthesis of a phosphinate analogue of cardiolipin has been reported.[259]

VIII. Phosphorylation

Phosphorylation is one of the most important of the steps in the synthesis of GPL. The formation of phosphate ester linkages has been reviewed extensively.[5,6,271]

Performance of phosphorylation in the synthesis of phospholipids requires the consideration of specific problems. These include: protection of functional groups which are not to be phosphorylated and their subsequent deprotection; the lability of acyl esters, alkenyl groups, and other labile functions; the tendency of acyl groups to migrate to available hydroxyl groups; the tendency of intramolecular transesterification of phosphate functions involving nearby hydroxyl groups; the shielding of the hydroxyl groups by long hydrophobic acyl or alkyl chains which can hinder phosphorylation; and the tendency of GPL to undergo hydrolysis and oxidation.

To accomplish phosphorylation a variety of reagents may be used. A prominent approach has been through the use of diaryl chlorophosphates, bis(2,2,2-trichloroethyl) chlorophosphate, and enolic chlorophosphates, all of which allow facile removal of the protecting phosphate ester linkages in the presence of unsaturated linkages.

Another simple and effective approach uses dimethyl chlorophosphate. The protecting methyl groups are readily removed in the presence of other functionalities by transsilylation.[271,272] Another new phosphorylating agent, dibenzyl fluorophosphate, has found use in GPL synthesis.[274]

The highly reactive system of phosphorus oxychloride and base has also been used for the preparation of phosphomonoesters,[6] but its applicability has been questioned on the grounds that it contains more than one reactive group leading to the formation of by-products and to the chlorination of the starting alcohol. However, it has been shown[2] that direct phosphorylation of disubstituted glycerol with this reagent is possible using the proper reaction conditions and ratio of reactants to eliminate side-reactions. Diacylglycerolphosphoryl dichlorides have been condensed with choline tosylate in the presence of pyridine to generate lecithin.[152] Alternative approaches starting with the diacylglycerolphosphoryldichloride include initial conversion into a

cyclic dioxaphospholane[275] or oxazaphospholane.[135] The mild reaction conditions, high yields, and the avoidance of protecting groups makes this approach efficient for the synthesis of a variety of GPL.[3]

Another approach involves the use of the silver salt of a phosphate diester in reaction with 1,2-diacyloxy-3-iodopropanes. This approach proceeds in high yield and is not accompanied by acyl migration, but is expensive and is not generally applicable to GPL containing unsaturated acyl groups. Protecting ester linkages suitable for use with unsaturated acyl groups have been developed, but there remain some difficulties.

Once a monoester has been generated, the preferred approach for the formation of the phosphodiester function is by the interaction of the phosphomonoester derivative with the appropriate alcohol in the presence of one of several monophosphate activating additives, such as trichloroacetonitrile or an arylsulfonyl chloride.[43,276-278] The use of activating agents such as the sterically hindered 2,4,6-triisopropylbenzenesulfonyl chloride or 2,4,6-trimethylbenzenesulfonyl chloride results in high yield phosphorylations, practically without by-products and under mild conditions, allowing the preparation of GPL bound to unstable, fluorescent, or isotopically labelled groups.

Another approach has been through the use of carbonyl diimidazole to generate the highly reactive imidazolide of the phosphatidic acid. This approach has overcome the poor solubility problems associated with choline salts and the low reactivity of secondary alcohols.

A classic approach to the formation of phosphate diester linkages in GPL involves the use of an activated phosphate associated with the ultimate head-group portion of the GPL. This is shown in the synthesis of lecithin starting with a 1,2-diacylglycerol and 2-bromoethyl phosphorodichloridate.[115] The reaction sequence is then completed by hydrolysis and methylation. Experimental details of the preparation, purification, and use of the critical reagent here have been summarized.[149,166,270,279] Variation in the distance between the phosphate and the ammonium ion site has been accomplished using various ω-bromoalkyl phosphorodichloridates.[280,281]

When poor yields were obtained using this approach,[282] owing to sterically hindered substituted glycerol substrates, a more reactive reagent, 2-chloro-2-oxo-1,3,2-dioxaphospholane was

used.[76,81,121,122,144,146,283-285] An attractive feature of this approach is the C-O bond fission that both deprotects and establishes the second desired ester bond simultaneously. A slight excess of trimethylsilyl triflate accelerates the nucleophilic opening of cyclic phosphates with tertiary amines, affording products in high purity, isolable without chromatography.[285a] The phosphate ester can also easily be converted to a polar head group other than choline.[81,132]

Even more reactive phosphorylating agents (for hindered alcohols) were prepared using tervalent phosphorus compounds. Phosphitylating reagents such as 2-chloro-1,3,2-dioxaphosphacyclopentane and its amide derivative have been prepared and used to obtain phosphatidylcholines and their thio analogues.[169,286-288] The cyclic phosphites, obtained in 83-93% yield, were readily oxidized by nitrogen dioxide or the addition of elemental sulfur. The cyclic phosphates (thiophosphates) were then alkylated with trimethylamine to form the choline derivatives. This method combines the advantages of the triester approach with the high reactivity of activated P(III) compounds.

Other reagents have been used as well. 2-Chloro-3-methyl-1,3,2-oxazaphosphacyclopentane, prepared from *N*-methylethanolamine and phosphorus trichloride, and 1,3-dimethyl-1,3,2-diazaphosphoacyclopentane were synthesized and used to prepare nitrogen analogues of phospholipids.[289,290] However, the hydrolysis step required drastic conditions due to the stability of phosphoric acid amides. It was found[290a] that hydrolysis with dimethylsulfate/water opened the ring under mild conditions and yielded the quaternary choline derivative directly. It was also found[290b] that cyclic phosphoramidates undergo P-N cleavage simply by treatment with water in the absence of added acid, probably catalyzed by traces of acid present from a previous oxidation stage.

Chloro(*N,N*-diisopropylamino)methoxyphosphine has been synthesized[172] and used for the synthesis of phosphorothioate analogues of PAF, phosphatidylserine, thiosphingomeylins, and phosphatidylinositol.[173,174,177-179,291] The utility of systems of the type $(RO)_2PNR_2$/tetrazole for ester formation with phosphomonoesters has been reported,[292] and has been applied successfully to the synthesis of *myo*-inositol phosphates.[186,192,199] Benzyloxybis(*N,N*-diethylamino)phosphine has been used in the synthesis of *rac*-distearoyl-phosphatidyl-

6-glucose and -6-galactose.[287,288] It has also been used in the preparation of analogues of phosphatidylinositol.[208]

Phenyl- and methyldichlorophosphine have been used as efficient phosphitylating agents in the preparation of a variety of GPL derivatives.[293] These reagents have been used successfully in syntheses without acyl migration and for the inclusion of unsaturated acyl functions. Other phosphitylating agents have been developed and used for a variety of syntheses.[200,294,295] It has been argued,[74] however, that phosphitylations still suffer from the same disadvantage afflicting the previous methods of phosphorylation, *i.e.* base catalysis which leads to mixtures of isomers which are difficult to separate. An acid-catalyzed approach has been claimed to be superior.[74]

The utility of the H-phosphonate approach has been demonstrated for a variety of phospholipids and analogues thereof,[296,297] as well as to the synthesis of other phosphate esters.[226,227]

IX. Conclusion

With the enormous amount of synthetic methods described in the literature, chemists appear to be well prepared for the synthesis of any specific GPL needed for membrane investigations, structure-function studies, or for the elucidation of biological mechanisms wherein GPL are involved.

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XI. Bibliography

1. Rosenthal, A.F. (1975). Chemical synthesis of phospholipids and analogues of phospholipids containing carbon-phosphorus bonds, *Methods Enzymol.*, *35*: 429.
2. Eibl, H. (1980). Synthesis of glycerophospholipids, *Chem. Phys. Lipids*, *26*: 405.

3. Eibl, H. (1984). Phospholipids as functional constituents of biomembranes, *Angew. Chem., Int. Ed. Eng., 23*: 257.
4. Mangold, H.K. (1988). Synthesis of biologically active ether lipids, *Prog. Biochem. Pharmacol., 22*: 1.
5. Ramirez, F., and Marecek, J.F. (1985). Synthesis of phosphodiesters: the cyclic enediol phosphoryl (CEP) method, *Synthesis*: 449.
6. Stepanov, A.E., and Shvets, V.I. (1986). Formation of phosphoester bonds in phosphoglyceride synthesis, *Chem. Phys. Lipids, 41*: 1.
7. Christie, W.W. (1987). Simple and complex lipids: their occurrence, chemistry and biochemistry, *Natural Product Reports, 4*: 113.
8. Fischer, H.O.L., and Baer, E. (1937). Synthesis of optically active glycerides, *Naturwissen., 25*: 588.
9. Baer, E., and Fischer, H.O.L. (1939). Studies on acetone-glyceraldehyde, *J. Biol. Chem., 128*: 263.
10. Baer, E., and Kates, M. (1950). Synthesis of enantiomeric α-lecithins, *J. Am. Chem. Soc., 72*: 942.
11. Baer, E. (1965). From the trioses to the synthesis of natural phospholipids: A research trail of forty years, *J. Am. Oil Chem. Soc., 42*: 257.
12. Tipson, R.S., and Cohen, A. (1968). Reaction of some sulfonic esters of D-mannitol with methoxide; synthesis of 2,3:4,5-dianhydro-D-itidol, *Carbohydr. Res., 7*: 232.
13. Kohan, G., and Just, G. (1974). A simplified synthesis of 1,2:5,6-di-*O*-isopropylidene-D-mannitol, *Synthesis*: 192.
14. Chittenden, G.J.F. (1980). Isopropylidenation of D-mannitol under neutral conditions, *Carbohydr. Res., 87*: 219.
15. Chittenden, G.J.F. (1980). An improved simplified synthesis of 1,2:5,6-di-*O*-isopropylidene D-mannitol, *Carbohydr. Res., 84*: 350.
16. DeBost, J.L., Gelas, J., and Horton, D. (1983). Selective preparation of mono- and diacetals of D-mannitol, *J. Org. Chem., 48*: 1381.
17. Kierstead, R.W., Faraone, A., Mennona, F., Mullin, J., Guthrie, R., Crowley, B., Simko, L.C., and Blaber, J. (1983). β_1-Selective adrenoreceptor antagonist. 1. Synthesis and β-andrenergic blocking activity of a series of binary-(aryloxy)propanolamines, *J. Med. Chem., 26*: 1561.

18. Kuszmann, J., Tomori, E., and Meerwald, I. (1984). The synthesis of 1,2:5,6-di-*O*-isopropylidene-D-mannitol: A comparative study, *Carbohydr. Res.*, *128*: 87.
19. Kuszmann, J., Tomori, E., and Meerwald, I. (1984). 1,2:4,6 And 1,2:3,6-di-*O*-isopropylidene-D-mannitol, *Carbohydr. Res.*, *132*: 178.
20. Yamauchi, K., Une, F., Tabata, S., and Kinoshita, M. (1986). Synthesis of glycerophosphonolipids containing aminoalkylphosphonic acids, *J. Chem. Soc., Perkin Trans. I*: 765.
21. Le Cocq, J., and Ballou, E.C. (1964). On the structure of cardiolipin, *Biochemistry*, *3*: 976.
22. Golding, B.T., and Ioannou, P.V. (1977). Rapid synthesis of 3-*O*-benzyl-*sn*-glycerol and 2-*O*--benzylglycerol, *Synthesis*: 423.
23. Eibl, H. (1981). An improved method for the preparation of 1,2-isopropylidene-*sn*-glycerol, *Chem. Phys. Lipids*, *28*: 1.
24. DuMont, R., and Pfander, H. (1983). Optisch aktiv C_5-Bausteine zur Synthese von naturlich vorkommenden Terpenen, *Helv. Chim. Acta*, *66*: 814.
25. Hafele, B., and Jager, V. (1987). A short synthesis of (*S*)-5-hydroxy-2-penten-4-olide from D-mannitol *via* 2,3-*O*-isopropylidene-D-glyceraldehyde, *Ann.*: 85.
26. Baldwin, J.J., Raab, A.W., Mensler, K., Arison, B.H., and McClure, D.E. (1978). Synthesis of (*R*)- and (*S*)-epichlorohydrin, *J. Org. Chem.*, *43*: 4876.
27. Peters, U., Bankova, W., and Welzel, P. (1987). Platelet activating factor synthetic studies, *Tetrahedron*, *43*: 3803.
28. Eibl, H., and Wooley, P. (1986). Synthesis of enantiomerically pure glyceryl esters and ethers. 1. Methods employing the precursor 1,2-isopropylidene-*sn*-glycerol, *Chem. Phys. Lipids*, *41*: 53.
29. Cubero-Robles, E., and van Berg, D. (1969). Synthesis of lecithins by acylation of D-(*sn*-glycero-3-phosphoryl)choline with fatty acid anhydride, *Biochim. Biophys. Acta*, *187*: 520.
30. Warner, T.G., and Benson, A.A. (1977). An improved method for the preparation of unsaturated phosphatidylcholines: acylation of *sn*-glycero-3-phosphorylcholine in the presence of methylsulfinylmethide, *J. Lipid Res.*, *18*: 548.
31. Lammers, J.G., Liefkens, T.J., Bus, J., and van der Meer, J. (1978). Synthesis and spectroscopic properties of α- and

β-phosphatidylcholines and phosphatidylethanolamines, *Chem. Phys. Lipids*, *22*: 293.
32. Kanda, P., and Wells, M.A. (1981). Facile acylation of glycerophosphocholine catalyzed by trifluoroacetic anhydride, *J. Lipid Res.*, *22*: 877.
33. Patel, K.M., Morrisett, J.D., and Sparrow, J.T. (1979). A convenient synthesis of phosphatidylcholine: acylation of *sn*-glycero-3-phosphocholine with fatty acid anhydride and 4-pyrrolidinopyridine, *J. Lipid Res.*, *20*: 674.
34. Radhakrishnan, R., Robson, R.J., Takagaki, Y., and Khorana, H.G. (1981). Synthesis of modified fatty acids and glycerophospholipid analogs, *Methods Enzymol.*, *72*: 408.
35. Gupta, C.M., Radhakrishnan, R., and Khorana, H.G. (1977). Glycerophospholipid synthesis: improved general method and new analogs containing photoactivable groups, *Proc. Natl. Acad. Sci. U.S.A.*, *74*: 4315.
36. Diyizou, Y.L., Genevois, A., Lazrak, T., Wolf, G., Nakatani, Y., and Ourrison, G. (1987). Synthesis and properties of photoreactive transmembrane probe, *Tetrahedron Lett.*, *28*: 5743.
37. Beck, A., Heissler, D., and Duportail, G. (1990). 1,1'-Thionyldi-imidazole in the synthesis of a long-chain phospholipidic membrane probe, *J. Chem. Soc., Chem. Commun.*: 31.
38. Keough, K.M., and Davis, P.J. (1979). Gel to liquid-crystalline phase transitions in water dispersions of saturated mixed-acid phosphatidylcholines, *Biochemistry*, *18*: 1453.
39. Perly, B., DuFourc, E.J., and Jarrell, H.C. (1984). Facile and high yielding syntheses of phosphatidylcholines and phosphatidylethanolamines containing deuterium-labeled acyl chains, *J. Labelled Compd. Radiopharm.*, *21*: 1.
40. Mangroo, D., and Gerber, G.E. (1988). Phospholipid synthesis: effects of solvents and catalysts on acylation, *Chem. Phys. Lipids*, *48*: 99.
41. Singh, A. (1990). An efficient synthesis of phosphatidylcholines, *J. Lipid Res.*, *31*: 1522.
42. Hermetter, A., Stutz, H., Franzmair, R., and Paltauf, F. (1989). 1-*O*-Trityl-*sn*-glycero-3-phosphocholine: a new intermediate for the facile preparation of mixed-acid 1,2-diacylglycerophosphocholines, *Chem. Phys. Lipids*, *50*: 57.
43. Ali, S., and Bittman, R. (1989). Mixed-chain phosphatidyl-

choline analogues modified in the choline moiety: preparation of isomerically pure phospholipids with bulky head groups and one acyl chain twice as long as the other, *Chem. Phys. Lipids*, *50*: 11.

44. Wang, Y.F., and Wong, C.H. (1988). Lipase-catalyzed irreversible transesterification for preparative synthesis of chiral glycerol derivatives, *J. Org. Chem.*, *53*: 3127.
45. Wang, Y.F., and Wong, C.H. (1988). Lipase-catalyzed irreversible transesterifications using enol ethers as acylating reagents: preparative enantio- and regioselective synthesis of alcohols, glycerol derivatives, sugars, and organometallics, *J. Am. Chem. Soc.*, *110*: 7200.
46. Ohno, M., Fujita, K., Nakai, H., Kobayashi, S., Inoue, K., and Nojima, S. (1985). An enantioselective synthesis of platelet-activating factors, their enantiomers and analogs from D- and L-tartaric acids, *Chem. Pharm. Bull. (Tokyo)*, *33*: 572.
47. Eibl, H. (1981). Phospholipid synthesis, in *Liposomes: From Physical Structure to Therapeutic Applications*, (Knight, C.G., ed.), Elsevier/North-Holland Biomedical Press, Amsterdam, Chapter 2.
48. Nakamura, N., Miyazaki, H., Ohkawa, N., Oshima, T., and Koike, H. (1990). An efficient synthesis of platelet-activating factor (PAF) *via* 1-*O*-alkyl-2-*O*-(3-isoxazolyl)-*sn*-glycero-3-phosphocholine. A new PAF agonist. Utilization of the 3-isoxazolyloxy group as a protected hydroxyl, *Tetrahedron Lett.*, *31*: 699.
49. Baer, E., and Fischer, H.O.L. (1939). Studies on acetone-glyceraldehyde. VII. Preparation of *l*-glyceraldehyde and *l*-(-)acetone glycerol, *J. Am. Chem. Soc.*, *61*: 761.
50. Kanda, P., and Wells, M. (1980). A simplified procedure for the preparation of 2,3-*O*-isopropylidene-*sn*-glycerol from L-arabinose, *J. Lipid Res.*, *21*: 257.
51. Kodali, D.R. (1987). Improved method for the synthesis of 1- or 3-acyl-*sn*-glycerols, *J. Lipid Res.*, *28*: 464.
52. Kanda, P., and Wells, M. (1981). Synthesis of *sn*-glycero-1-phosphocholine, *J. Lipid Res.*, *22*: 879.
53. Jung, M.E., and Shaw, T.J. (1980). Total synthesis of (*R*)-glycerol acetonide and the antiepileptic and hypotensive drug (-)-γ-amino-β-hydroxybutyric acid (GABA): use of vitamin C as a chiral starting material, *J. Am. Chem. Soc.*, *102*: 6304.

54. Hubschwerlen, C. (1986). A convenient synthesis of (*S*)-glyceraldehyde acetonide from L-ascorbic acid, *Synthesis*: 962.
55. Takano, K., Numata, H., and Ogasawara, K. (1982). A simple synthesis of (*R*)-glycerol acetonide from ascorbic acid, *Heterocycles*, *19*: 327.
56. Pressman, B.C., Anderson, L., and Lardy, H.A. (1950). 1,2-Isopropylidene-D-glucitol, 1,2:5,6-diisopropylidene-D-glucitol and a new synthesis of D,L-glyceraldehyde dimer, *J. Am. Chem. Soc.*, *72*: 2404.
57. Morgenlie, S. (1982). Synthesis of di-*O*-isopropylidene derivatives of L-fructose, *Carbohydr. Res.*, *107*: 137.
58. Maloneyhuss, K.E. (1985). A useful preparation of L-(*S*)-glyceraldehyde acetonide, *Synth. Commun.*, *15*: 273.
59. Al-Hakim, A.H., Haines, A.H., and Morley, C. (1985). Synthesis of 1,2-*O*-isopropylidene-L-threitol and its conversion to (*R*)-1,2-*O*-isopropylideneglycerol, *Synthesis*: 207.
60. DeWilde, H., De Clercq, P., Van deWalle, M., and Ropper, H. (1987). L-(*S*)-Erythrulose. A novel precursor to L-2,3-*O*-isopropylidene-C_3 chirons, *Tetrahedron Lett.*, *28*: 4757.
61. Mikkilineni, A.B., Kumar, P., and Abushanab, E. (1988). The chemistry of L-ascorbic and D-isoascorbic acids. 2. *R* and *S* glyceraldehyde from a common intermediate, *J. Org. Chem.*, *53*: 6005.
62. Lok, C., Ward, J., and van Dorp, D. (1976). The synthesis of chiral glycerides starting from D- and L-serine, *Chem. Phys. Lipids*, *16*: 115.
63. Froling, A., Pabon, H. and Ward, J. (1984). Synthesis of long-chain 1-saturated-2-unsaturated diacylglycerols *via* levulinoyl protection, *Chem. Phys. Lipids*, *36*: 29.
64. Zlantanos, S., Sagredos, A., and Papageorgiou, V. (1985). High yield monoglyceride preparation from glycidol and carboxylic acids, *J. Am. Oil Chem. Soc.*, *62*: 1575.
65. Katsuki, T., and Sharpless, K.B. (1980). The first practical method for asymmetric epoxidation, *J. Am. Chem. Soc.*, *102*: 5974.
66. Klunder, J.M., Ko, S.Y., and Sharpless, K.B. (1986). Asymmetric epoxidation of allyl alcohol: efficient routes to homochiral β-andrenergic blocking agents, *J. Org. Chem.*, *51*: 3710.
67. Klunder, J.M., Onami, T., and Sharpless, K.B. (1989).

Arenesulfonate derivatives of homochiral glycidol: versatile chiral building blocks for organic synthesis, *J. Org. Chem.*, *54*: 1295.

68. Caron, M., and Sharpless, K.B. (1985). $Ti(O\text{-}i\text{-}pr)_4$ Mediated nucleophilic openings of 2,3-epoxyalcohols. A mild procedure for regioselective ring-opening, *J. Org. Chem.*, *50*: 1557.
69. Burgos, C., Ayer, D., and Johnson, R.A. (1987). A new asymmetric synthesis of lipids and phospholipids, *J. Org. Chem.*, *52*: 4973.
70. Johnson, R.A., Burgos, C.E., and Nidy, E.G. (1989). An asymmetric synthesis of (*R*) and (*S*)-1-alkoxy-2,3-propanediols including precursors of platelet activating factor, *Chem. Phys. Lipids*, *50*: 119.
71. Ali, S., and Bittman, R. (1988). Facile diacylation of glycidyl tosylate. Chiral synthesis of symmetric chain glycerophospholipids, *J. Org. Chem.*, *53*: 5547.
72. Ali, S., and Bittman, R. (1990). Synthesis of optically active 1-acyl-2-*O*-alkyl-*sn*-glycero-3-phosphocholine *via* 1-*O*-benzyl-*sn*-glycerol-3-arenesulfonate, *Biochem. Cell Biol.*, *68*: 360.
73. Hasegawa, E., Eshima, K., Matsushita, Y., Nishide, H., and Tsuchida, E. (1987). A convenient synthesis of mixed-acid glycerophosphocholines, *Synthesis*: 60.
74. Hebert, N., and Just, G. (1990). Synthesis of phospholipids using an inverse phosphite triester approach, *J. Chem. Soc., Chem. Commun.*: 1497.
75. Baba, N., Yoneda, K., Tahara, S., Iwasa, J., Kaneko, T., and Matsuo, M. (1990). A regioselective, stereoselective synthesis of a diacylglycerophosphocholine hydroperoxide by use of lipoxygenase and lipase,*J. Chem. Soc., Chem. Commun*: 1281.
76. Chandrakumar, N.S., and Hajdu, J. (1982). Syntheses of enzyme-inhibitory phospholipid analogues. Stereospecific synthesis of 2-amidophosphatidylcholine and related derivatives, *J. Org. Chem.*, *47*: 2144.
77. Bonsen, P.M., de Haas, G.H., Pieterson, W.A., and van Deenen, L.L.M. (1972). Studies on phospholipase A and its zymogen from porcine pancreas. IV. The influence of chemical modifications of the lecithin structure on substrate properties, *Biochem. Biophys. Acta*, *270*: 364.
78. Gelb, M.H. (1986). Fluoroketone phospholipid analogues:

New inhibitors of phospholipase A_2, *J. Am. Chem. Soc.*, *108*: 3146.

79. Yuan, W., Berman, R.J., and Gelb, M.H. (1987). Synthesis and evaluation of phospholipid analogues as inhibitors of cobra venom phospholipase A_2, *J. Am. Chem. Soc.*, *109*: 8071.
80. Sunamoto, J., Goto, M., Iwamoto, K., Kondo, H., and Sato, T. (1990). Synthesis and characterization of 1,2-di-myristoylamido-1,2-deoxyphosphatidylcholine as an artificial boundary lipid, *Biochem. Biophys. Acta*, *1024*: 209.
81. Dijkman, R., Dekker, N., and de Haas, G.H. (1990). Competitive inhibition of lipolytic enzymes. II. Preparation of "monoacylamino" phospholipids, *Biochem. Biophys. Acta*, *1043*: 67.
82. Benveniste, J., Henson, P.M., and Cockane, G.C. (1972). Leukocyte-dependent histamine release from rabbit platelet. Role of IgE basophils and a platelet-activating factor, *J. Exp. Med.*, *136*: 1356.
83. Demopoulos, C.A., Pinckard, R.N., and Hanahan, D.J. (1979). Platelet-activating factor. Evidence of 1-*O*-alkyl-2-acetyl-*sn*-glyceryl-3-phosphorylcholine as the active component (a new class of lipid chemical mediators), *J. Biol. Chem.*, *254*: 9355.
84. Benveniste, J., Tence, M., Varenne, P., Bidault, J., Boullet, C., and Polonsky, J. (1979). Semisynthese et structure proposee du facteour activant les plaquettes (PAF): PAF-acether, un ether analogue de la lysophosphatidyl choline, *Compt. Rend.*, *289*: 1037.
85. Paltauf, F. (1983). Chemical synthesis of ether lipids, in *Ether Lipids. Biochemical and Biomedical Aspects*, (Mangold, H.K., and Paltauf, F., eds.), Academic Press, New York, pp. 49-84.
86. Mangold, H.K. (1983). Synthesis of 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-pohsphocholines and analogous compounds, in *Platelet Activating Factor and Structurally Related Ether Lipids*, (Benveniste, J., and Arnoux, M., eds.), Elsevier, Amsterdam, pp. 23-35.
87. Mangold, H.K. (1986). Chemistry of platelet activating factor (PAF, PAF-acether, AGEPC) - 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholines - and some PAF antagonists, in *Topics in Lipid Chemistry: from Structural Elucidation to Biological Function*, (Klein, H., and Schmitz, G., eds.),

Royal Society of Chemistry, London, pp. 3-13.
88. Venuti, M.C. (1985). Platelet activating factor: multifaceted biochemical and physiological mediator, *Ann. Rep. Med. Chem.*, *20*: 193.
89. Godfroid, J.J., Heymans, F., Michel, E., Redeuilh, C., Steiner, E., and Benveniste, J. (1980). Platelet activating factor (PAF-acether): total synthesis of 1-*O*-octadecyl-2-*O*-acetyl-*sn*-glycero-3-phosphoryl choline, *FEBS Lett.*, *116*: 161.
90. van Boeckel, C.A.A., van der Marel, G.A., Westerduin, P., and van Boom, J.H. (1982). Synthesis of 2-*O*-acetyl-3-*O*-hexadecyl-*sn*-1-glycerophosphoryl choline, the enantiomer of platelet activating factor (PAF), *Synthesis*: 399.
91. Bette-Bobillo, P., Bienvenue, A., Broquet, C., and Maurin, L. (1985). Synthesis and characterization of a radioiodinated, photoreactive and physiologically active analogue of platelet activating factor, *Chem. Phys. Lipids*, *37*: 215.
92. Tsai, Y.-M., Jiang, S.-L., Chen, H.-J., Chau, L.-Y., and Lin, J.-T. (1988). A practical formal synthesis of a physiologically active analog of platelet activating factor, *J. Chin. Chem. Soc.*, *35*: 429.
93. Chau, L.-Y., Tsai, Y.-M., and Chang, J.-R. (1989). Photoaffinity labeling of platelet activating factor binding sites in rabbit platelet membranes, *Biochem. Biophys. Res. Commun.*, *161*: 1070.
94. Heymans, F., Michel, E., Borrel, M.-C., Wichrowski, B., Godfroid, J.J., Convert, O., Coeffier, E., Tence, M., and Benveniste, J. (1981). New total synthesis and high resolution ^{1}H NMR spectrum of platelet-activating factor, its enantiomer and racemic mixtures, *Biochem. Biophys. Acta*, *666*: 230.
95. Hirth, G., and Barner, R. (1982). Synthese von Glyceryl-atherphosphatiden. 1. Mitteilung. Herstellung von 1-*O*-Octadecyl-2-*O*-acetyl-*sn*-glyceryl-3-phosphorylcholin (PAF), des Enantiomeren sowie einiger analoger Verbindungen, *Helv. Chim. Acta*, *65*: 1059.
96. Hirth, G., Saroka, H., Bannwarth, W., and Barner, R. (1983). Synthese von Glycerylatherphosphatiden. 2. Mitteilung. Herstellung von 2-*O*-Acetyl-1-*O*-[(*Z*)-9-octadecenyl]-*sn*- glyceryl-3-phosphocholin (oleyl-PAF), des Enantiomeren sowie einiger analoger, ungesattigter Verbindungen, *Helv. Chim. Acta*, *66*: 1210.

97. Surles, J.R., Wykle, R.L., O'Flaherty, J.T., Salzer, W.L., Thomas, M.J., Snyder, F., and Piantadosi, C. (1985). Facile synthesis of platelet-activating factor and racemic analogues containing unsaturation in the *sn*-1-alkyl chain, *J. Med. Chem.*, *28*: 73.
98. Corey, E.J., Gras, J.L., and Ulrich, P. (1976). A new general method for protection of the hydroxyl function, *Tetrahedron Lett.*: 809.
99. Baumann, W.J., and Mangold, H.K. (1974). Reactions of aliphatic methanesulfonates. I. Synthesis of long-chain glyceryl-(1) ethers, *J. Org. Chem.*, *29*: 3055.
100. Wyrick, S.D., McClanahan, J.S., Wykle, R.L., and O'Flaherty, J.T. (1985). Tritiated hexadecyl platelet activating factor (PAF), *J. Labelled Comp. Radiopharm.*, *22*: 1169.
101. Surles, J.R., Marx, M.H., and Piantadosi, C. (1988). Synthesis and evidence for the stability of a glycerophosphochloridate: *rac*-1-*O*-hexadecyl-2-*O*-(methylcarbamyl)-*sn*-glycero-3-phosphorochloridocholine, *J. Org. Chem.*, *53*: 899.
102. Agarwal, K., Bali, A., and Gupta, C.M. (1984). Synthesis of carbamyl and ether analogs of phosphatidylcholines, *Chem. Phys. Lipids*, *36*: 169.
103. Wichrowski, B., Michel, E., Heymans, F., Roy, J., Morgat, J.L., and Godfroid, J.J. (1983). A total synthesis of [9',10'-^{3}H]-labelled PAF-acether, *J. Labelled. Compd. Radiopharm.*, *20*: 991.
104. Kumar, R., Weintraub, S.T., McManus, L.M., Pinckard, R.N., and Hanahan, D.J. (1984). A facile route to semisynthesis of acetyl glycerylether phosphoethanolamine and its choline analogue, *J. Lipid Res.*, *25*: 198.
105. Ponpinpom, M.M., and Buglanesi, R.L. (1984). Synthesis of azide and amide analogs of platelet-activating factor and related derivatives, *Chem. Phys. Lipids*, *35*: 29.
106. Imbs, A.B., Smirnova, M.M., Molotkovsky, J.G., and Bergelson, L.D. (1985). Synthesis of a fluorescent analogue of the platelet-activating factor, *Bioorg. Khim.*, *11*: 1135.
107. Braquet, P., and Godfroid, J.J. (1987). Conformational properties of the PAF-acether receptor in platelets based on structure activity studies, in *Platelet Activating Factor*, (Snyder, J., ed.), Plenum Press, New York, pp. 191-236.
108. Braquet, P., Touqui, L., Shen, T.Y., and Vargaftig, B.B.

(1987). Perspectives in platelet activating factor research, *Pharmacol. Rev.*, *39*: 97.
109. Prashad, M., Tomesch, J.C., and Wareing, J.R. (1990). Synthesis of 1-*O*-(15-carboxypentadecyl)-2-*O*-acetyl-*sn*-glycero-3-phosphocholine as a potential platelet activating factor (PAF) hapten, *Chem. Phys. Lipids*, *53*: 121.
110. Wang, C.-J., and Tai, H.H. (1990). A facile synthesis of an aldehydic analog of platelet activating factor and its use in the production of specific antibodies, *Chem. Phys. Lipids*, *53*: 264.
111. Lai, C.-S., Joseph, J., and Shih, C.C.-Y. (1989). Molecular dynamics of antitumor ether-linked phospholipids in model membranes: a spin-label study, *Biochem. Biophys. Res. Commun.*, *160*: 1189.
112. Berchtold, R. (1982). Preparation of 1-*O*-octadecyl-2-*O*-methyl-*sn*-glycero-3-phosphocholine, *Chem. Phys. Lipids*, *30*: 389.
113. Patel, K.M., Sklar, L.A., Pownal, J.J., Morriset, J.D., and Sparrow, J.T. (1980). Synthesis of saturated, unsaturated, spin labeled and fluorescent cholesteryl esters: Acylation of cholesterol using fatty acid anhydride and 4-pyrrolidinopyridine, *Lipids*, *14*: 816.
114. Prakash, C., Taber, D.F., and Blair, I.A. (1989). Synthesis of trideuterated *O*-alkyl platelet activating factor and lyso derivatives, *Lipids*, *24*: 786.
115. Hirt, R., and Berchtold, R. (1958). Synthesis of phosphatides. A new synthesis of lecithin, *Pharm. Acta Helv.*, *33*: 349.
116. Murari, M.P., Murari, R., Parthasarathy, S., Guy, C.A., Kumar, V.V., Malewicz, B. and Baumann, W.J. (1990). Lyso platelet activating factor (lysoPAF) and its enantiomer. Total synthesis and carbon-13 NMR spectroscopy, *Lipids*, *25*: 606.
117. Marx, M.H., and Wiley, R.A. (1985). Synthesis of platelet activating factor (PAF) *via* a cyclic tin intermediate, *Tetrahedron Lett.*, *26*: 1379.
118. Anderson, R.C., and Nabinger, R.C. (1983). Synthesis of a novel platelet activating factor congener from diacetone glucose, *Tetrahedron Lett.*, *24*: 2741.
119. Fujita, K., Nakai, H., Kobayashi, S., Inoue, K., Nojima, S., and Ohno, M. (1982). An efficient and stereoselective synthesis of platelet-activating factors and enantiomers from

D- and L-tartaric acid, *Tetrahedron Lett.*, *23*: 3507.
120. Tsuri, T., and Kamata, S. (1985). An efficient and stereo-controlled synthesis of platelet activating factor from (*S*)-(-)-malic acid, *Tetrahedron Lett.*, *26*: 5195.
121. Chandrakumar, N.S., and Hajdu, J. (1982). A new method for the stereospecific synthesis of ether phospholipids. Preparation of the amide analog of platelet-activating factor and related derivatives, *Tetrahedron Lett.*, *23*: 1043.
122. Chandrakumar, N.S., and Hajdu, J. (1983). Stereospecific synthesis of ether phospholipids. Preparation of 1-alkyl-2-(acylamino)-2-deoxyglycerophosphoylcholines, *J. Org. Chem.*, *48*: 1197.
122a. Meyer, K.L., Marasco, C.J., Morris-Natschke, S.L., Ishaq, K.S., and Piantadosi, C. (1991). *In vitro* evaluation of phosphocholine and quaternary ammonium containing lipids as novel anti-HIV agents, *J. Med. Chem.*, *34*: 1377.
123. Guivisdalsky, P., and Bittman, R. (1989). An efficient stereocontrolled route to both enantiomers of platelet activating factor and analogues with long-chain esters at C_2: saturated and unsaturated ether glycerolipids by opening of glycidyl arenesulfonates, *J. Org. Chem.*, *54*: 4643.
124. Hendrickson, H.S., Hendrickson, E.K., and Rustad, T.J. (1987). Synthesis of a naphthylvinyl-labeled glycerol ether analog of phosphatidylcholine and its use in the assay of phospholipase A_2, *J. Lipid Res.*, *28*: 864.
125. Chattopadhyay, A. (1990). Chemistry and biology of *N*-(7-nitrobenz-2-oxa-1,3-diazol-4-yl) labeled lipids: fluorescent probes of biological and model membranes, *Chem. Phys. Lipids*, *53*: 1.
126. Tsushima, S., Yoshioka, Y., Tanida, S., Nomura, H., Nojima, S., and Hozumi, M. (1982). Synthesis and antimicrobial activities of alkyl lysophospholipids, *Chem. Pharm. Bull.*, *30*: 3260.
127. Baumann, W.J. (1987). Ether lipids in oncology, *Lipids*, *22*: 787.
128. Andreesen, R. (1988). Ether lipids in the therapy of cancer, *Prog. Biochem. Pharmacol.*, *22*: 118.
129. Berdel, W.E. (1987). Ether lipids and analogs in experimental cancer therapy. A brief review of the Munich experience, *Lipids*, *22*: 970.
130. Morris-Natschke, S.L., Mayer, K.L., Marasco, C.J., Piantadosi, C., Rossi, F., Godwin, P.L., and Modest, E.J.

(1990). Synthesis of quaternary amine ether lipids and evaluation of neoplastic cell growth inhibitory properties, *J. Med. Chem.*, *33*: 1812.
131. Guivisdalsky, P., and Bittman, R. (1989). Regiospecific opening of glycidyl derivatives mediated by boron trifluoride. Asymmetric synthesis of ether-linked phospholipids, *J. Org. Chem.*, *54*: 4637.
132. Bhatia, S., and Hajdu, J. (1987). A new approach to the synthesis of ether phospholipids. Preparation of 1,2-di-alkylglycerophosphoylcholines from L-glyceric acid, *Tetrahedron Lett.*, *28*: 271.
133. Bhatia, S., and Hajdu, J. (1988). Stereospecific synthesis of ether and thioether phospholipids. The use of L-glyceric acid as a chiral phospholipid precursor, *J. Org. Chem.*, *53*: 5034.
134. Abdelmageed, O.H., Duclos, R.I., Griffin, R.G., Siminovitch, D.J., Ruocco, M.J., and Makriyannis, A. (1989). Synthesis of ^{2}H and ^{13}C-labeled 1,2-di-*O*-hexadecyl-*sn*-glycero-3-phosphoethanolamine and 1,2-di-*O*-hexadecyl-*sn*-glycero-3-phosphocholine, *Chem. Phys. Lipids*, *50*: 163.
135. Eibl, H. (1978). Phospholipid synthesis: oxazaphospholanes and dioxaphospholanes as intermediates, *Proc. Natl. Acad. Sci. U.S.A.*, *75*: 4074.
136. Abdelmageed, O.H., Duclos, R.I., Abushanab, E., and Makriyannis, A. (1990). Chirospecific synthesis of ^{2}H and ^{13}C-labeled 1-*O*-alkyl-2-*O*-alkyl'-*sn*-glycero-3-phosphoethanolamine and 1-*O*-alkyl-2-*O*-alkyl'-*sn*-glycero-3-phosphocholine, *Chem. Phys. Lipids*, *54*: 49.
137. Bittman, R., Witzke, N.M., Lee, T.-C., Blank, M.L., and Snyder, F. (1987). Synthesis and biochemical studies of analogs of platelet-activating factor bearing a methyl group at C2 of the glycerol backbone, *J. Lipid Res.*, *28*: 733.
138. Bittman, R., and Witzke, N.M. (1989). Conversion of methylallyl alcohol into C2-methyl-1,2-di-*O*-hexadecyl-glycerophosphocholine, a conformationally restricted phospholipid, *Chem. Phys. Lipids*, *50*: 99.
139. Hancock, A.J., Stokes, M.H., and Sables, H.Z. (1977). Analogs of natural lipids. IV. Synthesis and properties of cyclopentanoid analogs of phosphatidic acid, *J. Lipid Res.*, *18*: 81.
140. Hancock, A.J., Stokes, M.H., and Sables, H.Z. (1982). Analogs of natural lipids. VII. Synthesis of cyclopentanoid

analogs of phosphatidylcholines, *J. Lipid Res.*, *23*: 183.
141. Hancock, A.J. (1981). Synthesis of cyclopentanoid analogs of diacylglycerophosphate, *Methods Enzymol.*, *72*: 640.
142. Barlow, P.N., Vidal, J.C., Lister, M.D., Hancock, A.J., and Sigler, P.B. (1988). Synthesis and some properties of constrained short-chain phosphatidylcholine analogue: (+) and (-)-(1,3/2)-1-*O*-(phosphocholine)-2,3-*O*-dihexanoyl-cyclopentane-1,2,3-triol, *Chem. Phys. Lipids*, *46*: 157.
143. Ahmad, T.Y., Morrisett, J.D., Pownall, H.J., Gotto, A.M., Brockman, H.L., Sable, H.Z., Lewis, E.O., and Hancock, A.J. (1990). Cyclopentanoid analogs of dipalmitoyl phosphatidic acid: effect of backbone geometry on thermotropic properties, *Chem. Phys. Lipids*, *55*: 231.
144. Miyazaki, H., Ohkawa, N., Nokamura, N., Ito, T., Sada, T., Oshima, T., and Koike, H. (1989). Lactone and cyclic ether analogs of platelet-activating factor. Synthesis and biological activities, *Chem. Pharm. Bull.*, *37*: 2379.
145. Hadvary, P., and Weller, T. (1986). Conformationally restricted analogs of platelet-activating factor (PAF), *Helv. Chim. Acta*, *69*: 1862.
146. Magolda, R.L., and Galbraith, W. (1989). Design and synthesis of conformationally restricted phospholipids as phospholipase A_2 inhibitors, *J. Cell Biochem.*, *40*: 371.
147. Phillips, M., and Bonjouklian, R.(1986). Cyclic platelet-activating factor analogues derived from 2-deoxy-D-erythro-pentose, *Carbohydr. Res.*, *146*: 89.
148. Meyer, K.L., Schwendner, S.W., and Counsell, R.E. (1989). Potential tumor or organ-imaging agents. 30. Radioiodinated phospholipid ethers, *J. Med. Chem.*, *32*: 2142.
149. Hansen, W., Murari, R., Wedmid, Y., and Baumann, W.J. (1982). An improved procedure for the synthesis of choline phospholipids *via* 2-bromoethyl dichlorophosphate, *Lipids*, *17*: 453.
150. Hendrickson, H.S., Hendrickson, E.K., Dybvig, R.H. (1983). Chiral synthesis of a dithiolester analog of phosphatidylcholine as a substrate for the assay of phospholipase A_2, *J. Lipid Res.*, *24*: 1532.
151. Virtanen, J.A., Brotherus, J.R., Renkonen, O., and Kates, M. (1980). Synthesis of monoacid 2,3-diacyl-*sn*-glycerols *via* 1,6-ditrityl-D-mannitol, *Chem. Phys. Lipids*, *27*: 185.
152. Brockerhoff, H.B., and Ayengar, N.K.N. (1979). Improved synthesis of choline lipids, *Lipids*, *14*: 88.

153. Lok, C.M. (1978). Versatile methods for the synthesis of mixed-acid 1,2-diacylglycerols, *Chem. Phys. Lipids*, *22*: 323.
154. Hendrickson, H.S., and Hendrickson, E.K. (1990). A facile asymmetric synthesis of glycerol phospholipids *via* tritylglycidol prepared by the asymmetric epoxidation of allyl alcohol. Thiolester and thioether analogs of phosphatidylcholine, *Chem. Phys. Lipids*, *53*: 115.
155. Bosies, E., Herrmann, D.B.J., Bicker, U., Gall, R., and Pahlke, W. (1987). Synthesis of thioether phosphocholine analogues, *Lipids*, *22*: 947.
156. Garrigues, B., Bertrand, G., Frehel, D., and Maffrand, J.P. (1984). Synthese de la *d,l*-(acetoxy-2-octadecylthio-1)-propyl-3-phosphoylcholine ou thia-PAF, *Phosphorus Sulfur*, *21*: 171.
157. Aarsman, A.J., Roosenboom, C.F.P., van der Marel, G.A., Shadid, B., van Boom, J.H., and van den Bosch, H. (1985). Synthesis of acylthioester phospholipids and their hydrolysis by phospholipase A_2, *Chem. Phys. Lipids*, *36*: 229.
158. Bhatia, S.K., and Hajdu, J. (1987). Stereospecific synthesis of PAF-analogues. Preparation of 1-hexadecyl-2-thioacetyl-2-deoxyglycerophosphocholine (2-thio-PAF), *Tetrahedron Lett.*, *28*: 1729.
159. Bhatia, S.K., and Hajdu, J. (1989). Stereospecific synthesis of 2-substituted ether phospholipids, *Synthesis*: 16.
160. Bhatia, S.K., and Hajdu, J. (1987). Stereospecific synthesis of 2-thiophosphatidylcholines: A new class of biologically active phospholipid analogues, *Tetrahedron Lett.*, *28*: 3767.
161. Garrigues, B., Bertrand, G., and Maffrand, J.-P. (1984). An efficient synthesis of azathia analogs of platelet-activating factor, *Synthesis*: 870.
162. Bhatia, S.K., and Hajdu, J. (1988). A new approach to the synthesis of thioether phospholipids. Preparation of 1-thiohexadecyl-2-*N*-acylaminodeoxyglycerophosphocholines, *Tetrahedron Lett.*, *29*: 31.
163. Zeidler, J.M. Zimmerman, W., and Roth, H. (1990). Synthesis of azathia analogues of platelet activating factor with polyhetero side chains, *Chem. Phys. Lipids*, *55*: 155.
164. Zeidler, J.M., Zimmerman, W., and Roth, H. (1989). Synthesis of azathia-analogs of platelet activating factor, *Sci. Pharm.*, *57*: 417.

165. Zeidler, J.M., Zimmerman, W., and Roth, H. (1990). Synthesis of azathia-analogues of platelet activating factor containing a methioninol backbone, *Chem. Phys. Lipids*, *56*: 175.
166. Snyder, W.R. (1987). Synthesis of a thiophosphate analog of dioctanoylphosphoatidylcholine: a phospholipase C substrate, *J. Lipid Res.*, *28*: 949.
167. Cox, J.W., Snyder, W.R., and Horrocks, L.A. (1979). Synthesis of choline and ethanolamine phospholipids with thiophosphoester bonds as substrates for phospholipase C, *Chem. Phys. Lipids*, *25*: 369.
168. Muller, C.E., and Roth, H.J. (1990). A new synthesis of thiophosphoric acid esters with a C-S-P bond, *Tetrahedron Lett.*, *31*: 501.
169. Nifant'ev, E.E., Predvoditelev, D.A., and Alarkon, K. (1978). Synthesis of lipids and their models based on glycerol alkylene phosphites. II. Phosphatidylcholines and their analogs, *Zh. Org. Khim.*, *14*: 63.
170. Vasilenko, I., de Kruijff, B., and Verkleij, A.J. (1982). The synthesis and use of thionophospholipids in ^{31}P-NMR studies of lipid polymorphism, *Biochem. Biophys. Acta*, *685*: 144.
171. Bruzik, K., Jiang, R.-T., and Tsai, M.-D. (1983). Phospholipids chiral about phosphorus. Preparation and spectral properties of chiral thiophospholipids, *Biochemistry*, *22*: 2478.
172. Bruzik, K.S., Salamonczyk, G., and Stec, W.J. (1986). A general method for the synthesis of glycerophospholipids, *J. Org. Chem.*, *51*: 2368.
173. Lamant, V., Chap, H., Klaebe, A., Perie, J.J., and Willson, M. (1987). Synthesis of a thiophospho analogue of platelet activating factor (*RS*)- and (*S*)-1-hexadecyl-2-acetylglycero-3-thiophosphocholine, *J. Chem. Soc., Chem. Commun.*: 1608.
174. Rosario-Jansen, T., Jiang, R.-T., Tsai, M.D., and Hanahan, D.J. (1988). Phospholipids chiral at phosphorus. Synthesis and stereospecificity of phosphorothioate analogues of platelet-activating factor, *Biochemistry*, *27*: 4619.
175. Baumann, W., and Mangold, H.K. (1964). Reaction of aliphatic methanesulfonates. I. Synthesis of long-chain glyceryl-(1) ethers, *J. Org. Chem.*, *29*: 3055.
176. Chacko, G.K., and Hanahan, D.J. (1968). Chemical

synthesis of 1-*O*-(D)- and 3-*O*-(L)-glyceryl monoethers, diethers and derivatives: glycerides, monoester phospholipids and diether phospholipids, *Biochem. Biophys. Acta*, *164*: 252.
177. Lin, G.L., and Tsai, M.-D. (1989). Phospholipid chiral at phosphorus. 18. Stereochemistry of phosphatidylinositide-specific phospholipase C, *J. Am. Chem. Soc.*, *111*: 3099.
178. Salmonczyk, G.M., and Bruzik, K.S. (1990). The synthesis of diastereoisomers of phosphorothioate analogue of dipalmitoylphosphatidylinositol, *Tetrahedron Lett.*, *31*: 2015.
179. Loffredo, W.M., and Tsai, M.-D. (1990). Phospholipids chiral at phosphorus. Synthesis and configurational assignment of phosphorothioate analogs of phosphatidylserine, *Bioorg. Chem.*, *18*: 78.
180. Yuan, W., Fearon, K., and Gelb, M.H. (1989). Synthesis of sulfur-substituted phospholipid analogues as mechanistic probes of phospholipase A_2 catalysis, *J. Org. Chem.*, *54*: 906.
181. Berridge, M.J., and Irvine, R.F. (1984). Inositol triphosphate, a novel second messenger in cellular signal transduction, *Nature*, *312*: 315.
182. Nishizuka, Y. (1984). The role of protein kinase C in cell surface signal transduction and tumour promotion, *Nature*, *308*: 693.
182a. Nozawa, Y., Nakashima, S., and Nagata, K.-i. (1991). Phospholipid-mediated signaling in receptor activation of human platelets, *Biochem. Biophys. Acta*, *1082*: 219.
183. Gigg, R. (1980). Synthesis of glycolipids, *Chem. Phys. Lipids*, *26*: 287.
184. Billington, D.C. (1989). Recent developments in the synthesis of *myo*-inositol phosphates, *Chem. Soc. Rev.*, *18*: 83.
185. Potter, B.V.L. (1990). Recent advances in the chemistry and biochemistry of inositol phosphates of biological interest, *Nat. Prod. Rep.*, *7*: 1.
186. Yu, K.-L., and Fraser-Reid, B. (1988). A novel reagent for the synthesis of *myo*-inositol phosphates: *N,N*-diisopropyl dibenzyl phosphoramidite, *Tetrahedron Lett.*, *29*: 979.
187. Cooke, A.M., Potter, B.V.L., and Gigg, R. (1987). Synthesis of DL-*myo*-inositol 1,4,5-triphosphate, *Tetrahedron Lett.*, *28*: 2305.
188. Meek, J.L., Davidson, F., and Hobbs, F.W. (1988).

Synthesis of inositol phosphates, *J. Am. Chem. Soc.*, *110*: 2317.
189. Ozaki, S., Watanabe, Y., Ogasawara, T., Kondo, Y., Shiotani, N., Nishii, H., and Matsuki, T. (1986). Total synthesis of optically active *myo*-inositol 1,4,5-tris(phosphate), *Tetrahedron Lett.*, *27*: 3157.
190. Vacca, J.P., deSolms, S.J., and Huff, J.R. (1987). Total synthesis of D- and L-*myo*-inositol 1,4,5-triphosphate, *J. Am. Chem. Soc.*, *109*: 3478.
191. Reese, C.B., and Ward, J.G. (1987). Synthesis of D-*myo*-inositol 1,4,5-triphosphate, *Tetrahedron Lett.*, *28*: 2309.
192. Dreef, C.E., Tuinman, R.J., Elie, C.J.J., van der Marel, G.A., and van Boom, J.H. (1988). Total synthesis of optically active *myo*-inositol 1,4,5-trisphosphate and *myo*-inositol 1,3,4,5-tetrakisphosphate, *Recl. Trav. Chim. Pays-Bas*, *107*: 395.
193. Liu, Y.-C., and Chen, C. (1989). An efficient synthesis of optically active D-*myo*-inositol 1,4,5-trisphosphate, *Tetrahedron Lett.*, *30*: 1617.
194. Vacca, J.P., deSolms, S.J., Huff, J.R., Billington, D.C., Baker, R., Kulagowski, J.J., and Mawer, I.M. (1989). The total synthesis of *myo*-inositol polyphosphates, *Tetrahedron*, *45*: 5679.
195. Stepanov, A.E., Runova, O.B., Schlewer, G., Spiess, B., and Shvets, V.I. (1989). Total synthesis of chiral *sn-myo*-inositol-1,4,5-trisphosphate and its enantiomer, *Tetrahedron Lett.*, *30*: 5125.
196. deSolms, S.J., Vacca, J.P., and Huff, J.R. (1987). The total synthesis of (±)-*myo*-inositol-1,3,4-trisphosphate, (±)-*myo*-inositol-2,4,5-trisphosphate, and (±)-*myo*-1,3,4,5-tetrakisphosphate, *Tetrahedron Lett.*, *28*: 4503.
197. Billington, D.C., and Baker, R. (1987). Synthesis of *myo*-inositol 1,3,4,5-tetraphosphate and *myo*-inositol 1,3-bisphosphate, *J. Chem. Soc., Chem. Commun.*: 1011.
198. Ozaki, S., Kondo, Y., Nakahira, H., Yamoka, S., and Watanabe, Y. (1987). Synthesis of D-*myo*-inositol 1,3,4,5-tetrakisphosphate, *Tetrahedron Lett.*, *28*: 4691.
199. Baudin, G., Glanzer, B.I., Swaminathan, K.S., and Vasella, A. (1988). A synthesis of 1-D- and 1-L-*myo*-inositol 1,3,4,5-tetraphosphate, *Helv. Chim. Acta*, *71*: 1367.
200. Watanabe, Y., Komoda, Y., Ebisuya, K., and Ozaki, S. (1990). An efficient phosphorylation method using a new

phosphitylating agent, 2-diethylamino-1,3,2-benzodioxaphosphepane, *Tetrahedron Lett.*, *31*: 255.
201. Lampe, D., and Potter, B.V.L. (1990). Synthesis of *myo*-inositol 1-phosphorothioate 4,5-bisphosphate: Preparation of a fluorescent labelled *myo*-inositol 1,4,5-trisphosphate analogue, *J. Chem. Soc., Chem. Commun.*: 1500.
202. Lampe, D., and Potter, B.V.L. (1987). *myo*-Inositol 1,4,5-trisphosphorothioate: A novel analogue of a biological second messenger, *J. Chem. Soc., Chem. Commun.*: 1525.
203. Carless, H.A.J., and Busia, K. (1990). Total synthesis of *chiro*-inositol 2,3,5-trisphosphate: A *myo*-inositol 1,4,5-trisphosphate analogue from benzene *via* photo-oxidation, *Tetrahedron Lett.*, *31*: 1617.
204. Shashidhar, M.S., Keana, J.F.W., Volwerk, J.J., and Griffith, O.H. (1990). Synthesis of phosphonate derivative of *myo*-inositol for use in biochemical studies on inositol-binding proteins, *Chem. Phys. Lipids*, *53*: 103.
205. Falck, J.R., Abdali, A., and Wittenberger, S.J. (1990). Total synthesis of the 5-methylenephosphonate analogue of D-*myo*-inositol 1,4,5-trisphosphate, *J. Chem. Soc., Chem. Commun.*: *953*.
206. Krylova, V.N., Gornaeva, H.P., Shvets, V.I., and Evstigneeva, R.P. (1979). Synthesis of a triphosphoinosite, *Dokl. Akad. Nauk S.S.S.R.*, *246*: 339.
207. Krylova, V.N., Lyutik, A.I., Gornaeva, N.P., and Shvets, V.I. (1981). Studies on derivatives of asymmetrically substituted *myo*-inositol. XXIX. Synthesis of triphosphoinositide, *Zh. Obshch. Khim.*, *51*: 210.
208. Dreef, C.E., Elie, C.J.J., Hoogerhout, P., van der Marel, G.A., and van Boom, J.H. (1988). Synthesis of 1-*O*-(1,2-di-*O*-palmitoyl-*sn*-glycero-3-phospho)-D-*myo*-inositol 4,5-bisphosphate: an analogue of naturally occurring (Ptd)Ins(4,5)P_2, *Tetrahedron Lett.*, *29*: 6513.
209. Elie, C.J.J., Dreef, C.E., Verduyn, R., van der Marel, G.A., and van Boom, J.H. (1989). Synthesis of 1-*O*-(1,2-di-*O*-palmitoyl-*sn*-glycero-3-phosphoryl)-2-*O*-α-D-mannopyranosyl-D-*myo*-inositol: a fragment of mycobacterial phospholipids, *Tetrahedron*, *45*: 3477.
210. Ward, J.G., and Young, R.C. (1988). Synthesis of 1,2-dipalmitoyl-*sn*-glycer-3-yl-D-*myo*-inositol-1-phosphate, *Tetrahedron Lett*, *29*: 6013.
210a. Jones, M., Rana, K.K., Ward, J.G., and Young, R.C.

(1989). Improved synthesis of inositol phospholipid analogues, *Tetrahedron Lett.*, *30*: 5353.
211. Yang, S.S., Beattie, T.R., and Shen, T.Y. (1982). Synthesis of fluorodeoxy*scyllo*inositol and phosphatidyl-fluorodeoxy*scyllo*inositol, *Tetrahedron Lett.*, *23*: 5517.
212. Young, R.C., Downes, C.P., Eggleston, D.S., Jones, M., Macphee, C.H., Rana, K.K., and Ward, J.G. (1990). Total synthesis of the four stereoisomers of dihexadecanoyl phosphatidylinositol and the substrate stereospecificity of human erythrocyte membrane phosphatidylinositol 4-kinase, *J. Med. Chem.*, *33*: 641.
213. Ishaq, K.S., Capobianco, M., Piantadosi, C., Noseda, A., Daniel, L.W., and Modest, E.J. (1989). Synthesis and biological evaluation of ether-linked derivatives of phosphatidylinositol, *Pharm. Res.*, *6*: 216.
213a. Yang, S.S., Beattie, T.R., Durette, P.L., Gallagher, T.F., and Shen, T.-Y. (1985). Phosphatidylinositol analogs useful as antiinflammatory/analgesic agents, *U.S. Patent 4,515,722*.
213b. Dreef, C.E., Elie, C.J.J., van der Marel, G.A., and van Boom, J.H. (1991). Synthesis of phosphonate analogue of *myo*-inositol phospholipids, *Tetrahedron Lett.*, *32*: 955.
214. Noda, H., and Keenan, R.W. (1990). Phosphatidylinositol isopropylidene derivatives: synthesis, characterization and use as synthetic intermediates, *Chem. Phys. Lipids*, *53*: 53.
215. Trouet, E. (1978). Increased selectivity of drugs by linking to carriers, *Eur. J. Cancer*, *14*: 105.
216. Ryu, E.K., Ross, R.J., Matsushita, T., McCoss, M., Hong, C.I., and West, R.C. (1982). Phospholipid-nucleoside conjugates. 3. Synthesis and preliminary biological evaluation of 1-β-D-arabinofuranosylcytosine 5'-monophosphate-L-1,2-dipalmitin and selected 1-β-D-arabinofuranosylcytosine 5'-diphosphate-L-1,2-diacylglycerols, *J. Med. Chem.*, *25*: 1322.
217. Hong, C.I., An, S.-H., Buchheit, D.J., Nechaev, A., Kirisits, A.J., West, C.R., and Berdel, W.E. (1986). Nucleoside conjugates. 7. Synthesis and antitumor activity of 1-β-D-arabinofuranosylcytosine conjugates of ether lipids, *J. Med. Chem.*, *29*: 2038.
218. Welch, C.J., Laarson, A., Ericson, A.C., Oberg, B., Datema, R., and Chattopadhyaya, J. (1985). The chemical

synthesis and structural properties of an acyclovir-phospholipid conjugate, *Acta Chem. Scand., B39*: 47.

219. McCoss, M., Ryu, E.K., and Matsushita, T. (1978). The synthesis, characterization, and preliminary biological evaluation of 1-β-D-arabinofuranosylcytosine-5'-diphosphate-L-1,2-dipalmitin, *Biochem. Biophys. Res. Commun., 85*: 714.
220. Hong, C.I., and West, C.R. (1986). Thiophospholipid conjugates of antitumor agents, *U.S. Patent 4,622,392*.
221. Hong, C.I., Kirisits, A.J., Buchheit, D.J., Nechaev, A., and West, C.R. (1986). 1-β-D-Arabinofuran- osylcytosine conjugates of thioether phospholipids as a new class of potential antitumor drugs, *Cancer Drug Delivery, 3*: 101.
222. Hong, C.I., Kirisits, A.J., Nechaev, A., Buchheit, D.J., and West, C.R. (1990). Nucleoside conjugates. 11. Synthesis and antitumor activity of 1-β-D-arabinofuranosylcytosine and cytidine conjugates of thioether lipids, *J. Med. Chem., 33*: 1380.
223. Hostetler, K.Y., Stuhmiller, L.M., Lenting, H.B.M., van den Bosch, H., and Richman, D.D. (1990). Synthesis and antiretroviral activity of phospholipid analogs of azidothymidine and other antiviral nucleosides, *J. Biol. Chem., 265*: 6112.

223a. Piantadosi, C., Marasco, C.J., Morris-Natschke, S.L., Meyer, K.L., Gumus, F., Surles, J.R., Ishaq, K.S., Kucera, L.S., Iyer, N., Wallen, C.A., Piantadosi, S., and Modest, E.S. (1991). Synthesis and evaluation of novel ether lipid nucleoside conjugates for anti-HIV-1 activity, *J. Med. Chem., 34*: 1408.

224. Ramirez, F., Mandel, S.B., and Marecek, J.F. (1982). Synthesis of phospholiponucleotides, *Synthesis*: 402.
225. Oltvoort, J.J., van der Marel, G.A., van Boeckel, C.A.A., and van Boom, J.H. (1983). An approach to the synthesis of liponucleotides, *Recl. Trav. Chim. Pays-Bas, 102*: 523.
226. Lindh, I., and Stawinski, J. (1987). Synthesis of phospholipids and nucleoside-phospholipid conjugates *via* hydrogenphosphonate intermediates, *Nucl. Acid Res., 18*: 189.
227. Stawinski, J., Thelin, M., Westman, E., and Zain, R. (1990). Nucleoside H-phosphonates. 12. Synthesis of nucleoside 3'-(hydrogen-phosphonothioate)monoesters *via* phosphinate intermediates, *J. Org. Chem., 55*: 3503.

228. Turcotte, J.G., Srivastava, S.P., Meresak, W.A., Rizkalla, B.A., Louzon, F., and Wunz, T.P. (1980). Cytotoxic liponucleotide analogs. 1. Chemical synthesis of CDP-diacylglycerol analogs containing the cytosine arabinoside moiety, *Biochem. Biophys. Acta*, *619*: 604.
229. Tyhach, R.J., Rosenthal, A.F., and Tropp, B.E. (1975). Substrate activity of phosphonic acid analogues of CDP-diglyceride in the synthesis of phosphoglycerides in *Escherichia coli*, *Biochem. Biophys. Acta*, *388*: 29.
230. Raetz, C.R.H., and Kennedy, E.P. (1973). Function of cytidine diphosphate-diglyceride and deoxycytidine diphosphate-diglyceride in the biogenesis of membrane lipids in *Escherichia coli*, *J. Biol. Chem.*, *248*: 1098.
231. Rosenthal, A.F., and Vargas, L.A. (1981). A synthetic phosphinate-phosphonate liponucleotide analogue, *J. Chem. Soc., Chem. Commun.*: 976.
232. Vargas, L.A., and Rosenthal, A.F. (1983). A reagent for introducing the phosphinic acid isostere of phosphodiesters, *J. Org. Chem.*, *48*: 4775.
233. Rosenthal, A.F., Vargas, L.A., and Han, S.C.H. (1972). Synthesis of optically active diether phosphinate analogs of lecithin, *Biochem. Biophys. Acta*, *260*: 269.
234. Vargas, L.A., Li, X.M., and Rosenthal, A.F. (1984). Inhibition of platelet phosphatidylinositol synthetase by an analog of CDP-diacylglycerol, *Biochem. Biophys. Acta*, *796*: 123.
235. Rosenthal, A.F., Gringauz, A., and Vargas, L.A. (1976). Bis(trimethylsilyl) trimethylsiloxymethylphosphonite: A useful reagent for the introduction of the hydroxymethyl-phosphinate group, *J. Chem. Soc., Chem. Commun.*: 384.
236. Engel, R. (1977). Phosphonates as analogues of natural phosphates, *Chem. Rev.*, *77*: 349.
237. Engel, R. (1983). Phosphonic acids and phosphonates as antimetabolites, in *Phosphonates in Biological Systems*, (Hilderbrand, R.L., ed.), CRC Press, Inc., Boca Raton, FL, pp. 97-138.
238. Blackburn, G.M. (1981). Phosphonates as analogues of biological phosphates, *Chem. Ind. (London)*: 134.
239. Moschidis, M.C. (1985). Phosphonolipids, *Prog. Lipid Res.*, *23*: 223.
240. Yamauchi, K., Ohtsuki, S., and Kinoshita, M. (1984). Synthesis of peptide analogues containing (2-aminoethyl)-

phosphonic acid (ciliatine), *J. Org. Chem.*, *49*: 1158.
241. Yamauchi, K., Ohtsuki, S., and Kinoshita, M. (1985). Phosphonodipeptides containing (2-aminoethyl)phosphonic acid (ciliatine): transition state analogue inhibitors of carboxypeptidase A, *Biochem. Biophys. Acta*, *827*: 275.
242. Moschidis, M.C., Demopoulos, C.A., and Kritikou, L.G. (1983). Phosphono-platelet activating factor. 1. Synthesis of 1-*O*-hexadecyl-2-*O*-acetyl-glyceryl-3-(2-trimethylammonium-methyl)phosphonate and its platelet activating potency, *Chem. Phys. Lipids*, *33*: 87.
243. Disselnkotter, H., Lieb, F., Oediger, H., and Wendisch, D. (1985). Synthese von Phosphonoanalogen des 2-*O*-Acetyl-1-*O*-hexadecyl(octadecyl)-*sn*-3-glycerylphosphoryl-cholins (Platelet-activating-factor), *Arch. Pharm.*, *318*: 695.
244. Nakamura, N., Miyazaki, H., Ohkawa, N., Koike, H., Sada, T., Asai, F., and Kobayashi, S. (1984). Synthesis and biological activities of bioisosteric *O*-carba-analogues of platelet activating factor (PAF), *Chem. Pharm. Bull.*, *32*: 2452.
245. Moschidis, M.C., and Demopoulos, C.A. (1985). Phosphono-platelet activating factor. II. Synthesis of 2-acetamido-2-deoxy-1-*O*-octadecylglycerol-3-(2-trimethylammoniumethyl) and (2-aminoethyl)phosphonates, *Chem. Phys. Lipids*, *37*: 45.
246. Bonsen, P.P.M., Burbach-Westerhuis, G.J., de Haas, G.H., and van Deenen, L.L.M. (1972). Chemical synthesis of some lecithin analogues . Potential inhibitors of phospholipase A, *Chem. Phys. Lipids*, *8*: 199.
247. Rosenthal, A.F., Vargas, L.A., Isaacson, Y.A., and Bittman, R. (1975). A simple synthesis of phosphonate-containing lipids. Introduction of the phosphonic acid moiety into hydrolytically-labile compounds, *Tetrahedron Lett.*, *12*: 977.
248. Orlov, N.F., Kaufman, B.L., Sukhi, L., Slesar, L.N., and Sudakova, E.V. (1966). Synthesis of triorganosilyl derivatives of phosphorous acid, *Khim. Prakt. Prim. Kremniiorg. Soldin., Tr. Sovesch.*: 111.
249. Belokrinitskii, M.A., and Orlov, N.F. (1971). Reaction of alkyl halides with triorganosilyl derivatives of phosphorous acid, *Kremniiorg. Mater.*: 145.
250. Deroo, P.W., Rosenthal, A.F., Isaacson, Y.A., Vargas, L.A., and Bittman, R. (1976). Synthesis of DL-2,3-diacyl-

oxypropylphosphonyl-cholines from DL-2,3-diacyloxy-iodopropanes, *Chem. Phys. Lipids*, *16*: 60.
251. Sekine, M., Mori, H., and Hata, T. (1982). Protection of phosphonate function by means of ethoxycarbonyl group. A new method for generation of reactive silyl phosphite intermediates, *Bull. Chem. Soc. Jpn.*, *55*: 239.
252. Rabinowitz, R. (1963). The reaction of phosphonic acid esters with acid chlorides. A very mild hydrolytic route, *J. Org. Chem.*, *28*: 2975.
253. McKenna, C.E., Higa, M.T., Cheung, N.H., and McKenna, M.C. (1977). The facile dealkylation of phosphonic acid dialkyl esters by bromotrimethylsilane, *Tetrahedron Lett.*: 155.
254. Doerr, I.L., Tang, J.-C., Rosenthal, A.F., Engel, R., and Tropp, B.E. (1977). Synthesis of phosphonate and ether analogs of *rac*-phosphatidyl-L-serine, *Chem. Phys. Lipids*, *19*: 185.
255. Hermetter, H., Paltauf, F., and Hauser, H. (1982). Synthesis of diacyl and alkylacylglycerophosphoserines, *Chem. Phys. Lipids*, *30*: 35.
256. Schwartz, P.W., Tropp, B.E., Engel, R. (1988). Phosphonolipids. The synthesis of chiral vinylic phosphonolipid analogues of phosphatidic acid and phosphatidyl choline, *Chem. Phys. Lipids*, *48*: 1.
257. Moschidis, M. (1985). Synthesis of 1,2-diacyloxypropyl-3-(1',2'-diacyl-*sn*-glycero)-phosphonate, *Chem. Phys. Lipids*, *36*: 297.
258. Moschidis, M.C. (1988). Synthesis of a phosphono analogue of cardiolipin and study of its silicic acid column chromatographic behaviour, *Chem. Phys. Lipids*, *46*: 253.
259. Moschidis, M.C. (1986). Synthesis of bis(diacyloxypropyl)-phosphinate, *Chem. Phys. Lipids*, *39*: 265.
260. Tang, K.-C., Tropp, B.E., and Engel, R. (1977). The synthesis of phosphonic acid and phosphate analogues of glycerol 3-phosphate and related metabolites, *Tetrahedron*, *34*: 2873.
261. Tyhach, R.J., Engel, R., and Tropp, B.E. (1976). Metabolic fate of 3,4-dihydroxybutyl-1-phosphonate in *Escherichia coli*, *J. Biol. Chem.*, *251*: 6717.
262. Cheng, P.-J., Hickey, R., Engel, R., and Tropp, B.E. (1974). Rabbit muscle L-glycerol-3-phosphate dehydrogenase substrate activity of 3,4-dihydroxybutyl-1-phosphonate

and 4-hydroxy-3-oxobutyl-1-phosphonate, *Biochem. Biophys. Acta*, *341*: 85.
263. Cheng, P.-J. Nunn, W.D., Tyhach, R.J., Goldstein, S.L., Engel, R., and Tropp, B.E. (1975). Investigations concerning the mode of action of 3,4-dihydroxybutyl-1-phosphonate in *Escherichia coli*, *J. Biol. Chem.*, *250*: 1633.
264. Lalinde, N., Tropp, B.E., and Engel, R. (1983). Isosteres of natural phosphates. 10. Synthesis of analogues related to glycerol 3-phosphate, *Tetrahedron*, *39*: 2369.
265. Schwartz, P.W., Tropp, B.E., and Engel, R. (1989). Phosphonolipids. 2. α-Hydroxyphosphonolipid analogues of phosphatidic acid, *Chem. Phys. Lipids*, *49*: 131.
266. Rosenthal, A.F., Vargas, L.A., and Dixon, J.F. (1977). Synthesis of long-chain ethers by phase-transfer. Improved preparation of D-mannitol 1,2,5,6-tetraoctadecyl ether, *Chem. Phys. Lipids*, *20*: 205.
267. Friedmann, H.H., and DuBois, R.A. (1975). An improved Williamson ether synthesis using phase transfer catalysis, *Tetrahedron Lett.*: 3251.
268. Moschidis, M.C. (1985). Synthesis of 1,2-dipalmitoyloxy-propyl-3-(2-trimethylammoniumethyl)phosphinate, *Chem. Phys. Lipids*, *36*: 343.
269. Moschidis, M.C. (1985). Synthesis of 1,2-dipalmitoyloxy-propyl-3-(2-ammoniumethyl)phosphinate, *Naturforsch.*, *40C*: 595.
270. Eibl, H., and Nicksch, A. (1978). The synthesis of phospholipids by direct amination, *Chem. Phys. Lipids*, *22*: 1.
271. Slotin, L.A. (1977). Current methods of phosphorylation of biological molecules, *Synthesis*: 737.
272. Bittman, R., Rosenthal, A.F., and Vargas, L.A. (1984). Synthesis of phospholipids *via* dimethyl phosphoryl chloride, *Chem. Phys. Lipids*, *34*: 201.
273. Witzke, N., and Bittman, R. (1985). Synthesis of phosphatidylcholine analogs with an alkyl group at C1 or C3 of the glycerol moiety, *J. Lipid Res.*, *26*: 623.
274. Watanabe, Y., Hyodo, N., and Ozaki, S. (1988). Dibenzyl phosphorofluoridate, a new phosphorylating agent, *Tetrahedron Lett.*, *29*: 5763.
275. Magolda, R.L., and Johnson, P.R. (1985). A new efficient and versatile synthesis of alkylphosphorylcholines, *Tetrahedron Lett.*, *26*: 1167.
276. Aneja, R., Chada, J.S., and Davies, A.P. (1970). A general

synthesis of glycerophospholipids, *Biochem. Biophys. Acta*, *218*: 102.
277. Aneja, R., and Davies, A.P. (1970). The synthesis of a spin-labelled glycero-phospholipid, *Chem. Phys. Lipids*, *4*: 60.
278. Isaacson, Y.A., Deroo, P.W., Rosenthal, A.F., Bittman, R., McIntyre, J.D., Bock, H.-G., Gazzotti, P., and Fleischer, S.J. (1979). The structural specificity of lecithin for activation of purified D-β-hydroxybutyrate apodehydrogenase, *J. Biol. Chem.*, *254*: 117.
279. Aarsman, A.J., van Deenen, L.L.M., and van den Bosch, H. (1976). Studies on lysophospholipases. VII. Synthesis of acylthioester analogs of lysolecithins and their use in a continuous spectrophotometric assay for lysophospholipases, a method with potential applicability to other lipolytic enzymes, *Bioorg. Chem.*, *5*: 241.
280. Wissner, A., Schaub, R.E., Sum, P.-E., Kohler, C.A., and Goldstein, B.M. (1986). Analogues of platelet activating factor. 4. Some modifications of the phosphocholine moiety, *J. Med. Chem.*, *29*: 328.
281. Ukawa, K., Imamiya, E., Yamamoto, H., Mizuno, K., Tasaka, A., Terashita, Z., Okutani, T., Nomura, H., Kasukabe, T., Hozomi, M., Kudo, I., and Inoue, K. (1989). Synthesis and antitumor activity of new alkylphospholipids containing modifications of the phosphocholine moiety, *Chem. Pharm. Bull.*, *37*: 1249.
282. Bonsen, P.P.M.., de Haas, G.H., Pieterson, W.A., and van Deenen, L.L.M. (1972). Studies on phospholipase A and its zymogen from bovine pancreas. IV. The influence of chemical modification of the lecithin structure on substrate properties, *Biochem. Biophys. Acta*, *270*: 364.
283. Thuong, N.T., and Chabrier, P. (1974). Nouvelle methode de preparation de la phosphorylcholine, de la phosphonylhomocholine et de leurs derives, *Bull. Soc. Chim. Fr.*: 667.
284. Phuong, N.H., Thuong, N.T., and Chabrier, P. (1975). Nouvelle methode de preparation des α et β glycerylphosphorylcholines et de leurs homologues et analogues, *Bull. Soc. Chim. Fr.*: 2326.
285. Nifant'ev, E.E., Predvoditelev, D.A., and Alarkon, K.K. (1976). Synthesis of lipids and their models based on glycerol ethylene phosphite. I. 1,2-Isopropylideneglycerol

ethylene phosphite. New approach to lecithin synthesis, *Zh. Obshch. Khim.*, *46*: 912.
285a. Gadek, T.R. Trimethylsilyl triflate mediated introduction of phospholipid head group, *Tetrahedron Lett.*, *30*: 915.
286. Letsinger, R.L., and Heavner, G.H. (1975). Synthesis of phosphoromonoamidate diester nucleotides *via* the phosphite-azide coupling method, *Tetrahedron Lett.*: 147.
287. Nifant'ev, E.E., Predvoditelev, D.A., and Shin, V.A. (1978). New approach used in the synthesis of glycophospholipids, *Mendelev Chem. J., Engl. Transl.*, *23*: 220.
288. Nifant'ev, E.E., Predvoditelev, D.A., Grachev, M.K., and Shin, V.A. (1978). Synthesis of 6-phosphatidylglucose and its analogs, *Sov. J. Bioorg. Chem., Engl. Transl.*, *4*: 877.
289. McGuigan, C. (1986). A new and rapid synthesis of phospholipids, *J. Chem. Soc., Chem. Commun.*: 533.
290. Anson, M.S., and McGuigan, C. (1987). The synthesis of novel phospholipids related to ethylenediamine, *J. Chem. Soc., Chem. Commun.*: 1275.
290a. Stumpf, R., and Lemmen, P. (1990). Syntheses of phospholipids *via* oxazaphospholanes, *Z. Naturforsch.*, *45B*: 1729.
290b. McGuigan, C., and Swords, B. (1990). Synthesis of phospholipids by phosphoramidite methodology, *J. Chem. Soc., Perkin Trans. I*: 783.
291. Bruzik, K.S. (1986). The synthesis and absolute configuration of thiosphingomyelins, *J. Chem. Soc., Chem. Commun.*: 329.
292. Perich, J.W., and Johns, R.B. (1987). A new, convenient and efficient general procedure for the conversion of alcohols into their dibenzyl phosphorotriesters using *N,N*-diethyl dibenzyl phosphoroamidite, *Tetrahedron Lett.*, *28*: 101.
293. Martin, S.F., and Josey, J.A. (1988). A general protocol for the preparation of phospholipids *via* phosphite coupling, *Tetrahedron Lett.*, *29*: 6513.
294. Lemmen, P., Buchweitz, K., and Stumpf, R. (1990). A synthesis of phospholipids using a phosphite-triester approach and uniform cleavage of β-halogenated protecting groups, *Chem. Phys. Lipids*, *53*: 65.
295. Arbuzov, B.A., Kadyrov, R.A., Klochkov, V.V., Arsminova, R.P., and Aganov, A.V. (1982). Steric structure of phosphorus-containing heterocycles. 26. Synthesis and structure of 2-dialkylamino-1,3,2-dioxaphosphepanes with a

planar atomic group in the ring, *Izv. Akad. Nauk S.S.S.R., Ser. Khim.*: 588.
296. Garegg, P.J., Lindh, I., Regberg, T., Stawinski, J., Stromberg, R., and Henrichson, C. (1986). Nucleoside H-phosphonates. III. Chemical synthesis of oligodeoxyribonucleotides by the hydrogenphosphonate approach, *Tetrahedron Lett.*, *27*: 4051.
297. Lindh, I., and Stawinski, J. (1989). A general method for the synthesis of glycerophospholipids and their analogues *via* H-phosphonate intermediates, *J. Org. Chem.*, *54*: 1338.

CHAPTER 13

THE APPLICATION OF PHOSPHINYL-STABILIZED YLIDS AND CARBANIONS IN THE SYNTHESIS OF PHOSPHONATES AND PHOSPHINATES OF BIOLOGICAL INTEREST

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I. Introduction

Phosphinyl compounds [-O-P(O)-R_2- in which at least one R = C and the other is -O-], in particular phosphonates and phosphinates, have enjoyed numerous commercial and scientific applications over the last few decades. One type of application comprises the myriad of such compounds which have found uses in biochemical studies and as antimetabolites. This subject was reviewed just over a decade ago[1,2] and is periodically updated on a regular basis.* As regards antimetabolites, phosphinyl compounds were originally utilized as simple "isosteric" analogues# of the phosphoryl moiety of the plethora of phosphorus-containing metabolites. For example, glyphosate (1), one of the most important commercial phosphonates, has been shown to provide its broad-spectrum herbicidal activity by acting as a potent inhibitor, competitive with respect to phosphoenolpyruvate, of enolpyruvyl-shikimate-phosphate synthetase.[3] More recently, phosphonates have been shown in many cases to be credible if not excellent mimics of the tetrahedral transition-state formed upon attack of a nucleophile upon a carbonyl center. As examples, compound (2) is

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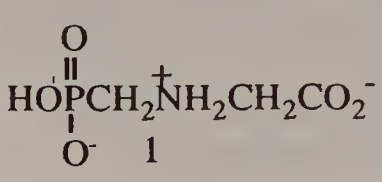
* The reader's attention is directed to the serial *Organophosphorus Chemistry* published by the Royal Society of Chemistry. Through Volume 17 (1986) this publication included a chapter entitled "Phosphates and Phosphonates of Biochemical Interest." Currently there is an annual chapter on Nucleotides and Nucleic Acids as well as other relevant coverages in chapters on tervalent, tetravalent, and quinquevalent phosphorus.

Here we shall refer to *isosteric* as the methylene group providing an exact replacement for a bridge oxygen without concern for the precision of that assumption.

an exceedingly potent ($K_i < 7 \times 10^{-11}$ *M*) and slow acting ($t_{1/2}$ for association ~2 hr) transition-state analogue inhibitor of pepsin,[4] (3) is a potent inhibitor of cytidine deaminase,[5] and (4) was designed to mimic the transition-state of glutamine synthetase.[6]



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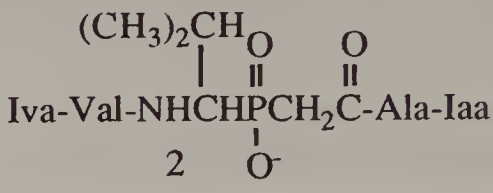

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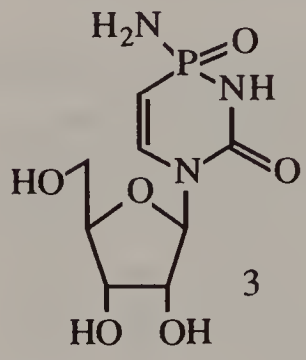

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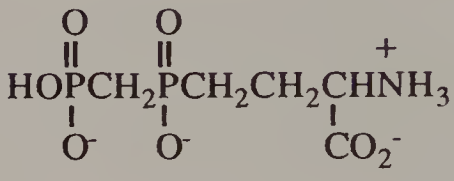

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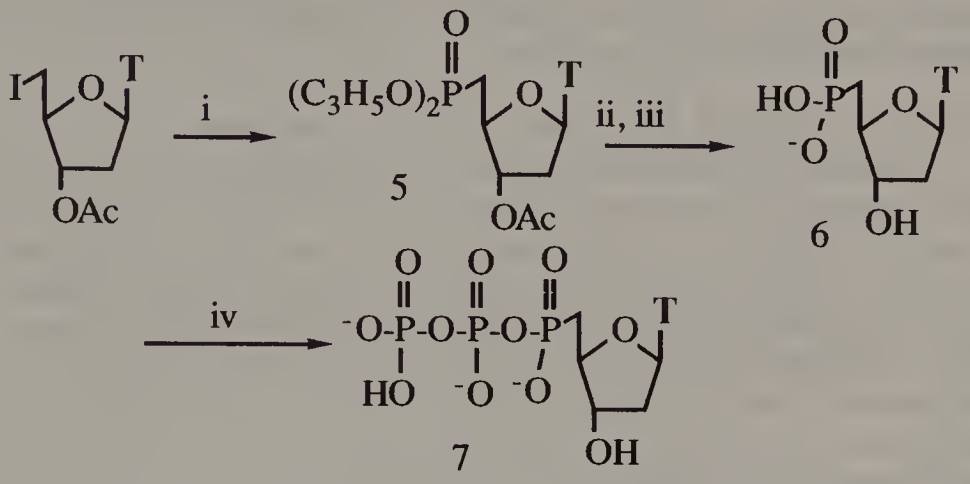
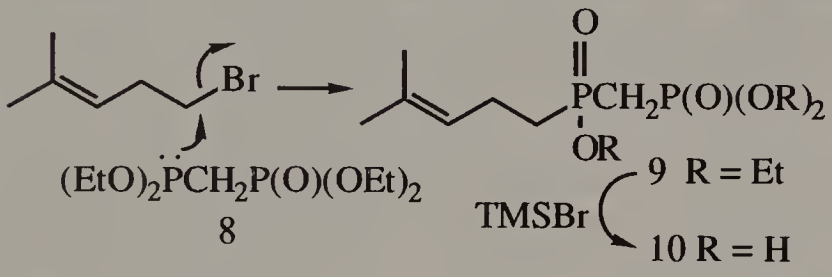
Many synthetic routes to phosphinyl compounds have been devised to prepare such materials and these approaches can be categorized into two main groups. One route could be broadly described as the Arbuzov-Michaelis-Becker reaction and involves the nucleophilic attack of a phosphite or phosphonite (either as the fully protected ester or as a salt) upon an appropriate carbon electrophile. For example, 3'-acetyl-5'-deoxy-5'-iodothymidine reacts with triallyl phosphite to yield the phosphonate (5) which, after ammonolysis and hydrogenolysis, yielded the phosphonate analogue (6) of thymidylate. Anhydride formation with diphosphate gave the dTTP analogue (7).[7] The hemioxidized methylene-bisphosphonate (8) can react with suitable electrophiles to yield (9) and, after treatment with TMSBr, (10), the phosphonylphosphinyl (P-C-P-C-) analogue of dimethylallyl diphosphate,[8] for example. In general, such reactions are very useful and numerous recent examples have demonstrated some interesting variations. The subject of carbon-phosphorus bond formation was covered thoroughly quite recently[9] and only some very recent examples of this approach will be discussed at the end of this Chapter.

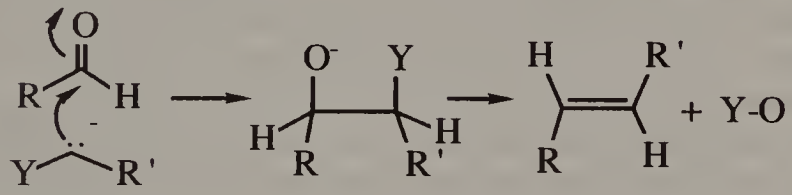
The other major route to the synthesis of the target compounds primarily involves the so-called Horner-Emmons-

Wadsworth (HEW) and Wittig reactions which involve the formation of C-C bonds and share several mechanistic features.



i. $(C_3H_5O)_3P$ ii. NH_3 iii. H_2/Pd iv. Im_2CO, $Bu_3NH^+H_3P_2O_7^-$





Wittig reaction: $Y = Ph_3P^+$, $Y\text{-}O = Ph_3P{=}O$

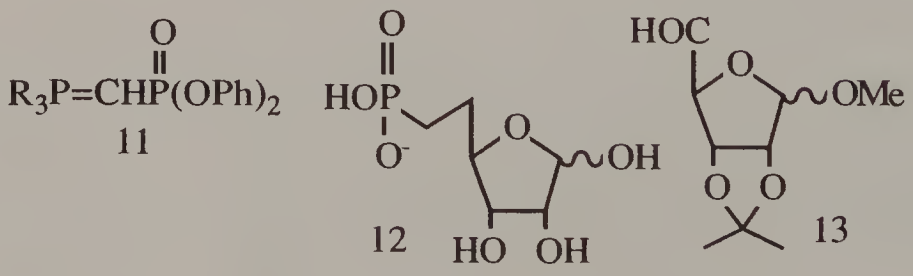
HEW reaction: $Y = (R''O)_2P(O)$ and $Y\text{-}O = (R''O)_2PO_2^-$

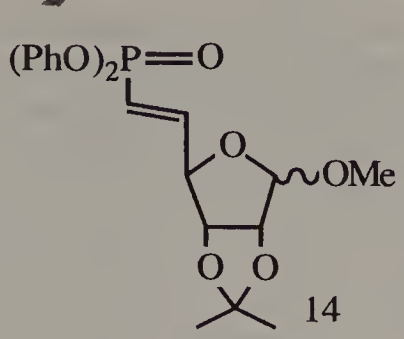
The mechanistic and general synthetic aspects of the Wittig and HEW reactions were very recently covered in an excellent review by Maryanoff and Reitz[10] and accordingly such details of these reactions will not be reexamined here. Instead we shall concentrate on a sampling of illustrative examples taken from our own work and the work of others in order to provide an introduction into the types of applications that have worked (or have not worked) for the preparation of phosphonates and

phosphinates of biological interest. Our purpose will not be to attempt to review the literature exhaustively, but to provide an overview of the subject. Included in this Chapter will be a discussion of the related applications of phosphinyl-enolates and their nucleophilic attack on carbon.

II. The "Moffatt" Ylid and Related Synthons

Perhaps the earliest example of the Wittig reaction in the direct synthesis of phosphonates was the introduction by Moffatt, *et al.*[11] of ylid (11) which was readily prepared (after base work-up) by either reaction of triphenylmethylphosphoranylidene with diphenyl chlorophosphate or by quaternization (triphenylphosphine or tributylphosphine) of diphenyl chloromethylphosphonate. The stable crystalline product was shown to react nicely with aldehydes, in particular 5'-aldehydo-nucleosides[12] to yield an appropriate vinylphosphonate that could be reduced by catalytic hydrogenation. Jones and Moffatt[13] demonstrated in a patent, for example, the straightforward synthesis of the isosteric phosphonate (12) of ribose 5-phosphate from methyl 2,3-isopropylidene-ribose. "Moffatt oxidation" led to the 5-aldehydo sugar (13), which then reacts with (11) (R = -Ph or -Bu) to give the *trans* vinylphosphonate ester (14). Reduction with hydrogen over palladium afforded the saturated phosphonate (15) which was converted to the dibenzyl ester by transesterification, debenzylated by hydrogenolysis, and then deblocked. This Wittig reaction has been used to generate, among many such examples, the fructose 1-phosphate analogue (16),[14] the GMP analogue (17),[15] the vinylic phosphonate analogue of ATP (18),[16] which comes from (19),[12] the acyclic GMP phosphonate analogue (20),[17] and (21), an interesting squalene synthase inhibitor derived from the cyclopropyl aldehyde (22).[18]





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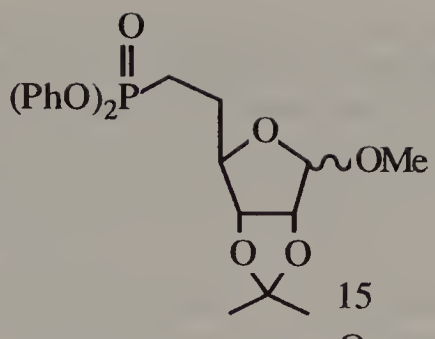

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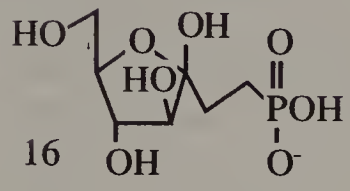

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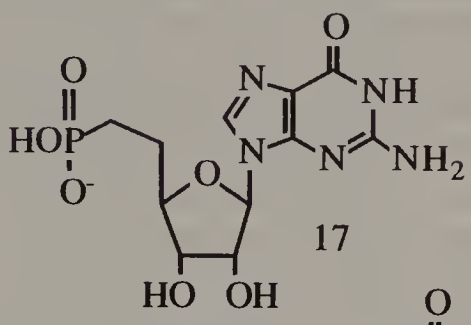

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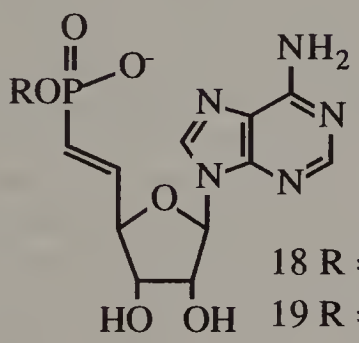
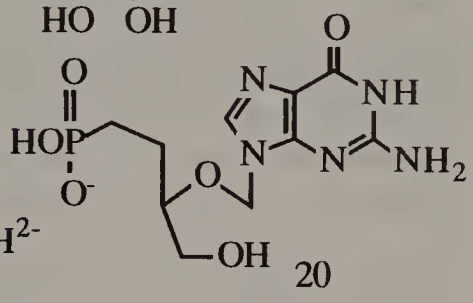


18 R = $P_2O_6H^{2-}$
19 R = H



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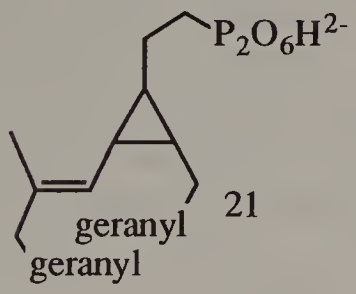

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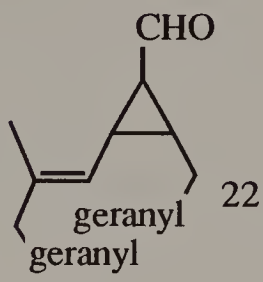
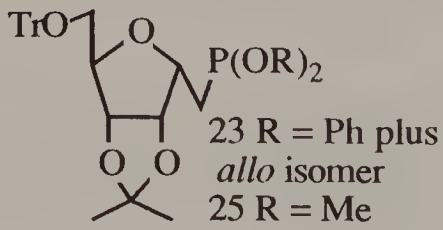


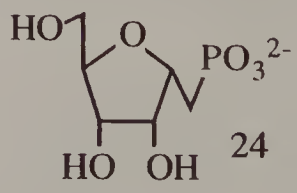
22

The ylid (11) also reacts nicely with 5-*O*-trityl-2,3-isopropylidene-D-ribose at the anomeric carbon to yield the diphenyl ester (23), which led to (24), the phosphonate analogue of ribose 1-phosphate,[19] an important intermediate in the metabolism of nucleosides. In accord with studies on related reactions with non-phosphinyl stabilized ylids,[20] this reaction proceeds first (kinetically) to the "β anomer"; upon equilibration with base (phenoxide ion) the desired α anomer (D-*altro* epimer) slowly

becomes the major product. The reaction produces an intermediate vinylphosphonate-alkoxide that undergoes Michael-type ring-closure.[20] Compound (24), which is a disappointingly weak inhibitor of nucleoside phosphorylase,[21] was also synthesized by way of an Arbuzov reaction[22] and by the HEW reaction,[21] the latter of which will be discussed below. Compound (25) [the dimethyl ester of (35); see preparation below] was detritylated, phosphorylated at C-6, and deesterified at the phosphonate to yield an intermediate which upon reaction with phenyl imidazolyl-phosphate gave (26). This compound was subjected to hydrogenation over platinum/platinum oxide in acidic solution to give (27), an analogue of 5-phosphorylribosyl 1-α-diphosphate. This analogue acts as an inhibitor of orotate phosphoribosyl-transferase[23] and presumably other phosphoribosyltransferases. Attempts to remove the isopropylidene moiety from (27) to yield the more exact analogue results in further hydrolysis of the anhydride due to attack on the phosphonyl phosphorus by the newly-released vicinal *cis* 3-OH. Interestingly, compound (11) does not react with benzyl protected sugars such as ribose or arabinose[24] or glucose,* and most peculiar, the dimethyl ester of (11) was reported not to react with tritylisopropylidene ribose.[21] It would thus appear that the 2,3-isopropylidene compound may be the only documented case where reaction of (11) occurs at a sugar hemiacetal. The intermediate (25) has also been detritylated and tosylated at C-6, substituted at C-6 by thiomethoxide, and deprotected to yield the crystalline single isomer (28), which is the isosteric phosphonate analogue of methylthioribosyl 1-α-phosphate,# an intermediate in the polyamine biosynthetic pathway.

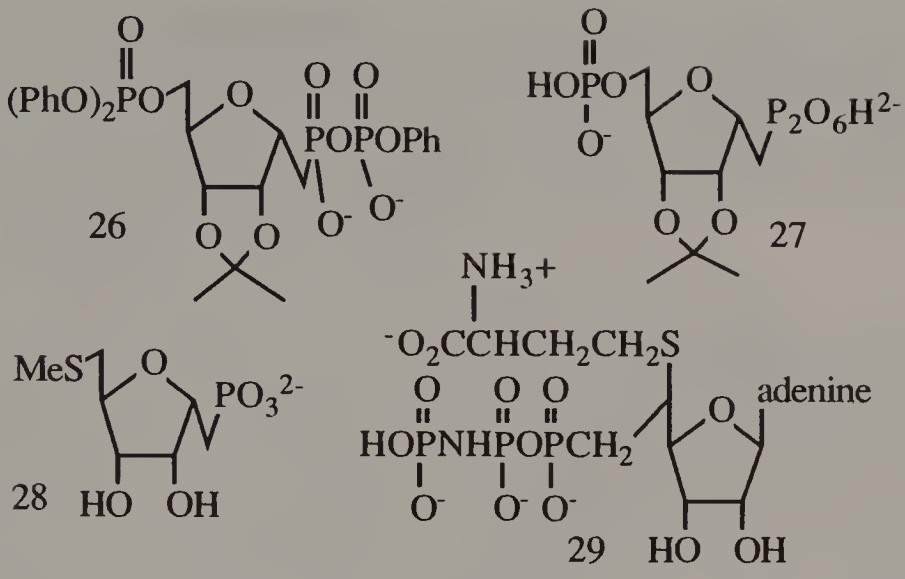


23 R = Ph plus *allo* isomer
25 R = Me



24

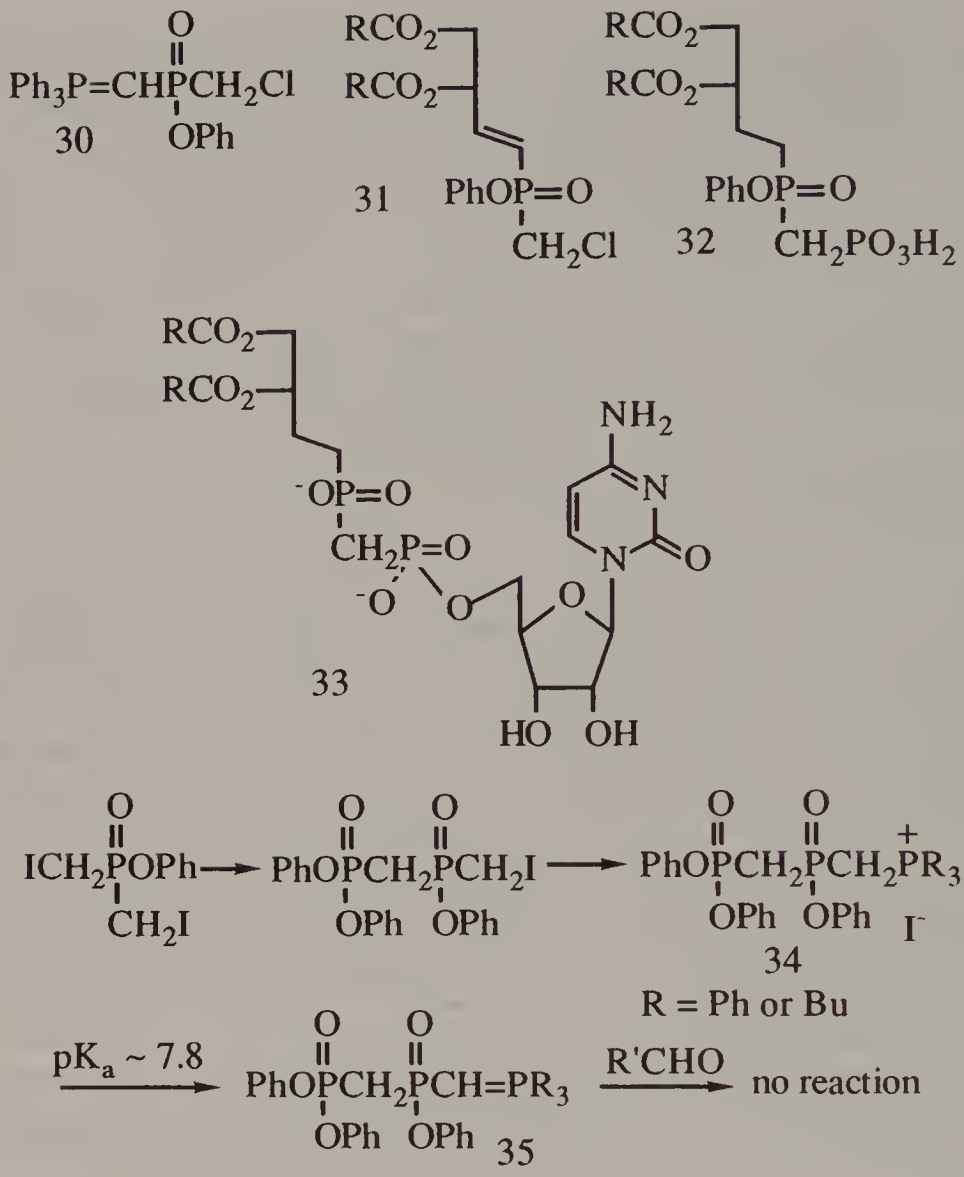
*Ray, William J., Jr., personal communication
#Witte, J.F., and McClard, R.W., unpublished results



The ability of vinylphosphonates to undergo readily Michael-addition reactions was cleverly exploited by Kappler, *et al.*,[25] who used the long-known (19)[12] as an acceptor of various S-nucleophiles. For example, reaction with homocysteine yielded compound (29), which is nominally a bisubstrate analogue of methionine adenosyltransferase.

In 1983, Vargas and Rosenthal[26] introduced the modified Moffatt ylid (30) which possesses an interesting and exploitable dipole of reactivity. This compound acts first as a nucleophile in a typical Wittig reaction to give the vinylic phosphinate (31), leaving the α-halomethyl functionality intact in good yield. A traditional Arbuzov reaction followed by reduction and partial deesterification led to the novel phosphonylphosphinate (32) which was coupled with cytidine to afford ultimately the very interesting compound (33),[27] which is the completely non-hydrolyzable (*i.e.* with respect to the diphosphate portion of the molecule) isosteric analogue of CDP-acylglycerol. This was probably the first published example of this class (P-C-P-C) of metabolite analogue.

Such compounds can also be synthesized by use of an Arbuzov reaction that employs either the hemioxidized tetraethyl ester of methylenebisphosphonite[8] or the methylenebisphosphonite itself.[6] We also reasoned that P-C-P-C compounds could be produced by analogy to the Moffatt synthesis for simple phosphonates by extending the synthon by an additional methylenephosphonate unit.[28]



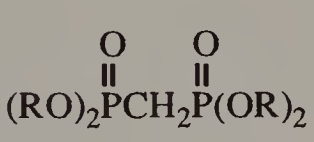
The penultimate phosphonium salt product (34) is prepared from phenyl bis(iodomethyl)phosphinate followed by quaternization. Titration by base to the ylid (35) occurs with a pK_a approximately 0.4 pH unit higher than the homologous Moffatt ylid (11). From

* McClard, R.W., Jackson, S.A., Bard, R., and Witte, J.F., unpublished results.

electronic considerations alone, one would therefore expect (35) to react with aldehydes. Surprisingly, it does not react at all, under a variety of conditions.[28]* Perhaps the added steric bulk creates a transition-state much too high in energy. More successful approaches to P-C-P-C compounds using various phosphinyl-enolates will be discussed in the next two sections.

III. Applications of the HEW Reaction

As mentioned above, this reaction is analogous to the Wittig reaction, the main differences being that the HEW reaction is generally more vigorous and the enthalpic driving force is associated with the formation of the P=O of an ionized phosphonate (and therefore often insoluble in the reaction solvent) instead of the P=O of a phosphine oxide. In the majority of organic synthetic schemes the phosphinyl moiety is thought of as material to be jettisoned away after the formation of the C-C bond is accomplished. However, here we are interested in leaving at least one phosphorus atom in the product. Thus, syntheses of phosphonates generally involve the use of easily-generated carbanions of protected symmetrical methylenebisphosphonates, such as the tetramethyl ester (36), as illustrated by the alternative synthesis of the phosphonate analogue of (24) of ribose 1-phosphate *via* the dimethyl ester (25).[21] The synthesis of the isosteric 3'-phosphoryl nucleoside analogues (37a-d) also employed compound (36).[29] This approach has been used for the syntheses of (38)[30] and (39),* the latter of which has also been produced *via* Arbuzov reaction schemes.[31,32]



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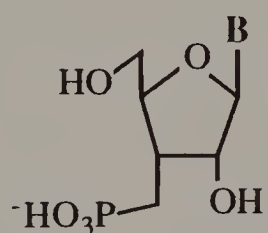
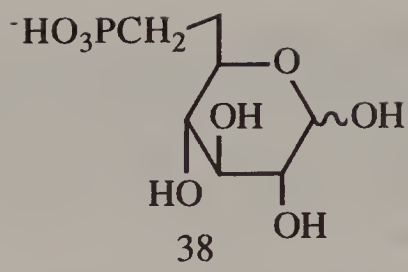


37a B = adenine
37b B = cytosine
37c B = thymine
37d B = uracil

*Ray, William J., Jr., personal communication.



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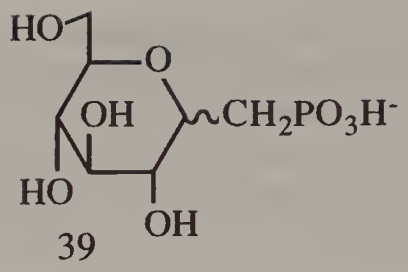
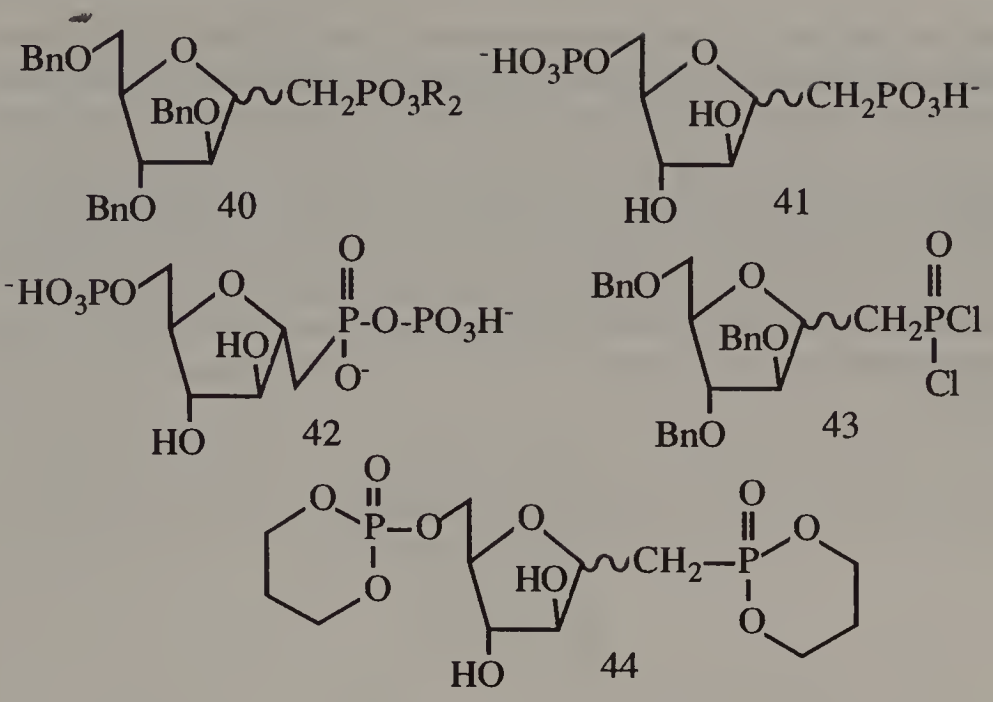


39

Because of the lack of reactivity of (11) in the case of tribenzyl arabinose, our laboratory also employed compound (36) (as either the tetraethyl or tetramethyl ester) recently to produce the intermediate phosphonate (40).[24] This compound was converted in several steps to the anomeric phosphonate analogue (41) of arabinose 1-phosphate with the expectation that this compound would serve as a modifier of phosphofructokinase and fructose bisphosphatase, which it did.[24] The D-*gluco* epimer of (41) was synthesized with a high degree of stereospecificity by Reitz, *et al.*[33] who employed an Arbuzov reaction. Partial deprotection at the 6-position, followed by deesterification at phosphorus, anhydride formation and deprotection leads to the 5-phosphoryl-ribose 1-α-diphosphate analogue (42), which is obtained as a single isomer because of selective hydrolysis of the D-*gluco* epimer from the neighboring *cis* hydroxyl.[23] Intermediate (40) can also be converted to the phosphinic dichloride (43) at low temperature,[34] diesterified by propanediol, and subsequently converted to (44), a protected derivative of (41) that is being evaluated as an *in vivo* modifier of glucose metabolism.*

The major advantage of the HEW approach is that one can usually obtain the product phosphonate in very high yields (the main "by-product" is usually a small amount of the open chain ene-ol, as in the case of the ylid reaction, which fails to close and shows up disproportionately on the TLC plate!) in a single reaction. The disadvantage is that one has little control over the relative amounts of epimers formed upon spontaneous ring closure at the prior anomeric carbon when reaction is conducted at the anomeric carbon of a sugar.

*Stowell, M.H.B., and McClard, R.W., manuscript in preparation.

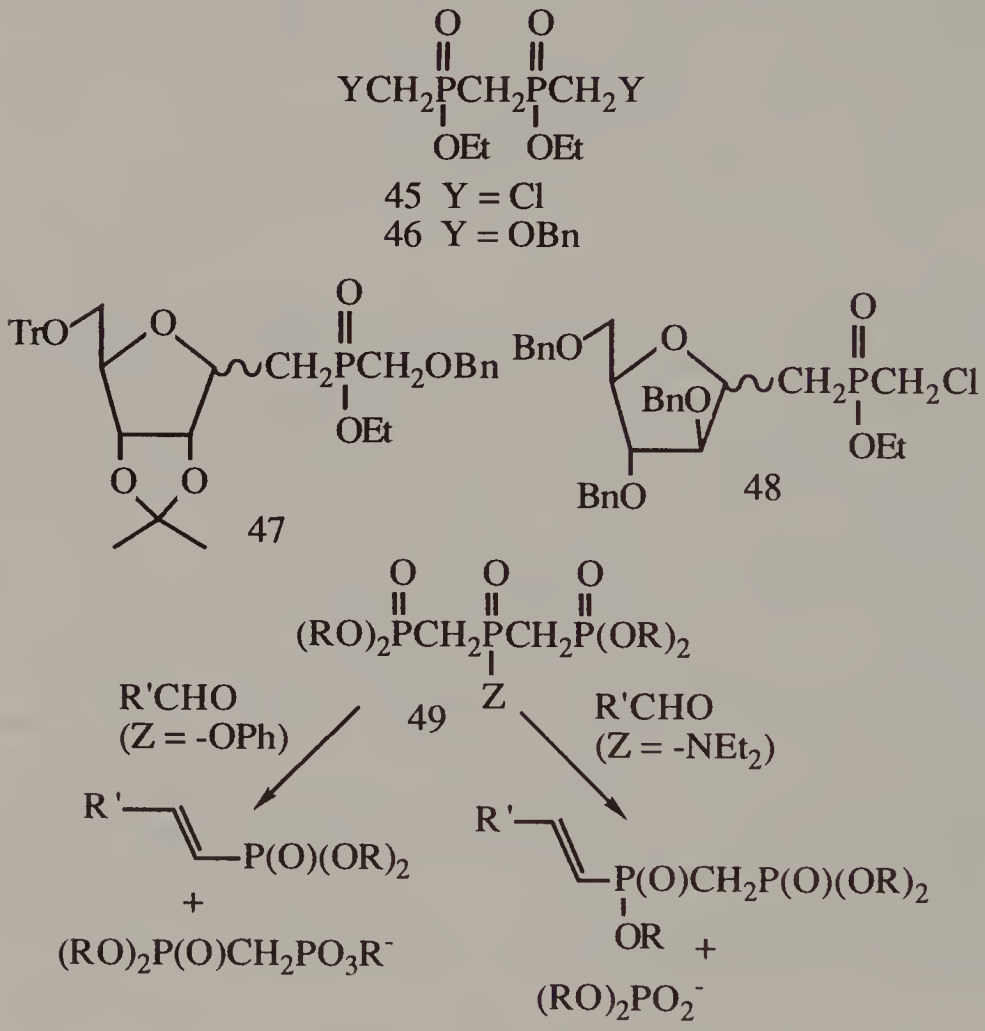


The HEW approach has also been attempted, with mixed success, to produce P-C-P-C- compounds. For example, we produced the symmetrical bisphosphonates (45) and (46) with the intention that they would carry out HEW reactions with appropriate electrophilic substrates and then either provide a center for Arbuzov attachment of the second phosphorus, as in (45), or allow for debenzylation followed by activation by a Tf or Ts and then an Arbuzov reaction, as with (46). We found, however, that (46) produced a compound (47) whose benzyl group was stubbornly resistent to hydrogenolysis.* Compound (45) underwent numerous side-reactions under HEW conditions; however, we did obtain tiny amounts of compound (48) from tribenzyl arabinose.* Although we have not investigated it further, (48) could be deprotected to give what might be an active-site-directed reagent for fructokinase. The problem with the synthesis of (45) and (46) is that the required intermediate is tetraethyl methylenebisphosphonite,[35] a compound which is both difficult to prepare and highly unstable.

Promise for the most successful approach to synthesizing P-C-P-C- compounds using the HEW reaction in one procedure came from the laboratory of Gilmore.[36,37] This group showed first that a symmetrical 3-phosphorus compound (49) [Z = OPh] could undergo a normal HEW reaction that unfortunately resulted in

*Fujita, T.S., Bard, R., and McClard, R.W., unpublished results.

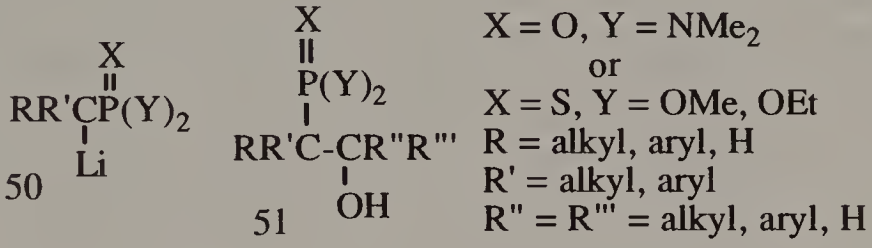
the production of a phosphonate and a bisphosphonate leaving group.[36] However, when the center phosphinate of (49) was changed to a phosphinamide [Z = -$N(CH_2CH_2CH_3)_3$], the reaction course went in the desired direction.[37] The authors attributed this result to the greater steric hindrance imposed by the bulkier dialkyl amide and not to electronic factors; this conclusion was corroborated by studies where Z was varied among a series of esters and amides. To date this approach does not seem to have been applied to the synthesis of P-C-P-C compounds of biological interest.



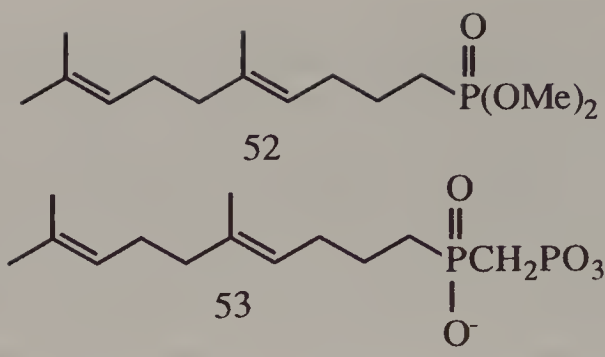
IV. Phosphinyl-stabilized (Non-ylid) Carbanions

In 1966 Corey and Kwiatkowski were the first to demonstrate that α-lithio alkyl carbanions, stabilized by phosphonic diesters such as (50),[38] thioate diesters,[39] and bisamides[40] could

be generated in high yield, were relatively stable, and underwent mono-addition or substitution reactions, again in excellent yield, with several classes of carbon electrophiles including aldehydes, ketones, esters, and those alkyl halides which are not prone to competing E2 elimination processes. Although the main thrust of these investigations was to utilize readily available phosphonic acid derivatives for the production of olefins (with outstanding success) from the isolable intermediate β-hydroxyphosphonyl addition intermediates, such as (51), derived from aldehydes or ketones, β-ketophosphonyl compounds also became available upon oxidation of these same substances. In addition, this method obviated the need to generate phosphonium salt intermediates required for the Wittig reaction.



Subsequently, carbanions of this type [most often (50) with R = R' = H, Y = OMe] have been utilized to introduce the phosphonyl moiety into organic molecules for a variety of reasons. For example, Corey and Volante[18] synthesized the phosphonate isostere (52) of geranyl phosphate from geranyl bromide. The phosphonate was subsequently transformed into the phosphonylphosphate analogue (53) of geranyl pyrophosphate *via* coupling through the morpholidate. Similarly prepared were the phosphonylphosphate analogues of isopentenyl-, farnesyl-, and γ,γ-dimethylallyl diphosphate - all of which, at appropriate concentrations, were capable of completely inhibiting the biochemical formation of squalene and kaurene, which arise from the mevalonate pathway of isoprenoid biosynthesis.



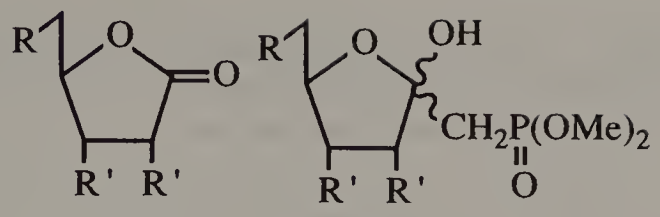
52

53

These phosphinyl enolates also react smoothly with lactones. Marquez, *et al.*[41] found that (50), upon reaction with 5-*O*-benzyl-2,3-di-*O*-isopropylidene-D-ribonolactone (54a) furnished, in quantitative yield, the lactol phosphonate (55a), a key intermediate in the multigram synthesis of the *C*-glycoside antineoplastic agent, Neplanocin A.[41] We have subsequently reinvestigated this reaction in some detail with the suitably protected derivatives of D-ribonolactone (54b-e) and have obtained the corresponding lactol phosphonates (55b-e) in quantitative yields when ~2.5 equivalents of (50) was allowed to react with (54b-e) at -78°.* Deprotection of any one of these products, (55b) for example, gives (56), a 1-deoxy-1-dihydroxyphosphinyl derivative of psicose. This product is expected to furnish a potential inhibitor of nucleoside phosphorylase. In addition, we have found that (54c) and (54e) undergo reaction with excess trifluoroacetic anhydride/acetic acid to furnish the corresponding vinylphosphonates (57a) and (57b) respectively in quantitative yield. These novel compounds may be well-suited to function as Michael acceptors and could therefore serve as agents for the introduction of carbon or nitrogen nucleophiles at C-2 of (57a) and (57b) to produce bisubstrate analogues of the nucleoside phosphorylase reaction as attempted recently and reported in an abstract from Montgomery, *et al.*[42]

In addition, Tanaka, *et al.*[43] recently utilized (50) in conjunction with boron trifluoride etherate to effect a Lewis acid-catalyzed nucleophilic displacement on the readily available oxetane (58) derived from thymidine,[44] as the key reaction in the preparation of the phosphonate isostere (59) of AZT 5'-phosphate.

*Witte, J.F., and McClard, R.W., unpublished results.



54a-e 55a-e

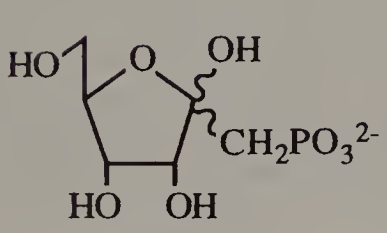
a R = OBn, R' = Me_2C(O)(O)

b R = OTr, R' = Me_2C(O)(O)

c R = R' = TBDPSiO

d R = TBDPSiO, R' = Me_2C(O)(O)(O)

e R = TBDPSiO, R' Me(MeO)C(O)(O)



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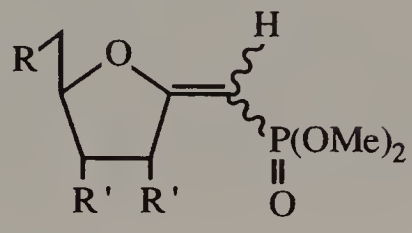
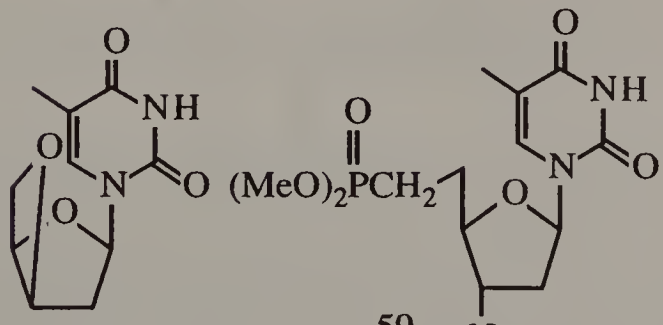


57a R = R' = TBDPSiO
57b R = TBDPSi, R' = OAc

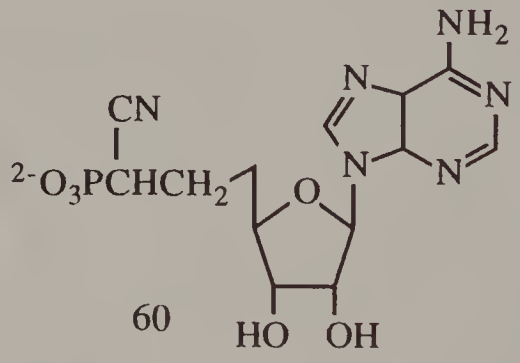


58 59

Carbanions derived from compounds of the general structure X-CH_2-P(O)$(OR)_2$ where X is an electron withdrawing group, such as -F, -CN, -C(O)(OR), or R-C(O)-, not surprisingly exhibit enhanced stability over the lithiated species we have been discussing above. Such "doubly stabilized anions" are easily prepared and effect S_N2 displacements with suitable carbon

electrophiles, R-Y (Y = -I, or OTs, for example). Such a reaction has been utilized to produce the phosphonate (60) for evaluation as an inhibitor of adenosyl binding enzymes.[45]

In some instances these enolates are far too reactive to be employed. For example, to circumvent the Perkow reaction in the attempted formation of β-ketophosphonates from α-haloketones, the use of an acyl halide and lithiated phosphinyl enolate is generally unsuccessful. Savignac and Mathey[46] addressed this problem by introducing a new and general method which utilizes a copper derivative of dimethyl methylphosphonate (61) for the synthesis of β-ketophosphonates [X = RC(O)-, above] such as (62). In this scheme (50) was allowed to react with cuprous bromide or iodide at -35°C in THF and then a carboxylic acid chloride was introduced. In this manner (62) and related alkyl compounds were prepared from (50) (R = OMe) or other appropriate starting material. β-Ketothioates, such as (63), also became accessible by this procedure and yields were uniformly high. Bone and Wolfenden* employed this approach to prepare compounds (64)-(66) which turned out to be rather disappointing effectors of enzymes primarily in aromatic amino acid biosynthesis.



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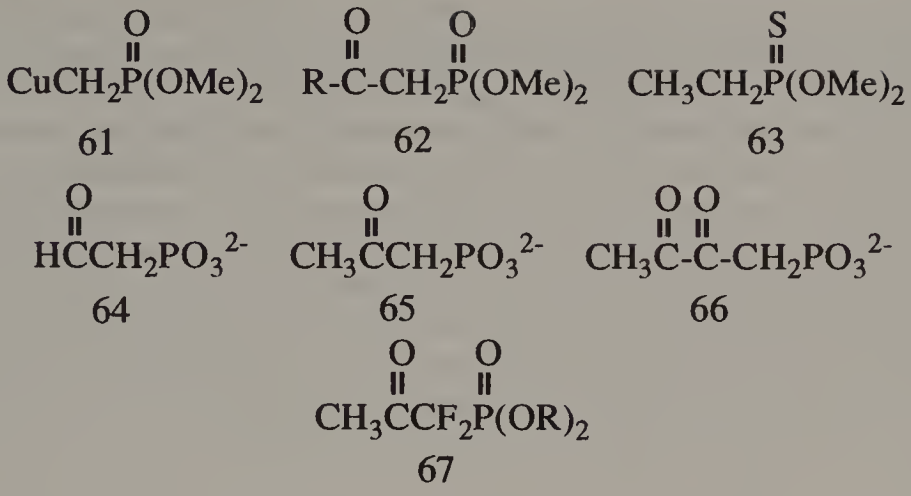
Burton, *et al.*[47] showed that zinc could be used to attenuate the reactivity of difluoromethylphosphinyl enolates and thus produced essentially the alkyl-protected difluoromethylphosphonate analogue (67) of acetyl phosphate, for example. More recently

*Bone, R., and Wolfenden, R.V., personal communication.



61 62 63

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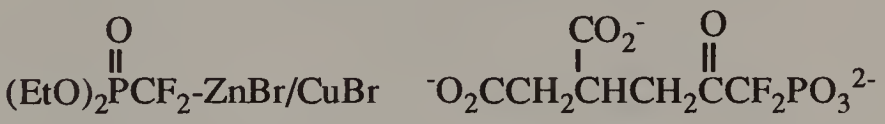
67

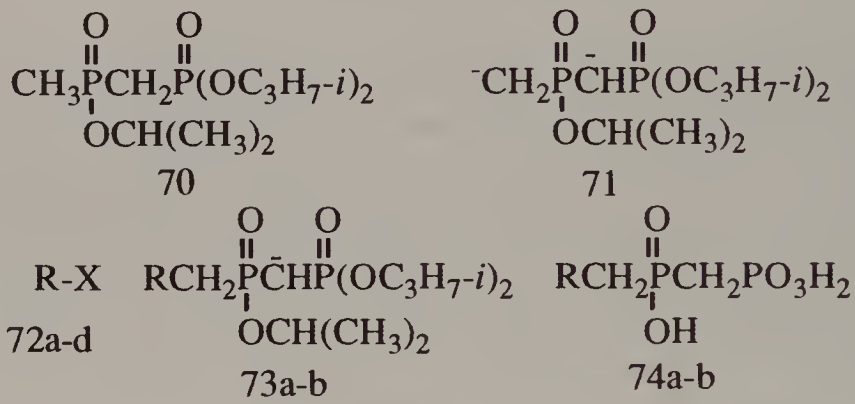
Lindell and Turner[48] utilized the difluoroalkyl-organozinc phosphonate reagent (68) prepared by the method of Burton and Sprague[49] and activated by the method of Knochel, *et al.*,[50] to achieve a potential inhibitor (69) of aspartate transcarbamylase. Although (69) proved not to inhibit the reaction catalyzed by aspartate transcarbamylase, it did provide an entry into difluoro β-ketophosphonates which, for reasons laid down by Blackburn,[51] might function as better mimics of phosphonates than their corresponding methylene counterparts.



68 69

An extension of the chemistry associated with phosphorus-stabilized carbanions was realized when we demonstrated that the phosphinylphosphonate (70) could be utilized to generate phosphonylphosphinyl stabilized dicarbanions, such as (71), and that (71) readily effected S_N2 displacements on both unhindered and hindered carbon electrophiles.[52] The precursor to the dianion reagent (70) was produced from the auto-dimerization of lithio diisopropyl methylphosphonate by a method similar to that described by Teulade, *et al.*[53] The dianion reaction was modelled upon similar chemistry developed by Grieco and Pognowski[54] for the alkylation of dianions derived from β-ketophosphonates. Careful formation of the dianion allowed reaction primarily at the

terminal methyl of (69) and not the more acidic methylene to give, upon reaction with (72a-d), high yields of the esters (73a-d). Deprotection yielded the phosphonylphosphinyl (P-C-P-C-) analogues (74a) and (74b) of the natural diphosphate precursors to the higher isoprenoids and both products have been shown to be competant competitive inhibitors of farnesyl diphosphate synthase involved in the isoprenoid pathway leading to squalene.[8] In addition, it was found that the competing E2 process could be minimized by the proper choice of the leaving group.[52] Triflate derivatives of hindered electrophiles, such as (72c) and (72d), proved extremely valuable reagents in this regard.[52]

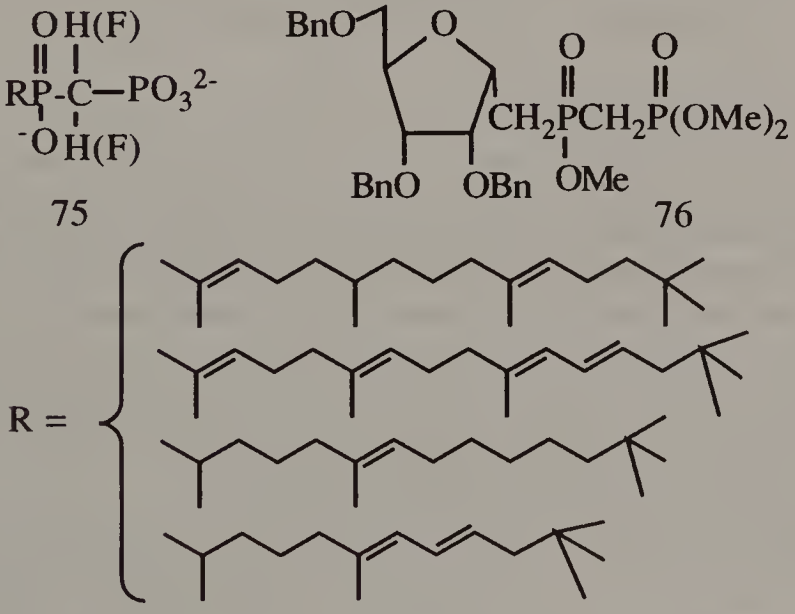


a R = $Me_2C{=}CCH_2$-, X = Br
b R = geranyl-, X = Br
c R = Me_2CH-, X = OTf
d R = Me_2CHCH_2-, X = OTf

Previously, the synthesis of P-C-P-C- mimics of diphosphates had employed either the multistep ylid/Arbuzov approach[26,27] or the horrendously unstable P^{III}-P^{V} Arbuzov reagent (8), obtianed in only 3% yield[8] *via* the bisphosphonite described by Novikova, *et al.*[35] The new dianion chemistry not only obviated the need to prepare and handle this extremely air and moisture sensitive reagent (8), but also had the additional advantage, as in the case of (8), that the homo-allylic electrophiles previously needed for the synthesis of these same analogues[8] were no longer required. Instead, the readily available derivatives, such as 1-bromo-3-methyl-2-butene, of naturally occurring isoprenoid alcohols could be employed to furnish these same P-C-P-C-isoprenoid analogues. In addition, this method should provide a

one step synthesis of P-C-P-C- compounds, previously available in three steps by the method of Vargas and Rosenthal[26]. In doing so the need to prepare the precursor aldehyde, often a difficult operation, and the subsequent low-yield Arbuzov reaction would not be required.

Another method for the synthesis of P-C-P-C- analogues of isoprenoid diphosphates has recently been developed by Biller, *et al.*[55] who invoked the reaction of preformed mono-phosphonic acid chloride esters, prepared from the diester by monodealkylation followed by reaction with oxalyl chloride, with lithiated phosphinyl-stabilized carbanions which included (50) and its difluoromethyl counterpart. The new compounds produced by this method, depicted collectively as (75), proved to be excellent inhibitors of squalene synthetase.[55] In addition, this method allowed the synthesis of the corresponding P-CF_2-P-C- analogues and has the additional advantage that the requisite mono-phosphonic acid chloride esters are, in general, readily prepared from the corresponding phosphonic diesters. Indeed, we have obtained promising results with the formation of (76), an intermediate in the synthesis of the P-C-P-C- analogue of 5'-phosphorylribose 1-α-diphosphate.* Thus the scheme may be quite general.



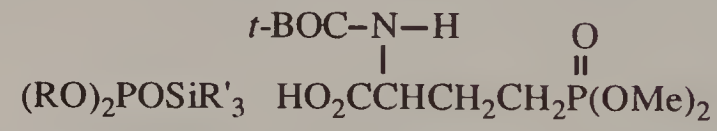
75 76

*Witte, J.F., and McClard, R.W., unpublished results.

V. Some Very Recent Methods for the Introduction of the Phosphonyl Moiety into Organic Molecules

The continuing interest in the production of phosphonyl and phosphinyl analogues of naturally occurring phosphorus-containing compounds has led to the development of new synthetic strategies. These strategies resemble the earlier work of Evans, *et al.*,[56] who in 1978 demonstrated that TMS- or TES-derivatives of dimethyl (or diethyl) phosphite (*ter*-valent phosphorus compounds) such as (77) functioned in the same manner as phosphorus anions which have been utilized in the familiar Michaelis-Becker modification of the Arbuzov reaction. These materials acted as phosphorus nucleophiles and underwent smooth reactions with a variety of carbon electrophiles including aldehydes, ketones (to yield TMS or TES ethers of α-hydroxyphosphonates) and α,β-unsaturated aldehydes and ketones to give, by 1,2- and/or 1,4-addition, the corresponding α- or γ-TMS or TES ether phosphonates.

The synthetic utility of this reaction has since been demonstrated by Valerio, *et al.*[57] to produce an optically active phosphonate isostere (78) of *O*-phosphoserine which was suitable for incorporation into peptides.

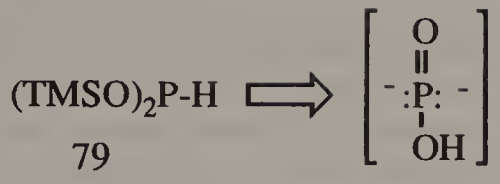


77a R = R' = Me
77b R = R' = Et

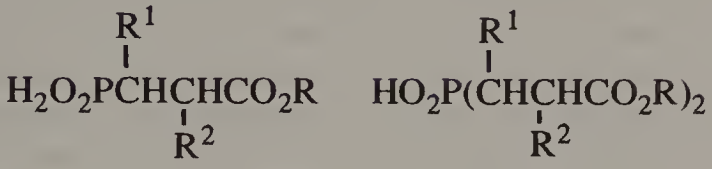
78

This reaction has been expanded by Boyd, *et al.*[58] who employed the *bis*-TMS ester of hypophosphorous acid (79). This reagent functioned as the phosphorus dianion equivalent of (80) and allowed the production of β-carboxylic acid esters of phosphonates (81) or phosphinates by controlling the amount of reagent that was employed. In this manner either symmetric (82) or dissymmetric (83) phosphinates could be obtained.

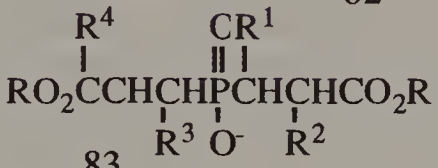
Indeed, Lindell and Turner[48] have introduced a variation on this procedure to produce the proposed P-C-P-C- inhibitor (84) of the enzyme aspartate transcarbamoylase. Thus another route to P-C-P-C- compounds of biological interest has become available which is convenient, versatile, and general.



79 80



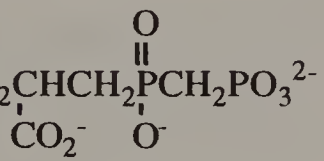
81 82



83

$R^1 = R^2 = H$; or R^1 = alkyl, $R^2 = H$; or $R^1 = H$, R^2 = alkyl

$R^3 = H$, R^4 = alkyl; or R^3 = alkyl, $R^4 = H$



84

Taken as a whole, the methods for the introduction of the phosphonylphosphinyl moiety(ies) into organic compounds, which we have described in this section, provide an attractive alternative to some of the chemistry presented in the previous sections. The methods just presented seem, in general, quite simple to employ, require no complex reagents, and thus should allow the synthesis of many of the compounds described earlier. Finally, it should be noted that this new chemistry involves the making of phosphorus-carbon bonds and not carbon-carbon bonds for the introduction of the phosphorus moiety into the organic molecule. Thus, the organic substrate needs to contain an additional carbon atom in order for these methods to succeed in producing certain of the compounds we have described in earlier sections.

VI. Summary

Phosphonates and phosphinates can be prepared by two

fundamentally different approaches. The Arbuzov-Michaelis-Becker reactions allow nucleophilic attack of a phosphorus center upon the carbon which, in the case of an isosteric analogue of a phosphate metabolite, ends up in place of the "bridge" oxygen. In such cases the electrophile must be the appropriate homolog (*i.e.*, one extra carbon) of the original phosphate alkyl group. The Horner-Emmons-Wadsworth, Wittig, and phosphinyl-enolate approaches, generally speaking, allow for the direct nucleophilic attack of a phosphorus-stabilized species upon a suitable (and generally more readily available) electrophilic derivative of a biologically interesting species. Each approach has its unique advantages and disadvantages. The latter approach has been used with great utility, including the use of stabilized dianions to form phosphonylphosphinyl compounds. Some of the more recent developments employ lithiated phosphinyl enolates and their less reactive - and thus, in many cases, their more selective - counterparts. Recent developments in silylated phosphonous compounds will no doubt renew interest in the Arbuzov-Michaelis-Becker approach.

VII. Bibliography

1. Engel, R. (1977). Phosphonates as analogues of natural phosphates, *Chem. Rev.*, *77*: 349.
2. Scheit, K.H. (1980). *Nucleotide analogs - Synthesis and biological function*, John Wiley and Sons, NY, Chapter 7.
3. Steinruecken, H.C., and Amrhein, N. (1984). 5-Enolpyruvylshikimate-3-phosphate synthase of *Klebsiella pneumoniae*. 2. Inhibition by glyphosate [*N*-(phosphonomethyl)glycine], *Eur. J. Biochem.*, *143*: 351.
4. Bartlett, P.A., and Kezer, W.B. (1984). Phosphinic acid dipeptide analogues: Potent slow-binding inhibitors of aspartic peptidases, *J. Am. Chem. Soc.*, *106*: 4282.
5. Ashley, G.W., and Bartlett, P.A. (1982). A phosphorus-containing pyrimidine analog as a potent inhibitor of cytidine deaminase, *Biochim. Biophys. Acta*, *108*: 1467.
6. Farrington, G.K., Kumar, A., and Wedler, F.C. (1987). Design and synthesis of phosphonate inhibitors of glutamine synthetase, *J. Med. Chem.*, *30*: 2062.
7. Rammler, D.H., Yengoyan, L., Paul, A.V., and Bax, P.C. (1967). Nucleoside phosphonic acids. II. The synthesis of 5'-deoxythymidine 5'-phosphonic acid and its pyrophosphate derivatives, *Biochemistry*, *6*: 1828.

8. McClard, R.W., Fujita, T.S., Stremler, K.E., and Poulter, C.D. (1987). Novel phosphonylphosphinyl (P-C-P-C-) analogues of biochemically interesting diphosphates. Synthesis and properties of P-C-P-C- analogues of isopentenyl diphosphates and dimethylallyl diphosphate, *J. Am. Chem. Soc.*, *109*: 5544.
9. Engel, R. (1988). *Synthesis of carbon-phosphorus bonds*, CRC Press, Boca Raton, FL.
10. Maryanoff, B.E., and Reitz, A.B. (1989). The Wittig olefination reaction and modifications involving phosphoryl-stabilized carbanions. Stereochemistry, mechanism, and selected synthetic aspects, *Chem. Rev.*, *89*: 863.
11. Jones, G.H., Hamamura, B.K., and Moffatt, J.G. (1968). A stable Wittig reagent suitable for the synthesis of α,β-unsaturated phosphonates, *Tetrahedron Lett.*: 5731.
12. Jones, G.H., and Moffatt, J.G. (1968). The synthesis of 6-deoxyhomonucleoside-6'-phosphonic acids, *J. Am. Chem. Soc.*, *90*: 5337.
13. Jones, G.H., and Moffatt, J.G. (1971). Hexose and heptose phosphonates, phosphonic acids, phosphonic acid salts and derivatives thereof, *U.S. Patent 3,583,974*.
14. Tang, J.-C., Tropp, B.E., and Engel, R. (1978). Isosteres of natural phosphates. 8. The preparation and biological properties of 1-deoxy-1-dihydroxyphosphinylmethylfructose, an analogue of fructose 1-phosphate, *Tetrahedron Lett.*: 723.
15. Martin, J.C., and Verheyden, J.P.H. (1988). Synthesis of 4'-(hydroxymethyl)guanosine and a phosphonate analog of guanylic acid, *Nucleosid. Nucleotid.*, *7*: 365.
16. Kappler, F., Hai, T.T., and Hampton, A. (1985). Use of a vinyl phosphonate analog of ATP as a rotationally constrained probe of the C5'-O5' torsion angle in ATP complexed to a methionine adenosyl transferase, *Bioorg. Chem.*, *13*: 289.
17. Prisbe, E.J., Martin, J.C., McGee, D.P.C., Barker, M.F., Smee, D.F., Duke, A.E., Matthews, T.R., and Verheyden, J.P.H. (1986). Synthesis and antiherpes virus activity of phosphate and phosphonate derivatives of 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine, *J. Med. Chem.*, *29*: 671.
18. Corey, E.J., and Volante, R.P. (1976). Application of unreactive analogs of terpenoid pyrophosphates to studies of multistep biosynthesis. Demonstration that "presqualene

pyrophosphate" is an essential intermediate on the path to squalene, *J. Am. Chem. Soc.*, *98*: 1291.
19. McClard, R.W. (1983). A facile route to methylene-phosphonate sugars substituted at the anomeric center, *Tetrahedron Lett.*, *24*: 2631.
20. Ohrui, H., Jones, G.H., Moffatt, J.G., Maddox, M.L., Christensen, A.T., and Byram, S.K. (1975). *C*-Glycosyl nucleosides. V. Some unexpected observations on the relative stabilities of compounds containing fused five-membered rings with epimerizable substituents, *J. Am. Chem. Soc.*, *97*: 4602.
21. Meyer, R.B., Stone, T.E., and Jeshti, P.K. (1984). 2,5-Anhydro-1-deoxy-1-phosphono-D-altritol, an isosteric analogue of α-D-ribofuranose 1-phosphate, *J. Med. Chem.*, *27*: 1095.
22. Nicotra, F., Panza, L., Ronchetti, F., and Toma, L. (1984). High stereoselective synthesis of diethyl (2,3-isopropyl-idene-5-trityl-α-D-ribofuranosyl)methanephosphonate, a precursor to the phosphono analog of α-D-ribose 1-phosphate, *Tetrahedron Lett.*, *25*: 5937.
23. McClard, R.W., and Witte, J.F. (1990). Stable and non-hydrolyzable *C*-glycosylphosphonyl analogs of 5-phosphorylribose 1-α-D-diphosphate that act as inhibitors of orotate phosphoribosyltransferase, *Bioorg. Chem.*, *18*: 165.
24. McClard, R.W., Tsimikas, S., and Schriver, K.E. (1986). Inhibition of fructose bisphosphatase and stimulation of phosphofructokinase by a stable isosteric phosphonate analog of fructose 2,6-bisphosphate, *Arch. Biochem. Biophys.*, *245*: 282.
25. Kappler, F., Hai, T.T., Cotter, R.J., Hyver, K.J., and Hampton, A. (1986). Isozyme-specific enzyme inhibitors. 11. L-Homocysteine-ATP S-C5' covalent adducts as inhibitors of rat methionine adenosyltransferases, *J. Med. Chem.*, *29*: 1030.
26. Vargas, L.A., and Rosenthal, A.F. (1983). A reagent for introducing the phosphinic acid isostere of phosphodiesters, *J. Org. Chem.*, *48*: 4775.
27. Vargas, L.A., Miao, L.X., and Rosenthal, A.F. (1984). Inhibition of platelet phosphatidylinositol synthetase by an analog of CDP-diacylglycerol, *Biochem. Biophys. Acta*,

796: 123.
28. McClard, R.W., and Jackson, S.J. (1988). Synthesis of an unreactive ylid designed as a -C-P-C-P diphosphate isostere synthon, *Phosphorus Sulfur*, *39*: 27.
29. Albrecht, H.P., Jones, G.H., and Moffatt, J.G. (1970). 3'-deoxy-3'-(dihydroxyphosphinylmethyl)nucleosides. Isosteric phosphonate analogs of nucleoside 3'-phosphates, *J. Am. Chem. Soc.*, *92*: 5511.
30. Roach, D.J.W., Harrison, R., Hall, C.R., and Inch, T.D. (1981). An improved synthesis of 6,7-dideoxy-α-D-*gluco*-heptose 7-phosphonic acid, *Biochem. J.*, *197*: 735.
31. Nicotra, F., Ronchetti, F., and Russo, G. (1982). Stereospecific synthesis of the phosphono analogues of α- and β-D-glucose 1-phosphate, *J. Org. Chem.*, *47*: 4459.
32. Chmielewski, M., BeMiller, J.N., and Cerreti, D.P. (1981). Synthesis of phosphonate analogs of α-D-glucopyranosyl and α-D-galactopyranosyl phosphate, *Carbohydr. Res.*, *97*: C1.
33. Reitz, A.B., Nortey, S.O., and Maryanoff, B.E. (1985). Stereoselectivity in the electrophile-promoted cyclizations of a hydroxyolefin derived from arabinose. Synthesis of a phosphonate isostere of β-D-arabinose-1,5-diphosphate, *Tetrahedron Lett.*, *26*: 3915.
34. Stowell, M.H.B., Ueland, J.M., and McClard, R.W. (1990). The mild preparation of synthetically useful phosphonic dichlorides: Application to the synthesis of cyclic phosphonic diesters and diamides, *Tetrahedron Lett.*, *31*: 3261.
35. Novikova, Z.S., Psishchenko, A.A., and Lutsenko, I.F. (1980). Synthesis of methylenebis[phosphonous dichloride] and its derivatives, *Zh. Obshch. Khim.*, *47*: 775.
36. Gilmore, W.F., and Huber, J.W. (1973). Base-catalyzed condensation of aldehydes with ethyl bis(diethylphosphonomethyl)phosphinate, *J. Org. Chem.*, *38*: 1423.
37. Gilmore, W.F., and Park, J.S. (1987). Base-catalyzed condensations of bis(diethylphosphonomethyl)phosphinic amides with aldehydes, *Phosphorus Sulfur*, *29*: 287.
38. Corey, E.J., and Kwiatkowski, G.T. (1966). The synthesis of olefins from carbonyl compounds and phosphonic acid

bisamides, *J. Am. Chem. Soc.*, *88*: 5652.
39. Corey, E.J., and Kwiatkowski, G.T. (1966). The synthesis of olefins from *O,O'*-dialkyl α-lithioalkylphosphonothioate esters, *J. Am. Chem. Soc.*, *88*: 5654.
40. Corey, E.J., and Kwiatkowski, G.T. (1966). The synthesis of *cis* and *trans* olefins *via* β-keto and β-hydroxy phosphonamides, *J. Am. Chem. Soc.*, *88*: 5653.
41. Marquez, V.E., Lim, M.-L., Tseng, C. K.-H., Markovac, A., Priest, M.A., Khan, M.S., and Kaskar, B. (1988). Total synthesis of (-)-neplanocin A, *J. Org. Chem.*, *53*: 5709.
42. Elliot, R.D., Niwas, S., Montgomery, J.A., and Secrist, J.A. (1989). Progress in the synthesis of a PNP transition state inhibitor, *Nucleosid. Nucleotid.*, *8*: 1103.
43. Tanaka, H., Fukui, M., Haraguchi, K., Masaki, M., and Miyasaki, T. (1989). Cleavage of a nucleosidic oxetane with carbanions: Synthesis of a highly promising candidate for anti-HIV agents - A phosphonate isostere of AZT 5'-phosphate, *Tetrahedron Lett.*, *30*: 2567.
44. Horowitz, J.P., Chua, J., Da Rooge, M.A., Noel, M., and Klundt, I.L. (1966). Nucleosides. IX. The formation of 2',3'-unsaturated pyrimidine nucleosides *via* a novel β-elimination reaction, *J. Org. Chem.*, *31*: 205.
45. Hampton, A., Sasaki, T., and Paul, B. (1973). Synthesis of 6'-cyano-6'-deoxyhomoadenosin-6'-phosphonic acid and its phosphoryl and pyrophosphoryl anhydrides and studies of their interaction with adenine nucleotide utilizing enzymes, *J. Am. Chem. Soc.*, *95*: 4404.
46. Savignac, P., and Mathey, F. (1976). Une voie et simple efficace d'access aux beta-cetophosphonates, *Tetrahedron Lett.*: 2829.
47. Burton, D.J., Ishihara, T., and Maruta, M. (1982). A useful zinc reagent for the preparation of 2-oxo-1,1-difluoroalkylphosphonates, *Chem. Lett.*: 755.
48. Lindell, S.J., and Turner, R.M. (1990). Synthesis of potential inhibitors of the enzyme aspartate transcarbamoylase, *Tetrahedron Lett.*, *31*: 5381.
49. Burton, D.J., and Sprague, L.P. (1988). Preparation of difluorophosphonoacetic acid and its derivatives, *J. Org. Chem.*, *53*: 1523.
50. Knochel, P., Yeh, M.C.P., Berk, S.C., and Talbert, J. (1988). Synthesis and reactivity toward acyl chlorides and

enones of the new highly functionalized copper reagents RCu(CN)ZnI, *J. Org. Chem.*, *53*: 2390.

51. Blackburn, G.M., Kent, D.E., and Kolkmann, F. (1984). The synthesis and metal binding characteristics of novel isopolar phosphonate analogues of nucleotides, *J. Chem. Soc., Perkin Trans. I*: 1119.
52. Stowell, M.H.B., Witte, J.F., and McClard, R.W. (1989). The phosphonylphosphinyl dianion: A convenient synthon for the preparation of biologically interesting phosphonyl-phosphinyl (P-C-P-C-) compounds, *Tetrahedron Lett.*, *30*: 411.
53. Teulade, M.P., Savignac, P., Aboujaound, E.E., Lietge, S., and Collignon, N. (1986). Alkylidinephosphonates and vinyl phosphonates: A selective synthetic course *via* carbanions, *J. Organomet. Chem.*, *312*: 283.
54. Grieco, P.A., and Pognowski, C.S. (1973). Alkylation of the dianion of β-keto phosphonates. A versatile synthesis of dimethyl (2-oxoalkyl)phosphonates, *J. Am. Chem. Soc.*, *95*: 3071.
55. Biller, S.A., Forster, C., Gordon, E.M., Harrity, T., Scott, W.A., and Ciosek, C.P. (1988). Isoprenoid (phosphinyl-methyl)phosphonates as inhibitors of squalene synthetase, *J. Med. Chem.*, *31*: 1869.
56. Evans, D.A., Hurst, K.M., and Takacs, J.M. (1978). New silicon-phosphorus reagents in organic synthesis. Carbonyl and conjugate addition reactions of silicon phosphite esters and related systems, *J. Am. Chem. Soc.*, *100*: 3467.
57. Valerio, R.M., Alewood, P.F., and Johns, R.B. (1988). Synthesis of optically active 2-(*tert*-butoxycarbonylamino)-4-dialkoxyphoryl-butanoate protected isosteres of *O*-phosphonoserine for peptide synthesis, *Synthesis*: 786.
58. Boyd, E.A., Corless, C., James, K., and Regan, A.C. (1990). A versatile route to substituted phosphonic acids, *Tetrahedron Lett.*, *31*: 2933.

CHAPTER 14

PHOSPHORUS-BASED FLAME RETARDANTS

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I. Introduction

Flame retardants used in plastics and textiles are principally of the following types: 1) halogen compounds, commonly used with antimony oxide as a synergist; 2) hydrates such as alumina trihydrate or magnesium hydroxide, used as "endothermic" fillers; 3) borates or boric acid; and 4) phosphorus compounds. Several earlier reviews of phosphorus flame retardants have been published.[1-5]

II. Mode of Action of Phosphorus Flame Retardants

A. General Remarks

A critical review of phosphorus flame retardant mechanisms was published by Granzow in 1978.[6] Another overview, based on results of a multi-sponsored basic research program on flame retardancy at Stanford Research Institute, was published by Brauman.[7] The following is a brief recapitulation of the present view regarding phosphorus flame retardants.

The action of phosphorus-based flame retardants has been shown to involve several concurrent or alternative mechanisms, exerted in the condensed phase (*i.e.* the pyrolyzing polymer phase) and in the vapor phase (*i.e.* the flame zone). Physical and chemical actions have been implicated in both phases. Flame inhibition, heat loss due to melt flow, surface obstruction by phosphorus-containing acids, acid-catalyzed char accumulation, and char enhancement have all been noted in particular polymer systems containing phosphorus-based flame retardants,[7] although the relative contribution of each mode of action depends on the polymer system and the fire exposure conditions.

B. Condensed-Phase Mechanisms

1. Charring and Related Mechanisms

There is ample evidence that in oxygen-containing polymers

such as cellulose and rigid polyurethane foam, phosphorus compounds can increase the char yield. The conversion of the combustible substance to char is beneficial from a flame retardancy standpoint in several ways: first, it represents material which escaped conversion to gaseous fuel; second, the char-forming reactions often produce water, so that any gasified fuel is diluted with high heat-capacity noncombustible water vapor; third, the char can form a heat- and mass-transfer barrier protecting the underlying polymer; fourth, the char-forming reactions are often endothermic.

The behavior of cellulose (cotton, paper, wood) under fire exposure conditions has been extensively studied, as has the flame retardant action of phosphorus in cellulose; reviews are available on the pyrolysis of cellulose and the effect of phosphorus and other retardants.[8-10]

Cellulose, when heated to its pyrolysis temperature, normally depolymerizes to a tarry product (levoglucosan) which further breaks down to alkanes, alkenes, alcohols, ketones, and other low molecular weight fuels.

When an effective phosphorus-containing flame retardant is present in cellulose, upon fire exposure, breakdown of the retardant generally yields phosphoric and polyphosphoric acid. In some cases where nitrogen components are present, phosphorylating agents are formed having P-N bonds. These reactive phosphorus species phosphorylate the cellulose, generally with release of water. The phosphorylated cellulose then undergoes thermal elimination. The flame retardant effect results from the endothermicity, the formation of a non-combustible outward-flowing vapor (water), the reduction in fuel release, and in some cases the protective barrier effect of the char. Further flame retardancy results if the char is not burned to carbon oxides. Moreover, if the char does smolder, the presence of a phosphorus compound may inhibit complete conversion to carbon dioxide, the main oxidation product being carbon monoxide. Thus, less heat is evolved than with complete combustion.

Beside having a chemical effect, the phosphorus flame retardant may, by coating the char, tend to prevent smoldering by mechanical obstruction of the surface. Smoldering is not only subject to chemical effects but, especially in the case of permeable materials such as open-cell foams, it is strongly favored by air flow through the material. Paradoxical examples are known, for example, in flexible polyurethane foams, where smoldering is sometimes made worse by the presence of a phosphorus flame retardant. The inter-

play of physical and chemical effects makes predictability of flame retardant action difficult.

Mechanisms involving phosphorylation and elimination, producing water and char, appear to be responsible for the action of phosphorus compounds in intumescent coatings. Mono-, di- or tripentaerythritol are commonly used as char-yielding polyols.[11-20]

It is often observed that certain nitrogen compounds, typically melamine, urea or dicyandiamide, will enhance the action of phosphorus in, for example, cellulose. The action is not general, being quite dependent on the specific nitrogen compound which is present. This effect has been attributed to formation of P-N bonded intermediates which are strong phosphorylating agents.[21,22] The formation of P-N bonded compounds may also prevent loss of phosphorus from the condensed phase.[23]

The enhancement of char in rigid polyurethane foams by phosphorus flame retardants has been determined to be the likely basis of the flame retarding action of phosphorus in these foams.[24-26] In such systems, phosphorus appears to be largely retained in the char;[28,29] also, the char appears to be more coherent and more effective as a physical barrier.[26-28] In a basic study on various phosphorus flame retardants in thermoplastic urethane elastomers, the flame retardant effect of formation of a charry intumescent foam residue was demonstrated but some vapor phase action was noted also, indicating a complex mode of action.[30]

Curiously, char formation does not seem to be the basis of the action of phosphorus retardants in flexible polyurethane foams (discussed further below).

It has been shown that in poly(ethylene terephthalate)[31,32,37] and in poly(methyl methacrylate),[33-36] phosphorus flame retardants produce an increase in the amount of residue and a retardation of the release of volatile fuel. Plausible acid-catalyzed crosslinking reactions involving C-O-C, C-C or C-O-P-O-C linkages have been postulated.

For substantially oxygen-free polymers which form char less readily, such as polyolefins and styrenics, phosphorus flame retardants typically are ineffective unless supplemental char forming additives are also present. However, even in the absence of any char-forming adjuvant, there is some action which may be a combination of vapor phase activity, melt-drip effects, plus some interaction of the phosphorus additive with oxygenated functional groups[38] and/or with sites of unsaturation[39] produced by oxidative reactions at or near the surface of the polymer prior to gasification.

A recent study of the chemistry of polypropylene flame retarded with pentaerythritol and diammonium pyrophosphate showed evidence for reaction of a phosphorus acid not only with the pentaerythritol but also with the oxidized product of the polymer degradation.[40-42]

Phosphorus can also inhibit the glowing combustion of char and carbon fibers;[43-45] the mechanism of action is not proven but may involve some sort of polyphosphoric acid coating[43,44] and/or deactivation of the active centers on the solid carbon[2] with diversion of the oxidant away from production of CO_2. Even in formulations where other elements are relied upon for flame retardancy, phosphorus compounds are often added to prevent afterglow.[43-45]

A further mechanism of action of phosphorus was revealed by Russian workers who have recently shown that a phosphorus flame retardant can reduce permeability of the char, thus providing an improved barrier to air and fuel passage.[46] The mechanistic details have not yet been elucidated, even as to whether the action is physical or chemical.

2. Coating Mechanisms

Condensed phase mechanisms of action based on coating the burning surface with a phosphorus-rich barrier, presumably polyphosphoic acid or the like) have often been proposed, but only in a few cases is any evidence presented. Brauman proposed that a phosphorus acid physically retards the vaporization of fuel from a hydrocarbon polymer flame retarded by ammonium polyphosphate or triphenyl phosphate.[47,48] Some infrared evidence was adduced in support of the postulate of a polyphosphoric acid coating.

3. Effects on Melt Viscosity

Paradoxically, phosphorus compounds can also perform as flame retardants by the opposite of char induction, namely, by catalyzing thermal breakdown of the polymer melt under fire exposure conditions, reducing the melt viscosity and favoring the flow or drip of the molten polymer from the combustion zone. In polystyrene, a bromoalkyl phosphate was shown to work in this manner.[49]

This melt viscosity depressant mechanism of action can be opposed or totally defeated by the presence of a filler or any material which can serve as a wick. Reinforcing glass fibers can negate the action of a melt viscosity depressant by retarding melt

flow. A few cotton threads sewn into a flame retardant PET fabric can have such an effect. A particularly impressive example is the antagonistic effect of even traces of silicone oil on flame retarded polyester fabric; the silica formed on pyrolysis impedes melt flow and renders the fabric flammable.[50] In the same manner, pigment printing can defeat the flame retardancy of a phosphorus-containing flame retarded polyester.[51]

4. Condensed Phase Free Radical Inhibition Mechanisms

This concept has been given consideration mainly by Russian and Czech researchers. Some evidence has been offered in support of a hypothesis of free radical inhibition, or at least of a condensed phase antioxidant effect, by nonvolatile (polymeric or grafted) phosphorus flame retardants.[52-54] ESR data indicate that aryl phosphate flame retardants can react with alkylperoxy radicals in the polymer surface to form phenoxy radicals which are probably less reactive.[53]

5. Condensed Phase Mechanisms Based on Surface Effects on Fillers

This relatively unexplored area has two principle aspects: phosphorus compounds having characteristics of surfactants or coupling agents can aid dispersion of solid flame retardants such as alumina trihydrate (ATH); second, some char enhancement is possible from the catalytic action of the surface active agent. Thus, certain alkoxytitanates and alkoxyzirconate coupling agents having alkyl acid pyrophosphate anions seem to enhance the UL 94 flammability ratings of polypropylene filled with barium sulfate, zirconium silicate or calcium sulfate.[55] Interestingly, on barium sulfate, the effect of the titanate seemed to peak at the 1% concentration, and was less at 0.5 and 3%, a phenomenon which deserves confirmation and further study.

C. Vapor Phase Mechanisms

1. Chemical Modes of Action

It has been shown that the introduction of a highly volatile phosphorus compound into a flame can be highly inhibitory.[56,57] Detailed studies carried out at the National Bureau of Standards[58-60] using mass spectroscopy showed that triphenyl phosphate and triphenylphosphine oxide break down in the flame

into small molecular weight species such as P_2, PO, PO_2, and HPO_2, and that the hydrogen atom concentration in the flame (a rate-controlling species) is thereby reduced. Scavenging of hydrogen atoms and the induction of hydrogen atom recombination were postulated to result from interaction of hydrogen atoms with these phosphorus species, The rate-controlling step in the flame chemistry which is inhibited thereby is the branching step, as follows:

$$H\cdot + O_2 \longrightarrow HO\cdot + O$$

Comparison of flame retardant efficiency with O_2 as oxidant compared to N_2O as oxidant (a diagnostic method believed to distinguish flame inhibition from condensed phase action) provides further evidence that phosphorus compounds, such as trialkylphosphine oxides or triaryl phosphates, can inhibit flame chemistry.[6,61] Vapor phase activity appears to be the basis of the flame retardant utility of triaryl phosphates in the commercial blends of polyphenylene oxide with high impact polystyrene; the polyphenylene oxide provides protective char while the triaryl phosphate provides the flame inhibition needed to suppress the combustion of the hydrocarbon pyrolysates formed from the styrenic component.[62]

2. Physical Modes of Action

It should be noted that a vapor phase action need not be chemical. A physical mode of flame inhibition, based on heat capacity and possibly endothermic dissociation in the vapor phase, may be an important component of the action of a relatively poor fuel vapor entering the flame zone. This physical aspect of vapor phase flame retardancy has been discussed in regard to the hydrogen halides by Larsen,[63,64] and the discussion is appropriate also for phosphorus compounds. Obviously, the release of water from systems such as phosphorus-catalyzed dehydration/charring of cellulose provides a non-fuel vapor which physically retards the flame by dilution of whatever fuel is produced; the high heat capacity of water vapor makes water particularly effective in this mode of action. Here, part of the endothermic action is in the condensed phase and part (bringing the water vapor up to flame temperature) is in the vapor phase.

A few attempts have been made to assess the relative efficacy of the vapor phase and condensed phase mode of action. For instance, comparisons were made by the present author with a var-

iety of phosphorus additives in poly(methyl methacrylate) (PMMA) at equivalent phosphorus loadings. The poorest elevation of oxygen index was found with trimethylphosphine oxide, a stable but volatile compound, and the best elevation of oxygen index was found with phosphoric acid or alkyl acid phosphates which are nonvolatile.[64a] This result suggests that the condensed phase mechanism is the more efficient one with PMMA, despite the fact that PMMA is a polymer which readily depolymerizes to volatile monomer.

In flexible polyurethane foams, various chloroalkyl phosphates (discussed individually later in this Chapter) are efficient flame retardants but do not increase char nor produce much of a chemical effect as detectible by infrared or pH indicators on the surface layer adjacent to the flame. They appear to volatilize, at least in part, undecomposed and they may well exert their action primarily in the flame[65,66] and by the endothermicity of their vaporization. Some contribution by condensed phase action cannot be totally excluded since chloroalkyl phosphates to some degree can become incorporated into the foam structure.[49]

D. Interaction with Other Flame Retardants

1. Interaction with Halogens

Synergism is defined as an effect of two or more agents which is greater than additive (by some chosen computational model), a deceptively simple concept which has been critically reviewed with reference to real and false examples in flame retardancy.[67] Halogen-phosphorus synergism is often postulated by analogy with the strong and well-established halogen-antimony synergism. In most cases where a quantitative study has been done, the elements are found to be additive in their action, sometimes even less than additive, so phosphorus-halogen synergism, unlike antimony-halogen synergism, is not a *general* phenomenon. Hypotheses regarding formation of phosphorus oxyhalides lack direct observational support. Good additive results are often obtained with combinations of halogen and phosphorus-containing retardants. However, at least one reasonably convincing case of phosphorus-halogen synergism was recently reported, a phosphonoalkyldibromophenol used as a retardant in ABS, where the joint action of phosphorus and bromine (in the same molecule) seems to be substantially greater than additive based on a graphical analysis of the data.[68]

2. Interaction with Antimony

Many published formulations show the attempted use of antimony oxide along with phosphorus and halogen. Results are sometimes reported as favorable, particularly in patents, but a number of quantitative studies show an apparent antagonism between antimony and phosphorus.[67] In the most pronounced cases, one element negates the other, and in less drastic cases, the flame retardant effects are merely less than might be expected from adding the known effects of the two separate compounds. A careful study of triaryl phosphate and antimony oxide in PVC showed antagonism only in part of the composition range.[67a] This antagonistic effect may be related to the formation of antimony phosphate, which is too unreactive to be an effective flame retardant.

3. Interactions with Mineral Fillers

Excellent flame retardant results are obtained with alumina trihydrate (ATH) in combination with dimethyl methylphosphonate or triethyl phosphate,[69] and the quantitative relations have been studied.[70] There is some suggestion of a positive interaction.

A systematic study was made of the effect of TiO_2 and SnO_2 on the flame retardant char-forming effect of ammonium polyphosphate with an intumescent nitrogenous resin.[71] Titanium oxide increased the flame retardant effect by giving a stronger and more continuous char, and enhanced the char yield; SnO_2 was antagonistic and made the char flakier and more porous, and did not enhance the yield. The beneficial action of TiO_2 was considered to be a physical bridging agent effect; the deleterious action of SnO_2 was attributed to some sort of chemical interaction with the polyphosphoric moiety.

4. Interactions between Different Phosphorus Flame Retardants

"Phosphorus-phosphorus synergism" has been occasionally reported in cases where a non-volatile and a volatile phosphorus compound are combined. Some examples are combinations of a phosphonium bromide or phosphine oxide (probably vapor phase active) in polypropylene or polystyrene.[71a,71b]

E. Built-in *vs.* Additive Flame Retardants

No definitive general answer can be given regarding the advanatge of building a phosphorus flame retardant into a polymer

as compared to merely adding it. A broad overview suggests that despite the large amount of work done on building phosphorus chemically into polymers,[72,73] very few such polymers are commercial in contrast to the large number of additives. This may be in part because of the greater technical difficulty and cost of a coreactant approach. One study comparing a built-in phosphine oxide structure to a similar structure merely added to a polyester showed no advantage to the built-in structure.[74] Oxygen index was used as the criterion. On the other hand, a study by Stackman[75-77] of additive *vs.* coreacted phosphonate structures in polyesters showed that at low %P, the additive had a small advantage. At higher %P, the coreactant was more efficacious. Many considerations involved in choosing additive *vs.* coreacted phosphorus flame retardants are discussed by Stackman.

III. Review of Commercially Used Phosphorus Flame Retardants

A. General Comments

A wide range of inorganic and organic phosphorus compounds have been disclosed in the patent literature as flame retardants. An older summary is available in a monograph by Lyons.[78] Many thousands of phosphorus compounds have been disclosed in the patent literature, and indeed practically any compound containing a substantial percentage of phosphorus, other than those which are too volatile (like phosphine) or which are too ceramic-like at fire temperatures (such as calcium phosphates), could be construed as having flame retardant activity. This review will be confined to those which have either reached commercial usage or are believed to be in commercial development at the present time.

B. Inorganics

1. Red Phosphorus

It may appear paradoxical that this flammable element is useful as a flame retardant. Yellow (white) phosphorus cannot be used in view of its severe toxicity and spontaneous flammability. However, the red allotrope of phosphorus (a crosslinked polymeric form) is stable to about 450°, not spontaneously flammable and substantially non-toxic. Commercially, red phosphorus is available from Albright & Wilson and Hoechst Celanese as a powder with various proprietary coatings and added stabilizers. Red phosphorus

appears to be useful as a flame retardant additive particularly in molded electrical nylon and epoxy resins.[79-81] It appears to be a condensed phase flame retardant which reduces pyrolytic and thermooxidative degradation, and which also increases char yield, at least in PET which was used for a basic study.[82] Because of reluctance of many compounders to handle the flammable powder, masterbatches of coated stabilized red phosphorus dispersed in various polymers are being offered by the phosphorus manufacturers.

2. Ammonium Phosphates (Water-Soluble Types)

The history of these compounds as flame retardants goes back to 1821 when they were used on theater curtains in France. They are still cost-effective flame retardants, especially for cellulosic disposable textiles, non-wovens, paper and wood, any place their water solubility can be tolerated. One important advantage over borax, which is also used in similar applications, is that they inhibit smoldering combustion as well as flaming combustion.[83]

Commercial formulations of mono- and diammonium phosphate blends are available which have a neutral pH and high water solubility. For example, a commercially available blend (Akzo's FYREX) consisting of 60% diammonium phosphate and 40% monoammonium phosphate has a solubility of 54 g/100 g of water at 25°. Formulations of ammonium phosphates are also available[84] with admixed ammonium bromide (to impart some vapor phase action important for mixed cellulosic/synthetic polymer blends) and with wetting and softening agents to assure penetration and to moderate the crystalline texture of the dried ammonium phosphate, thus producing an improved "hand" on the treated fabric. A water-soluble ammonium polyphos- phate (not to be confused with the insoluble solid discussed below) is available for use as a non-durable textile finish, having somewhat higher flame retardant activity on a weight basis than ammonium mono- or diphosphates.

3. Insoluble Ammonium Polyphosphates

High molecular weight ammonium polyphosphates, with a chain length of over 50 and having low water solubility, are produced by thermal dehydration of ammonium phosphates in the presence of urea or under ammonia pressure. Several crystalline forms exist[85] and commercial ammonium polyphosphates from different sources may differ in crystal morphology.

The original use for insoluble ammonium polyphosphate was in intumescent coatings where it provided the latent acid function

required to carbonize the char-forming ingredient such as pentaerythritol and in the presence of a blowing agent such as melamine to provide bubbles.[11,12] Such coatings are widely used on girders, walls, storage containers and bulkheads. For further improvement of water-resistance of such coatings, commercially available coated or encapsulated ammonium polyphosphates may be of some advantage.

More recently, a series of compounded flame retardants for thermoplastics has been developed by Hoechst Celanese, Montefluos (marketed by Monsanto) and V.A.M.P. (Italy) which comprises powdered mixtures of ammonium polyphosphate with char-forming nitrogenous resins. These are useful flame retardant additives for polymers which themselves are poor char formers, such as polyolefins, ethylene-vinyl acetate and urethane elastomers.[86,87] Although the exact composition of the char-forming components are proprietary, issued patents[88-93] show the use of a variety of nitrogenous resins based on cyclic ureas, triazines and piperazines.

Careful studies of the relative efficacy of these ammonium polyphosphate-nitrogen resin formulations show that the thermal degradation temperature of the intumescent flame retardant must be matched to that of the polymer, so each polymer requires optimization.[86,92]

C. Organics

1. Melamine Phosphates

Three such products are commercially available: melamine orthophosphate, dimelamine orthophosphate, and melamine pyrophosphate.[94] They are all finely divided particulate solids, suitable for dispersal in coatings and thermoplastics. The use pattern for all three is somewhat similar, namely for flame retardant coatings and for various newer uses in polyolefins and styrenics. Differences are in regard to solubility and efficiency. For instance, the orthophosphate (presumably the 1:1) is reported to have a solubility of 0.35 g/100 mL water at 20^{o} whereas the pyrophosphate has a solubility of 0.09 g/100 mL water.

A study of the thermal behavior of melamine phosphates shows that dehydrative condensation of the phosphoric acid moiety occurs first, followed by some dissociation to release melamine along with some condensation of the melamine, and further condensation of the phosphorus acid moiety.[95] Probably the endother-

micity of the dissociation and the condensed phase action of the phosphorus acids both contribute to the flame retardant action.

2. Aliphatic Organophosphorus Additives (Non-Halogenated Types)

Triethyl phosphate and other trialkyl phosphates. Triethyl phosphate is a colorless liquid (bp 210-218°) containing 17% phosphorus. It is made by Eastman from diethyl ether and phosphoric anhydride.[96,97] Triethyl phosphate is low in viscosity and therefore it has been used as a viscosity depressant and flame retardant adjuvant in alumina trihydrate-filled polyester resins, such as those used to fabricate bathtubs and shower stalls.[98,99] It adds substantially to the flame retardancy of halogenated polyester resins, even as low as the 0.2% phosphorus level of addition.[70]

Tributyl phosphate. This is a clear liquid, having 11.6% phosphorus content, used extensively as an antifoaming agent, as a metal extractant, and as a component of fire resistant hydraulic fluids. There are some specialized flame retardant plasticizer applications in nitrocellulose and cellulose acetate, but it is too volatile for most thermoplastics.

Trioctyl phosphate. This high boiling liquid having 7.1% phosphorus content has been employed as a special flame retardant plasticizer for vinyl goods intended to have exceptional low temperature flexibility at as low as -65° and good resistance to fungi.[100] It is used, for example, in military tarpaulins, air-supported structures and camouflage nets. It is also used in synthetic rubbers and nitrocellulose.

Dimethyl methylphosphonate (DMMP). This water-white liquid (bp 185°) has 25% phosphorus content, the highest phosphorus content of any organophosphorus flame retardant. It is made by the Arbuzov rearrangement of trimethyl phosphite:

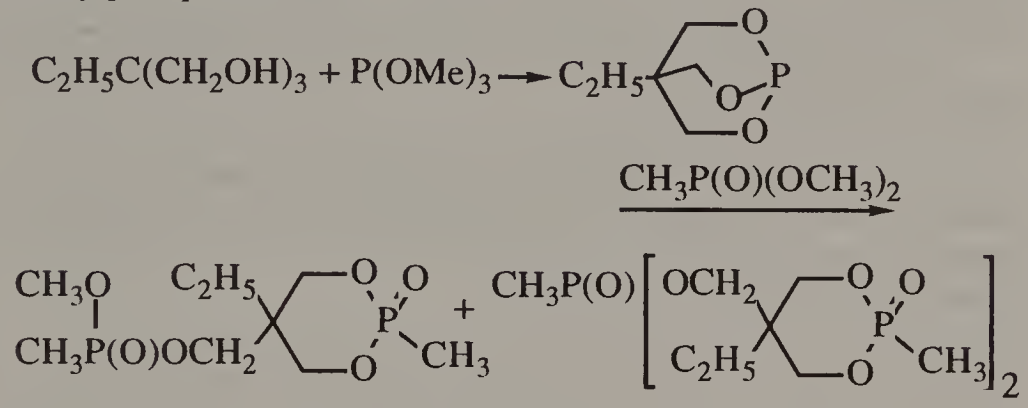
$$(CH_3O)_3P \longrightarrow CH_3P(=O)(OCH_3)_2$$

Applications include use as a viscosity reducer and flame retardant for ATH-filled polyester resins.[69] Because of its very low viscosity, it is used as a diluent at a few percent and permits high loadings of ATH in polyester resin with retention of convenient resin viscosity prior to cure. It also contributes a substantial increase in flame retardancy to halogenated polyester resins.[70]

DMMP also has been used as a highly efficient flame retard-

ant in rigid polyurethane foams which, being closed cell foams, tend to retain this somewhat volatile additive.[101,102] DMMP has also been used as an intermediate to make several other flame retardants - FYROL 76, FYROL 51 and ANTIBLAZE 19 which are discussed below.

Trimethylolpropane methylphosphonate oligomer (A&W's ANTIBLAZE 19 and 1045. These are proprietary low-volatility liquid products having somewhat over 20% P content, made by the reaction of trimethylolpropane phosphite with dimethyl methylphosphonate:[103,104]

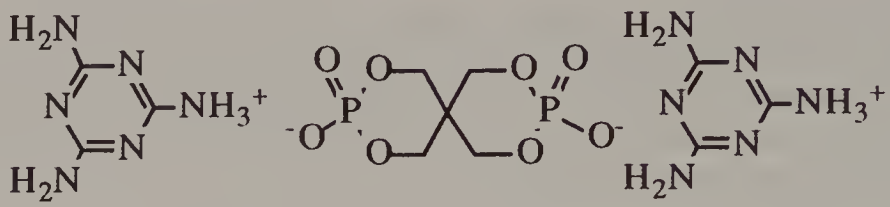


Even though the bicyclic intermediate is highly toxic, the product, wherein the bicyclic structure is completely converted to monocyclic components, is quite low in toxicity.

ANTIBLAZE 19 is useful as a flame retardant treatment for polyester fabric. It can be applied as an aqueous solution, dried down and then locked into the fabric by heating the polyester to incipient softening temperature. A less volatile analog, which gives less "smoke" during this process, is ANTIBLAZE 1045, which corresponds to the above formula with a preponderance of the higher molecular weight product. These products have also been found useful in nylon 6, polyester, and polycarbonate molding resins, and in textile backcoating.

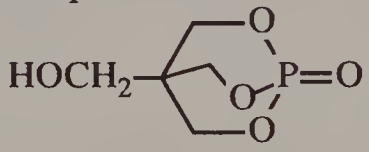
Pentaerythritol phosphates. Several solid high-melting bicyclic phosphates derived from pentaerythritol are in development for use in polyolefins, polyesters and other polymers. The carbon skeleton derived from pentaerythritol contributes several useful features: it provides char, it contributes to the high melting point of the phosphate derivative (which remains solid at the processing temperature of the polymer) and it contributes thermal stability to the phosphate. Three such products are on the market or in development at present.

"Dimelamine pentate" (Great Lakes' CHARGUARD 329) is a salt of the bis-monocyclic acid phosphate of pentaerythritol. It was developed by Halpern at Borg-Warner[105] and has the following structure:



A detailed study of the decomposition mode of the parent acid has been published.[19]

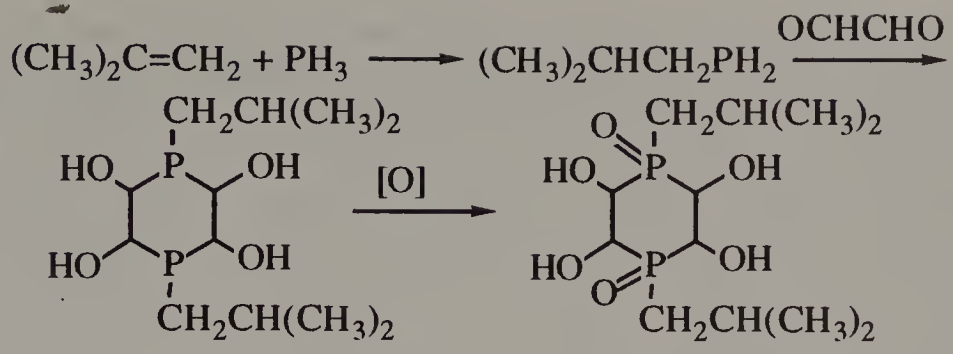
A more recent introduction by Great Lakes Chemical is their CN-1197 primarily for use in epoxides and unsaturated polyester laminates and composites.[106] Based on its phosphorus content and reported melting point information,[105] CN-1197 corresponds to another of the Halpern compounds:



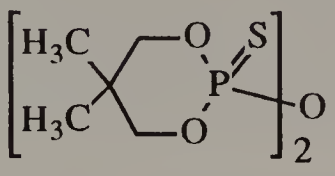
This additive is said by Halpern[107] to be most effective in the mode of an intumescent additive when used together with a nitrogen compound such as melamine.

Related acyl esters of the above alcohol are disclosed by Akzo Chemicals[108] for use in combination with an inorganic phosphate such as ammonium polyphosphate to flame retard polypropylene.

Tetrahydroxydiphosphorinane dioxide. This newly introduced flame retardant would appear to be a reactive polyol but is considered by its manufacturer, Cyanamid Canada, mainly to be used as a flame retardant additive for polypropylene.[109] It is made from isobutylene, phosphine and glyoxal as follows:



Cyclic neopentyl thiophosphoric anhydride. This unique flame retardant additive, commercialized by Sandoz in Europe, has the following structure:



It represents the outcome of a systematic study of phosphorus-rich additives for viscose rayon.[111,112] It is stable both in the alkaline spinning dope and in the acid coagulating bath, and moreover, it is stable to multiple launderings of the rayon fabric. The structure-activity study shows several interesting and significant features: first, the anhydride group contributes some extra flame retardant action; second, the sulfur atoms contribute additional flame retardant action; and third, the presence of the sulfur atoms and the steric hindrance caused by the dimethylneopentylene groups afford a remarkable hydrolytic stability. A basic study[113] showed that the flame retardant mode of action of this additive in cellulose involves enhanced endothermic water release with impedance of heat feedback from the flame, and a reduction in the formation of fuel-yielding levoglucosan.

3. Haloalkyl Phosphates and Phosphonates

There are a number of commercial phosphates and phosphonates having chloroalkyl groups, and one having a bromoalkyl group. The chloroalkyl groups may contribute somewhat to the flame retardant effect but the most important contribution of the chlorine is to reduce water solubility and volatility, thus making these additives resistant to loss by vaporization and leaching.

Tris(2-chloroethyl) phosphate. This is a nearly-colorless to light straw-colored liquid having 36.7% chlorine and 10.8% phos-

phorus content. It is made from phosphorus oxychloride and ethylene oxide.[114] It is quite versatile as a flame retardant additive, and relatively low in cost. It is used in flexible vinyls, cast acrylics, cellulosics, polyester resins, polyurethane foams, particularly rebonded and flame bonded, isocyanurate foams, urethane and other elastomers, flame retardant paints and mastics, epoxy resins, phenolic resins and foams, amino resins, wood-resin composites, and carpet backing. It finds usage in combination with melamine in flexible foam cushions and institutional mattresses. Its low viscosity (38 cP at 25°) is an advantage for many applications, especially where low temperature uses are involved.

Tris(1-chloro-2-propyl) phosphate. This liquid has 32.5% chlorine and 9.5% phosphorus content. It is made by reaction of phosphorus oxychloride with propylene oxide.[115] The ring opening occurs mainly to give the branched (isopropyl) structure. Surprisingly, despite lower % Cl and % P than the preceding compound, it is not always less active on a weight basis as a flame retardant.

The branched chains impart sufficient steric hindrance to the phosphate ester linkage that tris(1-chloro-2-propyl) phosphate is much less reactive toward reagents which might attack the phosphate structure.[115] For this reason it has advantages for use in urethane foams (especially rigid foams), where it shows good stability in the isocyanate or in the catalyst-polyol mixture. It is also useful to reduce friability and brittleness in rigid isocyanurate foams.

Tris(1,3-dichloro-2-propyl) phosphate. This liquid product contains 49% Cl and 7.2% P. It is made from phosphorus oxychloride and epichlorohydrin; the ring opening reaction gives mainly, but not exclusively, the branched chain isomer having the following structure:

$$[(ClCH_2)_2CHO]_3P{=}O$$

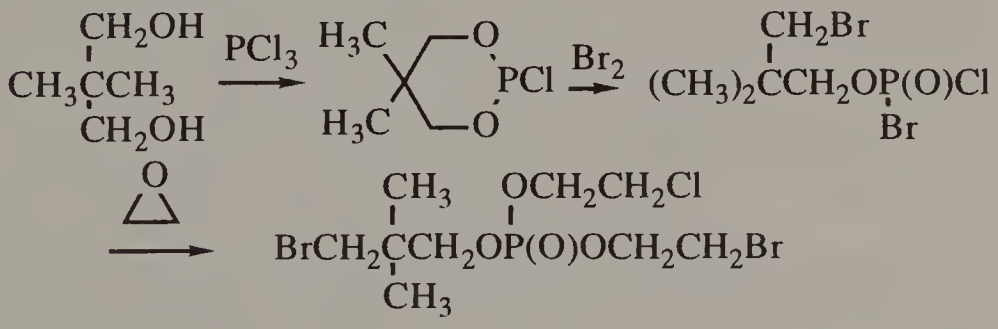
This product is, however, sufficiently isomerically pure that it has been known on rare occasions to freeze to a solid during storage. The numerous references to tris(2,3-dichloropropyl) phosphate scattered throughout the literature are mostly erroneous; although the 2,3-dichloro-1-propyl isomer can be made by addition of chlorine to triallyl phosphate, the high cost of the latter makes it an impractical starting material and the commercial product has always been made from epichlorohydrin.

This phosphate has very good resistance to attack by most

reagents, including water[115] and most importantly, the amine catalysts used in polyurethane foam manufacture; therefore, for many years, it has been a leading flame retardant for flexible foams;[116] it can be added to the isocyanate or to the polyol with good storage stability of either mixture. Because of its inertness toward the foam catalysts, foam formulation changes can often be avoided. Tris (1,3-dichloro-2-propyl) phosphate is also used in isocyanurate foam to reduce brittleness. This phosphate shows very little tendency to "scorch" (cause discoloration and degradation) even in high exotherm flexible foam formulations. This and other haloalkyl phosphate-containing flame retardant polyurethane systems can be further stabilized against scorch by inclusion of certain selected antioxidants and acid acceptors.[117,118] Furthermore, this and other chloroalkyl phosphates can be enhanced for protection of flexible urethane foam against both smoldering (cigarette ignition) and open flame ignition by addition of melamine.[118a]

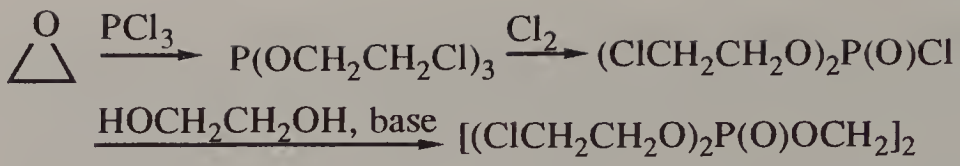
Tris(2,3-dibromopropyl) phosphate. This once-important additive had been used in many applications, notably polyester fabric flame retardant finishing, until it was found to be a mutagen and animal carcinogen.[119] Although the actual hazard was subject to dispute,[120] the manufacture and use of this compound has been discontinued.

2-Bromoethyl 2-chloroethyl 3-bromopentyl phosphate. This product is a liquid flame retardant made by Great Lakes Chemical Co. The process is believed to be the following:[121]



It is principally recommended for use in flexible polyurethane foam, although it is also effective as a flame retardant in PMMA, vinyls, and polyesters.

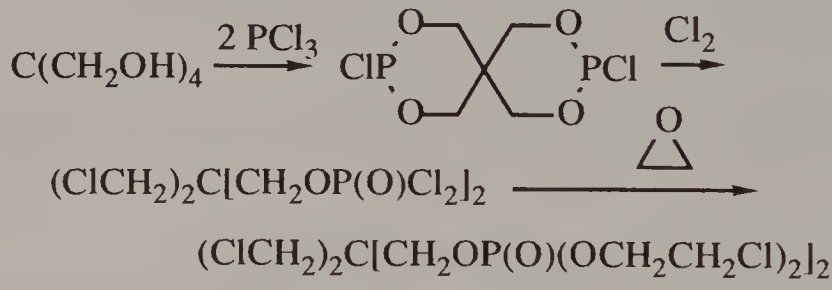
Tetrakis(2-chloroethyl) ethylene diphosphate (Olin's THERMOLIN 101). This is a liquid of medium viscosity (about 242 cP at 25°) and containing 31% Cl and 13% P. It is made by the following route:[122]



The principal use of this diphosphate has been in flexible polyurethane foam where it is somewhat less volatile than any of the monophosphates and, compared to tris(1,3-dichloro-2-propyl) phosphate, it is somewhat more efficient.[123,124] However, it also sometimes causes "scorch" during foam manufacture.

Other tetrakis(2-chloroalkyl) diphosphates. A close relative of the above-described diphosphate, made from diethylene glycol instead of ethylene glycol, has been commercially available as Monsanto's PHOSGARD 1227, having been described earlier in a Russian publication.[125] It has a similar pattern of use. In Japan, this compound and the homologous tetrakis(chloroisopropyl) diethylene glycol diphosphate are on the market for use in polyurethanes.

A further variant on the diphosphate theme is the product originally marketed as Monsanto's PHOSGARD 2XC20 and later as A&W's ANTIBLAZE 100. It is a liquid containing about 10.6% phosphorus and 36% chlorine. The production route described by Monsanto,[126] although seemingly complex, can probably be carried out in a single reactor:

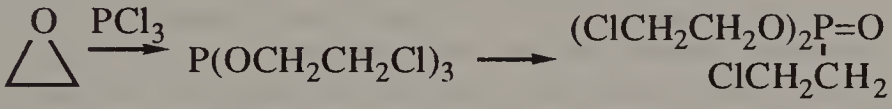


The bulky dichloroneopentyl structure is conducive to chemical stability and reduced volatility. This product is used mainly in flexible urethane foams, and has advantageous stability in flexible packaging components.

Oligomeric chloroethyl ethylene phosphate (Akzo's FYROL 99). This type of oligomer is manufactured either by self-condensation of tris(2-chloroethyl) phosphate[127,128] or by ethoxylation of the chloroethyl metaphosphate made by reaction of phosphorus

pentoxide with tris(2-chloroethyl) phosphate and a small amount of phosphite.[129] The product typically has 26% chlorine and 14% phosphorus and is a viscous liquid of low volatility. It is useful as a flame retardant additive in resin-impregnated paper air filters for internal combustion vehicles, in other thermoset systems, in textile backcoating, in flexible urethane foam, and in fire retardant coatings.

Bis(2-chloroethyl) 2-chloroethylphosphonate (A&W's ANTIBLAZE 78). This product, solid when pure, liquid in its commercial form where it contains diphosphonate byproducts, is made by the Arbuzov rearrangement of tris(2-chloroethyl) phosphite.[130,131] This phosphite is the product of the reaction of ethylene oxide with phosphorus trichloride:[130]



The intramolecular Arbuzov rearrangement is accompanied by a substantial amount of intermolecular Arbuzov reaction producing isomeric diphosphonates:[132]

$$(ClCH_2CH_2O)_2P(O)CH_2CH_2OP(O)(OCH_2CH_2Cl)CH_2CH_2Cl$$

$$(ClCH_2CH_2O)_2P(O)CH_2CH_2P(O)(OCH_2CH_2Cl)_2$$

The 2-chloroethylphosphonate group is very easily dehydrochlorinated by base, forming bis(2-chloroethyl) vinylphosphonate.[133] Bis(2-chloroethyl) 2-chloroethylphosphonate also can be hydrolyzed to 2-chloroethylphosphonic acid, an important commercial plant growth regulator used, for example, to stimulate latex production by rubber trees; the means by which it works is the release of ethylene which is a plant growth regulator.

In the role of a flame retardant additive, bis(2-chloroethyl) 2-chloroethylphosphonate is used in certain rigid foam applications.[134]

4. Aromatic Phosphates

The triaryl phosphates were first produced over 80 years ago for use originally in flame retarding cellulosic plastics, such as the highly flammable cellulose nitrate[135] and later cellulose acetate, uses for which they are still employed. They have also found major

uses in flame retardant hydraulic fluids, as lubricant additives, and as dispersing media for peroxide initiators.

Since the advent of polyvinyl chloride as a major commercial polymer, the triaryl phosphates and the related alkyl diphenyl phosphates have been used as flame retardant vinyl plasticizers. They are often added in combination with non-phosphate plasticizers such as the phthalates. The usual proportion of the more expensive phosphate is that needed to pass reliably the flammability requirements.[136-138]

The principal uses for the triaryl phosphates are in automotive interiors (to pass Federal Motor Vehicle Safety Standards 302 requirements), wire and cable insulation, conveyor belts, building insulation (moisture barriers), furniture, and vinyl foams. Recently, combinations of aryl phosphates with polybrominated additives have come into use for flexible polyurethane foams.[138a]

Beside flame retardant properties, the aryl phosphates have useful vinyl plasticizer characteristics, including fast processing and gelation, good resistance to extraction by oil, gasoline and other solvents, good tolerance to other plasticizers and extenders, thermal and microbial resistance, and good dielectric heat sealing characteristics. On the other hand, the triaryl phosphates have relatively poor low temperature properties compared to the phthalates, and where low temperature uses are important, the alkyl diphenyl phosphates are advantageous.

All of the triaryl phosphates are produced by reaction of the corresponding phenols with phosphorus oxychloride, often in the presence of a catalyst.[139] They are distilled and washed with aqueous base. Alternative processes involving direct esterification of phenols with phosphoric acid have been proposed in patents, but are not known to be in commercial operation.[140,141]

Commercial aryl phosphates are the following:

Triphenyl phosphate. This is a colorless solid, usally sold in flaked form (mp 48-49°). Triphenyl phosphate is made from phenol and phosphorus oxychloride and is purified by washing with alkali and distillation. An earlier application was as a flame retardant plasticizer for cellulose acetate photographic safety film, which is still a major use, and more recently it has been used as a flame retardant additive in cellulose nitrate, various coatings, cast triacetate film and sheeting, engineering thermoplastics and rigid urethane foam. Where compatibility is limited with pure triphenyl phosphate, combinations with other plasticizers such as phthalates are used.

The following group of products are plasticizers for polyvinyl chloride (PVC):

Cresyl diphenyl phosphate. This is the most efficient plasticizer of the liquid triaryl phosphate type, but also relatively volatile. Its use in vinyls has declined, but recently it has reportedly been used in Europe in styrenic thermoplastics as an alternative to halogenated flame retardants.

Tricresyl phosphate. The earliest versions of tricresyl phosphate used cresol mixtures with *o*-, *m*- and *p*-isomers, but when in the 1940's, the neurotoxicity of the *o*-cresyl phosphates became known, the product was thereafter made using low *o*- isomer cresols to achieve a product of low neurotoxicity. The so-called "natural cresylics" (cresols) from either coal tar or petroleum sources have been used. Supplies from both sources have been declining and prices of low *o*- isomer cresols have been increasing. However, tricresyl phosphates from the "natural cresylics" are still on the market, for instance Akzo's LINDOL. This product, bp 260-275° at 10 Torr, is used in flexible PVC, cellulose nitrate, and ethylcellulose coatings. It has low volatility, good saponification resistance, and good resistance to extraction by oil. An even lower volatility product, trixylyl phosphate, is also available; it is a complex mixture of isomers.[142] Typical applications for both products are in vinyl tarpaulins, conveyor belts, air ducts, cable insulation, and films.

The trend in recent years has been away from the "natural" cresols (cresylic acids) to synthetic alternatives, the isopropylphenol/phenol mixtures and *t*-butylphenol/phenol mixtures made by partial alkylation of phenol by propylene or isobutylene.[143-145] The isopropylphenols are isomer mixtures.[142,146]

Isopropyl diphenyl phosphate. This is a reasonably close approximation in plasticizer efficiency to tricresyl phosphate. It is available as FMC's KRONITEX 100, Akzo's PHOSFLEX 41P, and a Ciba-Geigy RHEOPHOS. These competitive products are not necessarily identical compositions. The isopropylphenol used is an isomer mixture made by alkylation of phenol by propylene, and since the phosphate is made by reaction of a phenol-isopropylphenol mixture with phosphorus oxychloride, the product can be expected to contain triaryl phosphates having from zero to three isopropylphenyl groups.

Isopropylphenyl diphenyl phosphate is an excellent flame retardant plasticizer for polyvinyl chloride. As was the case with tricresyl phosphate, this newer phosphate is also usually used in

blends with non-flame-retardant plasticizers such as dialkyl phthalates.

tert-*Butylphenyl diphenyl phosphate*. The triaryl phosphate is made from a mixed isomer *t*-butylphenol, phenol and phosphorus oxychloride. This phosphate shows rapid solvation of PVC and has a fairly wide range of compatibility. It is a somewhat less efficient plasticizer than the isopropylphenyl analog, but is more stable and more biologically inert. It has found use as a flame retardant in polyphenylene oxide blends with high impact polystyrene, in chemically-blown vinyl foams and vinyl emulsions. In the last case, it aids film formation, film flexibility and water resistance of the films, beside its flame retardant action. It is also of use as a fire resistant hydraulic fluid.

2-Ethylhexyl diphenyl phosphate. Since it was found early in the development of plasticized vinyls that the triaryl phosphates have relatively poor low temperature properties, the alkyl diphenyl phosphates were developed by Monsanto.[147] These phosphates overcome the low temperature flexibility problem although at some sacrifice of flame retardant efficiency. The two commercial examples are 2-ethylhexyl diphenyl phosphate and isodecyl diphenyl phosphate. The first of these has FDA approval for certain food wrapping applications.

Isodecyl diphenyl phosphate. This phosphate is a more effective plasticizer at lower temperatures although less effective at ambient temperatures, compared with its 2-ethylhexyl analog.

Tetraphenyl m- *and* p-*phenylene diphosphates*. These relatively new aromatic phosphates are mainly of interest as flame retardant additives for engineering thermoplastics, such as polyphenylene oxide blends with high impact polystyrene or rubber blends.[148] They are less volatile and have a higher percentage of phosphorus than the triaryl phosphates. The *m*- isomer is a liquid; the *p*- isomer is a solid. They have been made available recently by Akzo in the U.S. and by Dai Hachi in Japan.

Tris(2,4-dibromophenyl) phosphate. This is a solid, mp 110°, introduced recently by FMC as KRONITEX PB-460 (4% P, 60% Br) for use as a flame retardant additive for thermoplastic polyesters (especially PBT), polycarbonate, ABS, and blends.[149,150] Unlike most brominated aromatic flame retardants, it is recommended for use without antimony oxide. Formulations containing this additive flux and mold readily and have good thermal stability. This phosphate has outstanding thermal stability and does not discolor when heated in air at up to 300°.

5. Organophosphorus Diols and Other Hydroxyl-functional Compounds

Early in the development of rigid polyurethane foams as insulation materials for buildings and transport vehicles, their flammability hazard was recognized and much effort was devoted to flame retardants. One approach was to build the flame retardancy into the urethane structure by use of phosphorus-containing diols or polyols; much effort has been expended on this topic,[151] with only a few commercial products as the result. As an alternative, additives such as the tris(chloroalkyl) phosphates and related di- and polyphosphates are used, as discussed above.

VIRCOL 82. The first of the reactive polyols appears to have been a diol from the reaction of dibutyl acid pyrophosphate and propylene oxide, VIRCOL 82, having the approximate structure:

$$HO(C_3H_6O)_x\overset{\overset{O}{\|}}{\underset{\underset{OC_4H_9}{|}}{P}}OC_3H_6O\overset{\overset{O}{\|}}{\underset{\underset{OC_4H_9}{|}}{P}}(OC_3H_6)_yOH$$

where (x + y) approximately equals 3.4. This product has a hydroxyl number of 205 mg KOH/g and has a phosphorus content of 11.3%.[151,152]

FYROL 6. Slightly later, a phosphorus diol of somewhat greater phosphorus content and better hydrolysis resistance was introduced by Victor Chemical Works, and currently made by Akzo.[153] This diol, diethyl *N,N'*-bis(2-hydroxyethyl)aminomethylphosphonate, is synthesized by a Mannich-type reaction as follows:

$$(C_2H_5O)_2POH + HCHO + HN(CH_2CH_2OH)_2 \xrightarrow{-H_2O} (C_2H_5O)_2P(O)CH_2N(CH_2CH_2OH)_2$$

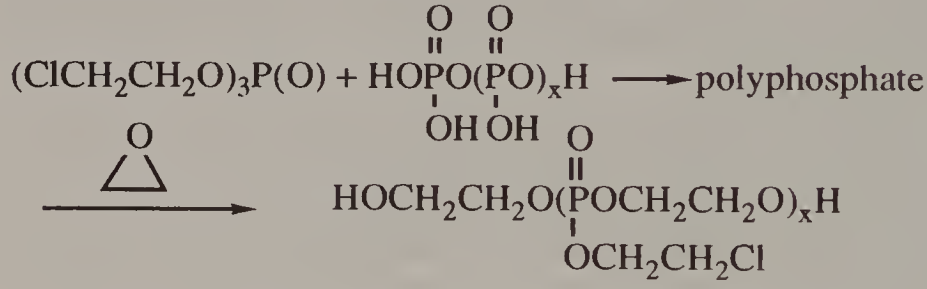
This diol has an OH number of 450 mg KOH/g and a phosphorus content of 12.6%. It has become a leading flame retardant used to impart a permanent Class II E-84 flame spread rating to rigid polyurethane foam insulation in walls and roofing. Foams made using this diol have good humid aging resistance and dimensional stability. This diol is also convenient to use because it can be mixed with the polyol-catalyst component and is low in viscosity.

FYROL 6 is especially useful in spray, froth or pour-in-place foam applications.

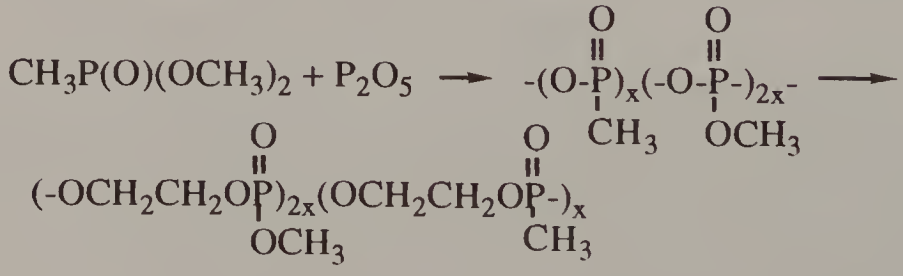
Other phosphorus diols. Several phosphorus-containing polyols have been made and marketed based on the reaction of propylene oxide with polyphosphoric acid or phosphoric acid.[151] Because of the formation of polyoxypropylene chains, these products tend to have a low % P and are also somewhat more hydrolyzable than desired. For example, BASF's PLURACOL 648 is a high functionality polyol containing 4.5% P, sold for use in E-84 class II rigid foams. WESTON 430 is a tris(dipropylene glycol) phosphate used for less rigorous flame requirements such as ASTM D 1962.

The only reactive polyol for flexible foams appears to be Hoechst's EXOLIT 413, a polyol containing 13% P and 19.5% Cl. The patent believed to describe it[154] shows the reaction of ethylene oxide with a prereacted mixture of tris(2-chloroethyl) phosphate and polyphosphoric acid. This product is used in automotive seating in Europe.

The synthesis of EXOLIT 413 appears to be as follows:



Oligomeric phosphonate-phosphate (Akzo's FYROL 51). Low volatility fluids of high phosphorus content have been made by a route such as the following:[155]



The end groups of this oligomer are mainly primary alcohol groups, and thus it can be incorporated into aminoplasts, phenolic

resins, and polyurethanes.

One significant application of the above phosphorus-containing diol is the treatment of paper automotive air filters; the phosphorus compound is cured under acid conditions with an amino resin (typically a melamine-formaldehyde resin) or with a resol to produce a wash-durable paper finish. A similar mode of application is employed to use FYROL 51 as a flame retardant in backcoating of upholstery fabric, to pass the British or California flammability standards.

This phosphorus rich oligomer can also be incorporated into polyurethanes. One application is in RIM (Reaction Injection Molding) applications. Combinations of FYROL 51 with FYROL 6 permit the OH number to be adjusted to a desired level, typically about that of the polyol used in polyurethane[156] or in polyurethane-polyoxazolidone RIM compositions.[157]

Tris(3-hydroxypropyl)phosphine oxide and isobutylbis(3-hydroxypropyl)phosphine oxide. This diol and triol were made available on a development basis in the 1980's by FMC. Their synthesis is from phosphine and allyl alcohol.[158] In the case of the diol, there is a prior step of addition of phosphine to 2-butene, as shown:[159]

$$CH_3CH{=}CHCH_3 + PH_3 \longrightarrow CH_3CH_2CH(PH_2)CH_3$$

$$\xrightarrow{2\ H_2C{=}CHCH_2OH} CH_3CH_2CH(CH_3)P(CH_2CH_2CH_2OH)_2$$

$$\longrightarrow CH_3CH_2CH(CH_3)P(O)(CH_2CH_2CH_2OH)_2$$

These products were offered for both urethane foam and epoxy applications,[4,160-161] although at the present time they have not reached commercial use.

6. Phosphorus-containing Reactive Methylol Compounds

The principal application for this class of reactive phosphorus flame retardants is in textile finishing, particularly for cotton and blends. Markets have been developed for flame retardant cotton in industrial garments, military uniforms, hospital goods, curtains, and bedding. For a time, children's sleepwear was also a significant market for cotton finishes. A review of flame retardant finishing has recently been published by Horrocks.[162]

Tetrakis(hydroxymethylphosphonium chloride, sulfate or

acetate. This family of closely related salts is produced by reaction of phosphine with formaldehyde in the presence of acid, for example as shown in the following equation:

$$4\ HCHO + PH_3 + HCl \longrightarrow (HOCH_2)_4\overset{+}{P}\ \overset{-}{Cl}$$

These salts are produced commercially as stable aqueous solutions.

A wide variety of curing methods have been developed by Albright & Wilson, Hooker Chemical (now Oxychem), American Cyanamid and the USDA Southern Regional Laboratory, by which these tetrakis(hydroxymethyl) salts can be converted to stable durable finishes on cellulosic substrates such as cotton. Many reactions with amino resins, urea, ammonia and the like have been described and reviewed.[163-167] The most significant curing method consists of three steps, as follows:

First, the reactant is converted to THPOH by neutralization.

$$(HOCH_2)_4\overset{+}{P}\ \overset{-}{Cl} + \overset{-}{OH} \longrightarrow \text{"}(HOCH_2)_4\overset{+}{P}\ \overset{-}{OH}\text{"}$$

THPOH is believed to be a mixture of tris(hydroxymethyl)-phosphine and hemiformals thereof.[168] THPOH solution is applied to the fabric by padding (passage through a bath and then through pressure rollers) followed by partial drying and exposure to ammonia vapors in a special chamber. This causes crosslinking to occur with formation of linkages of the P-CH_2-N-CH_2-P type. The cured finish is then oxidized by air or exposure to dilute hydrogen peroxide or perborate, to produce stable P(O)-CH_2-N-CH_2-P(O) linkages.

The resultant finish produced on cotton is colorless, odorless except for any residual loosely bound formaldehyde, and highly resistant to multiple (50 or more) home launderings. Flame retardancy to the Federal sleepwear standard is achieved, as is resistance to the highly alkaline conditions of industrial laundering.

An improvement developed by Albright and Wilson is to have the THPC prereacted with urea.[169] This avoids formaldehyde emissions and facilitates the rapid curing of the finish. It is also possible to combine durable press with the flame retardant feature of this finish.[170] This prereacted version of the THPOH ammonia cured finish has become the dominant method of using the THPC

type of reagent. The U.S. Navy has begun to use this flame retardant cotton finish for seamen's uniforms.[171]

Dimethyl 3-[(hydroxymethyl)amino]-3-oxopropylphosphonate. This compound, Ciba-Geigy's PYROVATEX CP is a cotton finishing reagent based on the addition of dimethyl phosphite (or alternatively, trimethyl phosphite with a proton donor) to acrylamide, followed by methylolation.[172,173]

$$H_2C{=}CHCONH_2 + (CH_3O)_2PHO \longrightarrow (CH_3O)_2\overset{\overset{\displaystyle O}{\|}}{P}(O)CH_2CH_2C(=O)NH_2$$

$$\xrightarrow{CH_2O} (CH_3O)_2\overset{\overset{\displaystyle O}{\|}}{P}CH_2CH_2CONHCH_2OH$$

PYROVATEX CP is used in conjunction with an amino resin coreactant and a latent acid curing catalyst to prepare a wash-durable finish for cotton and viscose rayon. Originally, its major use was on children's sleepwear. It subsequently has become more important as a finish for upholstery, curtains and industrial garments. PYROVATEX CP NEW, a higher purity version of PYROVATEX CP, has recently been reintroduced for use on cotton sleepwear.

7. Unsaturated Phosphorus Monomers

Although much research effort has been directed to vinyl and allyl phosphorus monomers for use in making flame retardant polymers and copolymers,[133] commercial examples are few.

Bis(2-chloroethyl) vinylphosphonate. This monomer is sold as Akzo's FYROL Bis-Beta, made by dehydrochlorination of bis(2-chloroethyl) 2-chloroethylphosphonate:

$$ClCH_2CH_2\overset{\overset{\displaystyle O}{\|}}{P}(OCH_2CH_2Cl)_2 \xrightarrow{\text{base}} H_2C{=}CH\overset{\overset{\displaystyle O}{\|}}{P}(OCH_2CH_2Cl)_2$$

It has found specialized applications in flame retardant copolymers, for a time being used in unsaturated polyesters[174] and acrylic copolymers. It is also used as a precursor for vinylphosphonic acid, the polymer of which has application for coating of photolithography plates. Some promising inherently-plasticized vinyl chloride-acrylate-vinylphosphonate copolymer films[175-177]

and emulsions[178,179] were developed by Stauffer Chemical Co. but ultimately not commercialized.

Oligomeric vinylphosphonate (Akzo's FYROL 76). This water-soluble multiply unsaturated oligomer is made from bis(2-chloroethyl) vinylphosphonate and dimethyl methylphosphonate with elimination of substantially all the chlorine as methyl chloride:[180-183]

$$H_2C{=}CHP(O)(OCH_2CH_2Cl)_2 + CH_3P(O)(OCH_3)_2 \xrightarrow{-\,CH_3Cl}$$

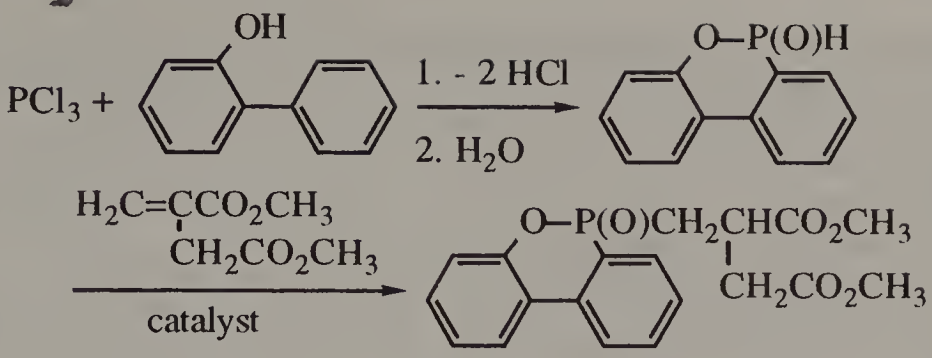
$$(\text{-}OCH_2CH_2O\overset{\overset{O}{\|}}{\underset{\underset{CH_3}{|}}{P}}OCH_2CH_2O\overset{\overset{O}{\|}}{\underset{\underset{CH{=}CH_2}{|}}{P}}\text{-})_x$$

FYROL 76 is curable by free radical catalysis such as by use of persulfate or electron beam, and is cocurable with monomers such as *N*-methylolacrylamide and *N*-vinylpyrrolidone. Originally, it was marketed for cotton children's sleepwear, and later for industrial goods. Some formulations effective on polyester-cotton blends have been developed.[184]

8. Flame-retardant Fibers with Built-in Phosphorus Structures

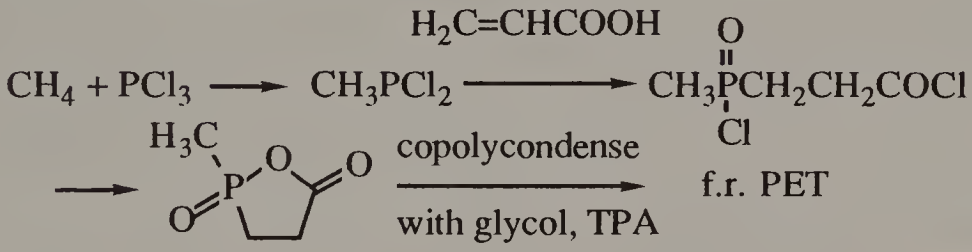
The patent literature is replete with many examples but apparently few such systems have had adequate fiber performance and acceptable economics. Two flame retardant PET fibers are on the market with built-in phosphorus, as follows:

Toyobo GH. This flame retardant polyethylene terephthalate (trade name in Japan: HEIM) is useful for sleepware and curtains; in Japan, home furnishings are the largest use. The fibers have processing and dyeing characteristics close to those of non-flame-retarded polyester. The chemistry, which has been developed commercially in Japan, is believed to be as follows:[185]



The phosphinate is then copolycondensed by way of its carboxylate ester groups with the other components of PET. The ressultant structure has good hydrolytic and thermal stability, and can be processed and dyed in a manner similar to ordinary PET.

Hoechst-Celanese's TREVIRA FR. This flame retardant polyethylene terephthalate, developed in Germany, incorporates phosphorus in the PET chain by means of a phosphinate coreactant made by the following chemistry:[186,187]



A phosphorus content of as low as 0.6% is reported[51] to render this fabric flame retardant for uses such as draperies and upholstery if melt-drip is not retarded.

9. Flame Retardant Thermoset Polymers with Built-in Phosphorus

A wide variety of phosphorus-containing polymers have been synthesized in academic and industrial laboratories,[72,133] but only a very few have been commercialized; among those few are the modified PET products already discussed.

Epoxy resins with phosphorus incorporated in the epoxy moiety and in the curing agent have been described in patents[72] but at present none is known to be used as a flame retardant product.

Unsaturated polyester resins either with phosphorus built into the polyester backbone or with a vinylphosphonate comonomer added along with styrene have been the subject of much research

but have been only briefly commercialized.[174] The problems have been cost, hydrolytic stability, and the tendency of phosphorus esters to bind the cobalt cations which are often an essential part of the ambient temperature curing peroxide catalyst system. This interference with cure can be overcome by using vanadium activators which are not deactivated by phosphorus esters.

Numerous thermosets of the phenolic and aminoplast type have been described in which phosphorus structures, such as diethyl bis(2-hydroxyethyl)aminomethylphosphonate, are reacted into the crosslinked resin. Additive approaches however seem to dominate these resin systems.

10. Polyphosphazenes

The reaction of phosphorus pentachloride with ammonia or ammonium chloride gives a group of linear and cyclic products having $-N=P(Cl)_2-$ repeating units. The linear material is elastomeric but hydrolytically very sensitive. By purifying the cyclic phosphonitrilic chlorides and then subjecting them to a controlled polymerization, high molecular weight polymeric phosphonitrlic chlorides can be prepared, which can be converted by nucleophilic displacement of the chlorine atoms to a wide variety of polymers.[188-190] As the result of research at Firestone, Armstrong, Ethyl Corp. and Penn State University, useful but expensive fire retardant polymers have thus been prepared.

The products made by displacing the chlorine atoms by trifluoroethoxy or other polyfluoroalkoxy groups are useful elastomers having good wide service temperature range (-65^{o} to 175^{o}), good flex fatigue resistance, chemical resistance and good damping properties, for uses such as O-rings and insulation. A related product made by displacing the chlorine atoms of polymeric phosphonitrilic chloride by phenoxy and ethylphenoxy groups is useful for making fire resistant low-smoke wire and cable insulation and thermal insulating foams.[189,190]

Both types of phosphazene polymers are finding limited uses, especially in military applications.

In the 1970's, a liquid ether made by replacing all of the chlorine from mixed cyclic phosphonitrilic chloride by propoxy groups was briefly introduced as a durable flame retardant additive which could be introduced into viscose rayon prior to spinning.[191] It proved uneconomic and has since has been discontinued.

IV. Toxicity, Other Safety and Environmental Considerations

A. Toxicology

1. General Comments

A good general review[191a] of the toxicological, pharmacokinetic and environmental factors involved with phosphate esters was published in 1984. The present review will focus on the more recent information.

No general statement with regard to the toxicity of phosphorus compounds can be true, since phosphorus compounds range from essential food ingredients at one extreme to neurotoxic war gases at the other extreme. However, most phosphorus compounds fall into the substantially non-toxic to slightly toxic range. Phosphoric acid and various salts of phosphoric and pyrophosphoric acid are on the FDA-approved (GRAS) list of food additives.

The structure-activity relationships are rather better understood among phosphorus compounds than in many other groups of chemicals because of the intense study to which they have been subjected in food, pharmaceutical, agricultural and military research.[192,193] For phosphorus compounds to have high acute toxicity, they must have the necessary reactivity and steric fit to bind strongly with enzymes such as esterases or with certain receptor groups, or they must be strong alkylating agents.

2. Acute Toxicity

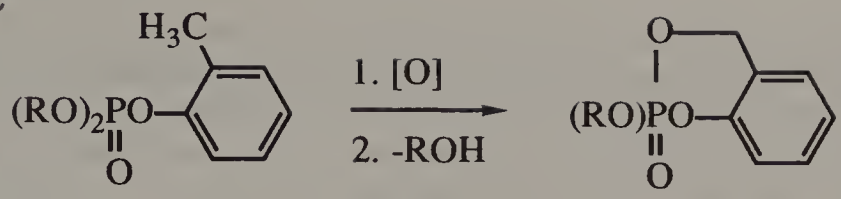
The flame retardant phosphorus compounds appear to have a low order of acute toxicity. Representative acute toxicity data (LD50 oral, rat data) is given in the table shown below.

A critical review of the toxicity of the haloalkyl phosphates and their potential metabolic products is available.[204] The toxicity of phosphorus flame retardants used on textiles has also been reviewed.[205] Slow skin absorption of tricresyl phosphate was demonstrated by one of the earliest uses of radiotracers,[206] and confirmed by later studies of this phosphate and others.[206a]

Compound	Oral LD50 (rat)	Ref.
mono-/diammonium phosphate	3160-4500	194
dimethyl methylphosphonate	>5000	195
triethyl phosphate	1311	196
tris(2-chloroethyl) phosphate	390 (female)	197
tris(2-chloro-1-propyl) phosphate	2800 (female)	198
tris(1,3-dichloro-2-propyl) phosphate	2830	199
triphenyl phosphate	>4640	200
tricresyl phosphate (comm. mixture	>4640	201
isopropylphenyl diphenyl phosphate	>10,000	202
t-butylphenyl diphenyl phosphate	>4640	203

3. Neurotoxicity in the Aryl Phosphate Series

It was discovered in the 1930's that tricresyl phosphate could cause a characteristic paralysis when ingested. Most such incidents have occurred when individuals have consumed massive amounts in adulterated beverages or cooking oils.[206b-206d] The neurotoxic character of tricresyl phosphate was traced principally to the presence of the *ortho*-cresyl isomer, although the *p*-ethylphenyl group was also shown to produce this effect. The structure-activity relationships and the mechanism of action have been studied extensively as well as the clinical manifestations in animal and human poisoning.[207-210] The basis for the specific toxicity of the *o*-cresyl phosphates is believed to be biooxidation of the *ortho*-alkyl group to form a cyclic phosphate ester which has phosphorylation capabilities for a membrane-bound enzyme, "neurotoxic esterase" (NTE). Phosphorylation of NTE appears to initiate delayed peripheral neuropathy, expressed as axonal degeneration and demyelination of the peripheral nerves, with some effects on the spinal cord. Since the half-life of the enzyme's regeneration is about 5 days, low level cumulative exposure is not likely to result in delayed neuropathy. The principal neurotoxic phosphorylating agent is formed as follows:



As can be seen from this mode of action, it is not necessary to have tri-*o*-cresyl phosphate (TOCP) in the composition to have a neurotoxic effect; a single methylphenyl group with an *ortho* methyl suffices to allow the high-energy ring to form, and thus *o*-cresyl diphenyl phosphate and other *o*-cresyl diaryl phosphates were also found to be neurotoxic. When the importance of the *o*-cresyl isomer became known, manufacturers of tricresyl phosphate elected to use only the low *ortho* isomer content cresols. Standard tests were developed using chickens sensitive to this type of paralysis, so as to permit checking aryl phosphates for absence of this type of toxicity. Testing of isopropylphenyl diphenyl phosphate for neurotoxicity in hens showed no adverse clinical effects or neurohistological abnormalities.[209]

That the aryl phosphate group also encompasses not only toxic compounds but also some very innocuous compounds is indicated by the fact that the FDA has approved 2-ethylhexyl diphenyl phosphate for food wrapping plasticizer applications.

4. Chronic, Subchronic and Repeated Exposure Toxicity

For details on individual flame retardants, the reader is referred to the material safety data sheets of the manufacturers. A subchronic study of FYROL 6, a diethyl phosphonate diol, showed low toxicity and liver enzyme induction (an adaptive response) by the test rats.[211] Long-term administration of commercial tricresyl phosphate (low *o*-cresyl content) to rats and mice resulted in reduced reproductive ability.[212,213] This latter symptom has been reported with some other flame retardants in material safety data sheets.

5. Mutagenicity and Carcinogenicity Considerations

The one flame retardant that had been discovered to have strong mutagenic and probably carcinogenic properties was voluntarily removed from the market in the mid-1970's following discovery of these properties. It was tris(2,3-dibromopropyl) phosphate, which had been used in a number of applications including, briefly,

children's sleepwear. This otherwise very useful flame retardant was found by the Ames Test (Salmonella mutation assay) to be strongly mutagenic, and later implicated as a carcinogen.[119,214-217] By means of the Salmonella assay, tris(2-chloroethyl) phosphate and tris(1,3-dichloro-1-methylethyl phosphate were found nonmutagenic or only weakly active.[214-217] The mutagenicity and carcinogenicity of tris(2,3-dibromopropyl) phosphate seem to be related to the dibromopropyl group and in fact mechanistic studies later showed that bioconversion to 2-bromoacrolein is a key step in the mutagenic and carcinogenic action.[218]

Chloroalkyl phosphate flame retardants have been found to have weak or equivocal oncogenic properties.[197,199]

6. Effects on the Toxicity of Combustion Products

There are no documented examples of fire victims being killed or injured by the vapors of flame retardants; most fire victims succumb to carbon monoxide, with cyanide being occasionally implicated. One survey of data from small scale pyrolysis or combustion data showed that the presence of a phosphorus flame retardant sometimes was accompanied by increases, sometimes by decreases in the amount of CO and HCN formed.[219,220,224] It should be noted that toxicity of combustion products is highly dependent on test conditions and does not seem to be mainly a material characteristic. Even the ranking of smoke toxicity of materials is dependent on burning conditions, whether flaming or smoldering, and on external energy input.[221,222]

A study covering thermal oxidative degradation of a number of triaryl, trialkyl, and tris(haloalkyl) phosphates[223] showed that tricresyl phosphate underwent only minimal degradation whereas the other compounds decomposed extensively. Butene was the main product from tributyl phosphate; hydrogen halides and halogenated C_2 and C_3 species were the main products from the halogenated phosphates. In the case of tris(1,3-dichloro-2-propyl) phosphate, acrolein (a decomposition product also formed from wood and other cellulosics) was judged to be the main toxic hazard, not hydrogen chloride.

One special case of a toxic product formed from a phosphorus flame retardant was that of a particular neurotoxic bicyclic phosphate. This bicyclic phosphate was produced, under specific heat input conditions, from rigid urethane foam based on

trimethylolpropane polyol and containing a number of diverse phosphorus flame retardants, both organic or inorganic. Although large scale corridor fire tests did not confirm the formation of enough of this compound to produce a measurable toxicity increment in the smoke, nevertheless, the U.S. foam manufacturers have refrained from using low molecular weight trimethylolpropane polyols and phosphorus flame retardants in combination.[219,220]

Combustion toxicity data show no consistent pattern regarding the effects of flame retardants, including phosphorus flame retardants, on the toxic hazard of fire gases.[219,220]

7. Effects on Visible Smoke

This topic bears a close relationship to the topic of combustion toxicity, since both matters relate to the ability of people to escape from a fire situation. Visible smoke appears to be as dependent on burning conditions[222] as on the composition of the material burned, and no generalization is valid regarding the effect of phosphorus flame retardants on visible smoke. In a careful Japanese study, ammonium phosphate was shown to either raise or lower smoke production from wood depending on the pyrolysis temperature.[224]

Various comparisons are reported where the visible smoke from a given polymer flame retarded with phosphorus is substantially less than from the same polymer flame retarded with a halogen-antimony system. Cases are reported where the presence of the phosphorus retardant resulted in reduction of smoke, presumably by increasing char residue.[225] Other cases are reported where the inclusion of a phosphorus retardant increased smoke, such as in a dimethyl methylphosphonate-ATH-polyester system.[101]

The subtle dependence of smoke on the total formulation is shown by the case of plasticized PVC, where an alkyl diphenyl phosphate increased smoke when calcium carbonate was used as filler but decreased smoke when magnesium minerals were used as fillers.[226,227]

8. Environmental Considerations

The discharge of large amounts of inorganic phosphates into streams or the leaching of phosphates into ground water are considered undesirable because of the stimulation of undesirable eutrophication; however, the contribution of phosphorus flame retardants is miniscule compared to phosphates from detergents or

fertilizers.

Aquatic toxicity studies by the EPA have shown some haloalkyl phosphates and some aryl phosphates to be fairly toxic at aquatic fauna, others not.[228,229] However, the general level of aquatic toxicity even for the worst examples does not appear to be in the range of severe pollutants such as PCBs.[229] A non-halogenated phosphonate flame retardant, A&W's ANTIBLAZE 19 was reported to have an LC50 > 1000 ppm for sunfish and trout.[230] A study by the U.S. Fish and Wildlife Service indicated that the toxicity of a series of triaryl and alkyl diphenyl phosphates appeared to relate to the triphenyl phosphate content; comparison of toxic effect levels with environmental concentration data led to the conclusion that these phosphates may not pose a threat to fish.[231] Reversible bioaccumulation in fish has been shown.[232]

The disappearance of phosphorus esters from soil and water should be favored by the natural occurrance of phosphatases in all living organisms, and by the non-enzymatic hydrolysis capability of the C-O-P bond. Some data are available on the rate of non-catalyzed non-enzymatic hydrolysis of organic phosphates at pH 7 and 25°: dimethyl methylphosphonate has a half-life of 5.5 years and triphenyl phosphate has a half-life of 1.3 years.[233] However, biodegradation rate measurements in river water and activated sludge indicate that the various aryl and alkyl aryl phosphates degrade much more rapidly than the rates determined in pure water would suggest.[234,235] The C-P bond of phosphonates is considerably more stable than the C-O-P linkage but is cleaved by certain microorganisms.[236-238]

V. Market Aspects

Detailed production or consumption figures on the individual phosphorus flame retardants are difficult to obtain because most of these compounds are made by only one or two manufacturers. A market assessment in 1990 indicates that phosphorus-based flame retardants total $124 million in 1990 (28% of the total flame retardant market) growing to $150.9 million (still 28% of the market) in 1994.[239] The largest uses are the plasticized vinyl, urethane foam, textile, and possibly wood applications. Usage in styrenics (other than PPO blends) and polyolefins is probably miniscule, but new intumescent formulations for polyolefins are promising, and research is underway to find effective phosphorus systems for styrenics.

Because of environmental and toxicological concerns, as well as because of smoke and corrosivity considerations, there is considerable interest in finding phosphorus-based flame retardants to use in place of halogen-antimony retardant systems.

VI. Bibliography

1. Weil, E.D. (1980). Flame retardants (phosphorus compounds), *Kirk-Othmer encyclopedia of chemical technology, Vol. 10, 3rd Ed.*, (Mark, H.F., *et al.*, eds.) John Wiley & Sons, Inc., New York, pp. 396-419.
2. Aseeva, R.M., and Zaikov, G.E. (1985). *Combustion of polymeric materials*, Hanser Publishers, Munich/New York, pp. 229-241.
3. Weil, E.D. (1978). Phosphorus-based flame retardants, *Flame-retardant polymeric materials, Vol. 2*, (Lewin, M., Atlas, S.M., and Pearce, E.M., eds.) Plenum Press, New York, pp. 103-128.
4. Green, J. (1984). Phosphorus-containing flame retardants, *Plastics Compounding*, *7*: 30.
5. Green, J. (1987). Influence of coadditives in phosphorus-based flame retardant systems, *Plastics Compounding*: 57.
6. Granzow, A. (1978). Flame retardation by phosphorus compounds, *Acct. Chem. Res.*, *11*: 177.
7. Brauman, S.K., and Fishman, N. (1977). Phosphorus flame retardance in polymers. III. Some aspects of combustion performance, *J. Fire Ret. Chem.*, *4*: 93.
8. Lewin, M. (1984). Flame retardance of fabrics, *Handbook of fiber science and technology: chemical processing of fibers and fabrics, Vol. 2, Part B*, (Lewin, M., and Sello, S., eds.), Marcel Dekker, Inc., New York, pp.1-141.
9. Barker, R.H., and Hendrix, J.E. (1979). Flame retardance of cotton, *Flame retardance of polymeric materials, Vol. 5*, (Kuryla, W.C., and Papa, A.J., eds.), Marcel Dekker, Inc., New York, pp. 1-65.
10. LeVan, S. (1984). Chemistry of fire retardancy, *The chemistry of solid wood*, (Rowell, R., ed.) American Chemical Society, Adv. Chem. Ser. 207, Washington, D.C., pp. 531-574.
11. Vandersall, H.J. (1971). Intumescent coating systems, their development and chemistry, *J. Fire Flamm.*, *2*: 97.
12. Camino, G., and Costa, L. (1986). Mechanism of intumescence in fire retardant polymers, *Rev. Inorg. Chem.*, *8*: 69.

13. Camino, C., Costa, L., and Trossarelli, L. (1984). Study of the mechanism of intumescence in fire retardant polymers. I. Thermal degradation of ammonium polyphosphate-pentaerythritol mixtures, *Polym. Degrad. Stabil.*, *6*: 243.
14. Camino, G., Costa, L., and Trossarelli, L. (1984). Study of the mechanism of intumescence in fire retardant polymers. II. Mechanism of action in polypropylene-ammonium polyphosphate-pentaerythritol mixtures, *Polym. Degrad. Stabil.*, *7*: 25.
15. Camino, G., Costa, L., and Trossarelli, L. (1984). Study of the mechanism of intumescence in fire retardant polymers. III. Effect of urea on the ammonium polyphosphate-pentaerythritol system, *Polym. Degrad. Stabil.*, *7*: 221.
16. Camino, G., Costa, L., Trossarelli, L., Costanzi, F., and Landoni, G. (1984). Study of the mechanism of intumescence in fire retardant polymers. IV. Evidence of ester formation in ammonium polyphosphate-pentaerythritol mixtures, *Polym. Degrad. Stabil.*, *8*: 13.
17. Camino, G., Costa, L., and Trossarelli, L. (1984). Study of the mechanism of intumescence in fire retardant polymers. V. Mechanism of formation of gaseous products in the thermal degradation of ammonium polyphosphate, *Polym. Degrad. Stabil.*, *12*: 203.
18. Camino, G., Costa, L., Trossarelli, L., Costanzi, F., and Pagliari, A. (1985). Study of the mechanism of intumescence in fire retardant polymers. VI. Mechanism of ester formation in ammonium polyphosphate-pentaerythritol mixtures, *Polym. Degrad. Stabil.*, *12*: 213.
19. Camino, G., Martinasso, G., and Costa, L. (1990). Thermal degradation of pentaerythritol diphosphate, model compound for fire resistant intumescent systems. I. Overall thermal degradation, *Polym. Degrad. Stabil.*, *27*: 285.
20. Bertelli, G., Camino, G., Marchetti, E., Costa, L., and Locatelli, R. (1989). Structural studies on chars from fire retardant intumescent systems, *Angew. Makromol. Chem.*, *169*: 137.
21. Hendrix, J.E., Drake, G.L., and Barker, R.H. (1972). Pyrolysis and combustion of cellulose. II. Thermal analysis of mixtures of methyl alpha-D-glucopyranoside and levoglucosan with model phosphate flame retardants, *J. Appl. Polym. Sci.*, *16*: 41.
22. Willard, J.J., and Wondra, R.E. (1970). Quantitative evalu-

ation of flame retardant cotton finishes by the limiting-oxygen index (LOI) technique, *Textile Res. J.*, *40*: 203.
23. Bakos, D., Kosik, M., Antos, K., Karolyova, M., and Vyskocil, L. (1982). The role of nitrogen in nitrogen-phosphorus synergism, *Fire & Materials*, *6*: 10.
24. Papa, A.J. (1975). Flame retarding polyurethanes, *Flame retardancy of polymeric materials, Vol. 3*, (Kuryla, W.C., and Papa, A.J., eds.), Marcel Dekker, Inc., New York, pp.1-133.
25. Zabski, L., Walczyk, W., and Jedlinski, Z. (1976). Influence of phosphorus content and of increase of cyclic structures content in crosslinked cellular urethane copolymers upon their physical properties, *Chem. Zvesti., Engl. Transl.*, *30*: 311.
26. Anderson, J.J. (1963). Retention of flame properties of rigid polyurethane foams, *Ind. Eng. Chem. Prod. Res. Dev.*, *2*: 260.
27. Kresta, J.E., and Frisch, K.C. (1975). Comparative study of the effect of phosphorus and chlorine in urethane and isocyanurate-urethane foams, *J. Cell. Plast.*, *11*: 68.
28. Piechota, H. (1965). Some correlations between raw materials, formulations and flame retardant properties of rigid urethane foams, *J. Cell. Plast.*, *1*: 186.
29. Papa, A.J., and Proops, W.R. (1972). Influence of structural effects of halogen and phosphorus polyol mixtures on flame retardancy of flexible polyurethane foams, *J. Appl. Poly. Sci.*, *16*: 2631.
30. Hall, D.R., Hirschler, M.M., and Yavornitzky, C.M. (1986). Halogen-free flame retardant thermoplastic polyurethanes, *Fire safety science - proceedings of the first international symposium*, (Grant, C.E., and Pagni, P.J., eds.), Hemisphere Publishing, Washington, D.C., pp. 421-430.
31. Avondo, G., Vovelle, C., and Delbourgo, R. (1978). The role of phosphorus and bromine in flame retardancy, *Combust. Flame*, *31*: 7.
32. Suebsaeng, T., Wilkie, C.A., Burger, V.T., Carter, J., and Brown, C.E. (1984). Solid products from thermal decomposition of poly(ethylene terephthalate); investigation by CP/MAS, C13 NMR and Fourier transform IR, *J. Polym. Sci.; Polym. Let. Ed.*, *22*: 625.
33. Gruntfest, I.J., and Young, E.M. (1962). The action of

flame proofing additives on PMMA, *ACS Div. Org. Coatings & Plastics Preprints*, *2*: 133.
34. Camino, G., Grassie, N., and McNeill, I.C. (1978). Influence of the fire retardant, ammonium polyphosphate, on the thermal degradation of poly(methyl methacrylate), *J. Polym. Sci., Polym. Chem. Ed.*, *16*: 95.
35. Wilkie, C. (1990). The design of flame retardants, *Fire and polymers*, (Nelson, G.L., ed.), American Chemical Society Symposium Series 425, Washington, D.C., pp. 178-188.
36. Brown, C.E., Wilkie, C.A., Smukalla, J., Cody, R.B., and Kinsinger, J.A. (1986). Inhibition by red phosphorus of unimolecular thermal chain-scission in poly(methyl methacrylate): investigation by NMR, FT-IR and laser desorption/Fourier transform mass spectroscopy, *J. Polym. Sci.: Part A: Polym. Chem.*, *24*: 1297.
37. Brauman, S.K. (1980). Phosphorus fire retardance in polymers. IV. Poly(ethylene terephthalate)-ammonium polyphosphate, a model system, *J. Fire Ret. Chem.*, *7*: 61.
38. Steutz, D.E., DiEdwardo, A.H., Zitomer, F., Barnes, B.P. (1975). Polymer flammability. II., *J. Polym. Sci., Polym. Chem. Ed.*, *13*: 585.
39. Martel, B. (1988). Charring processes in thermoplastic polymers: effect of condensed phase oxidation on the formation of chars in pure polymers, *J. Appl. Polym. Sci.*, *35*: 1213.
40. Delobel, R., Ouassou, N., Le Bras, M., and Leroy, J.-M. (1989). Fire retardance of polypropylene: action of diammonium pyrophosphate-pentaerythritol intumescent mixture, *Polym. Degrad. Stabil.*, *23*: 349.
41. Delobel, R., Le Bras, M., Ouassou, N., and Alistiqsa, F. (1990). Thermal behaviors of ammonium polyphosphate-pentaerythritol and ammonium pyrophosphate- pentaerythritol intumescent additives in polypropylene formulations, *J. Fire Sciences*, *8*: 85.
42. Delobel, R., Le Bras, M., Ouassou, N., and Descressain, R. (1990). Fire retardance of polypropylene by diammonium pyrophosphate-pentaerythritol: spectroscopic characterization of the protective coatings, *Polym. Degrad. Stabil.*, *30*: 41.
43. Lewin, M., Isaacs, P., Sello, S.B., and Stevens, C. (1974). Flame-resistance cellulose esters, *Text. Res. J.*, *47*: 700.
44. Lewin, M., Isaacs, P., Sello, S.B., and Stevens, C. (1974). Flame retardant modification of cellulose, *Textilveredlung*, *8*:

158.
45. Ermolenko, I.N., Lyubliner, I.P., and Gulko, N.V. (1990). *Chemically modified carbon fibers*, VCH Publishers, Inc., New York, pp. 202.
46. Gibov, K.M., Shapovalova, L.N., and Zhdanov, B.A. (1986). Movement of destruction products through the carbonized layer upon combustion of polymers, *Fire & Materials*, *10*: 133.
47. Brauman, S. (1977). Phosphorus fire retardance in polymers. I. General mode of action, *J. Fire Ret. Chem.*, *4*: 18.
48. Brauman, S. (1977). Phosphorus fire retardance in polymers. II. Retardant-polymer substrate interactions, *J. Fire Ret. Chem.*, *4*: 38.
49. Benbow, A.W., and Cullis, C.F. (1975). The combustion of flexible polyurethane foams: mechanisms and evaluation of flame retardance, *Combustion & Flame*, *24*: 217.
50. Swihart, T.J., and Campbell, P.E. (1974). How silicones affect flame retardancy, *Text. Chem. Color.*, *6*: 109.
51. Mach, H.-R. (1990). How can the low flammability of a polyester fibre type be retained in textile printing?, *Melliand Textilberichte, Engl. Transl.*, *1*: E29.
52. Serenkova, I.A., and Shlyapnikov, Y.A. (1989). Phosphorus containing flame retardants as high temperature antioxidants, *Proc. intl. symp. on flame retardants, Nov. 1989*, Intl. Academic Publ. (Pergamon), Beijing, China, pp. 156-161.
53. Tkac, A. (1981). Radical processes in polymer burning and its retardation, *J. Polym. Sci. A, Polym. Chem. Ed.*, *19*: 1495.
54. Citovichy, P., Kosik, M., and Spilda, I. (1985). Thermoanalytical investigation of grafted polypropylene with fixed flame retardant compounds, *Thermochem. Acta*, *93*: 171.
55. Walter, S. (1981). Filled polypropylene can be flexible - and flame retardant, too, *Plastics Engineering*, *37*: 24.
56. Rosser, W.A., Inami, S.H., and Wise, H. (1966). Quenching of premixed flames by volatile inhibitors, *Combust. Flame*, *10*: 287.
57. McHale, E.T. (1969). Survey of vapor phase chemical agents for combustion suppression, *Fire Research Abstracts & Reviews*, *11*: 90.
58. Hastie, J.W., and Bonnell, D.W. (1980). Molecular chemistry of inhibited combustion systems, *Natl. Bureau*

Stds. Report NBSIR 80-2169, Washington, D.C.
59. Hastie, J.W. (1973). Molecular basis of flame inhibition, *J. Res. NBS -A. Physics & Chem., 77A*: 733.
60. Hastie, J.W., and McBee, C.L. (1975). Mechanistic studies of triphenylphosphine oxide-poly(ethylene terephthalate) and related flame retardant systems, *Natl. Bureau Stds. Report NBSIR 75-741*, Washington, D.C.
61. Weil, E.D., Jung, A.K., Aaronson, A.M., and Leitner, G.C. (1979). Recent basic and applied research on phosphorus flame retardants, *Proc. 3rd Eur. conf. on flamm. and fire ret.*, (Bhatnagar, V.M., ed.), Technomic Publ., Westport, CT.
62. Carnahan, J., Haaf, W., Nelson, G., Lee, G., Abolins, V., and Shank, P. (1979). Investigations into the mechanism for phosphorus flame retardancy in engineering plastics, *Proc. 4th intl. conf. flammability and safety*, Product Safety Corp., San Francisco, CA.
63. Larsen, E.R. (1975). Halogenated fire extinguishants: flame suppression by a physical mechanism?, *Halogenated fire suppressants*, (Gann, R.G., ed.) American Chemical Society Symposium Series 16, Washington, D.C.
64. Larsen, E.R., and Ludwig, R.B. (1979). On the mechanism of halogen's flame suppressing properties, *J. Fire Flamm., 10*: 69.
64a. Weil, E.D., unpublished results.
65. Weil, E.D. (1987). Flame retardant chemicals for polyurethane applications, *Polyurethane Technol. Conf. (Preprints)*, Clemson Univ. Clemson, SC.
66. Batt, A.M., and Appleyard, P. (1989). The mechanism and performance of combustion modified flexible foams in small scale fire tests, *J. Fire Sciences, 7*: 338.
67. Weil, E.D. (1975). Additivity, synergism and antagonism in flame retardancy, *Flame retardancy of polymeric materials, Vol. 3*, (Kuryla, W.C., and Papa, A.J., eds.), Marcel Dekker, Inc., New York, pp. 186-243.
67a. Morgan, A.W. (1972). Formulation and testing of flame-retardant systems for plasticized poly(vinyl chloride), *Advances in fire retardants, Vol. 1*, (Bhatnagar, V.M., ed.), Technomic Publishing Co., Westport, CT.
68. Yang, C.-P., and Lee, T.-M. (1989). Synthesis and properties of 4-hydroxy-3,5-dibromobenzyl phosphonates and their flame-retarding effects on ABS copolymer, *J.*

Polym. Sci., Polym. Chem. Ed., 27: 2239.
69. Bonsignore, P.V., and Manhart, J.H. (1974). Alumina trihydrate as a flame retardant and smoke suppressive filler in reinforced polyester plastics, *Proc. 29th ann. conf. reinf. plast. compos. inst. SPE, 23C*: 1.
70. Larsen, E.R., and Ecker, E.L. (1979). On the use of phosphorus as an FR adjunct with halogenated unsaturated polyesters, *J. Fire Retardant Chem., 6*: 182.
71. Scharf, D., Nalepa, R. Heflin, R., and Wusu, T. (1990). Studies on flame retardant intumescent char, Part I. *Proc. Int. Conf. on Fire Safety, 15*: 306.
71a. Granzow, A., and Savides, C. (1980). Flame retardancy of polypropylene and impact polystyrene: phosphonium bromide/ammonium polyphosphate system, *J. Appl. Polym. Sci., 25*: 2195.
71b. Savides, C., Granzow, A., and Cannelongo, J.F. (1979). Phosphine-based flame retardants for polypropylene, *J. Appl. Polym. Sci., 23*: 2639.
72. Weil, E.D. (1988). Phosphorus-containing polymers, *Encyclopedia of polymer science and engineering, Vol. 11*, (Kroschwitz, J., ed.), John Wiley & Sons, Inc., New York, pp. 96-126.
73. Weil, E.D. (1987). Recent advances in phosphorus-containing polymers for flame retardant applications, *Proc. Int. Conf. on Fire Safety, 12*: 210.
74. Deshpande, A.B., Pearce, E.M., Yoon, H.S., and Liepins, R. (1977). Some structure-property relationships in polymer flammability: studies on poly(ethylene terephthalate), *J. Appl. Polym. Sci., Appl. Polym. Symp., 31*: 257.
75. Stackman, R. (1980). Flammability of phosphorus-containing aromatic polyesters: a comparison of additives and comonomer flame retardants, *Modification of polymers*, (Carraher, C.H., and Tsuda, M., eds.), American Chemical Society Symposium Series 121, Washington, D.C., pp. 425-434.
76. Stackman, R. (1982). Phosphorus based additives for flame retardant polyester - 1. Low molecular weight additives, *Ind. Eng. Chem. Prod. Res. Dev., 21*: 328.
77. Stackman, R. (1982). Phosphorus based additives for flame retardant polyester - 2. Polymeric phosphorus esters, *Ind. Eng. Chem. Prod. Res. Dev., 21*: 332.
78. Lyons, J.W. (1970). *The chemistry and use of flame*

retardants, Wiley-Interscience, New York, pp. 29-74.
79. Taylor, D. (1989). Use of red phosphorus as a flame retardant, *Fire retardant engineering polymers & alloys*, (papers presented at San Antonio, TX, Mar. 12-15, 1989), Fire Ret. Chem. Assn., Lancaster, PA, pp. 133-142.
80. Staendeke, H. (1988). Red phosphorus - recent development for safe and efficient flame retardant applications, paper presented at Fire Retardant Chemicals Assoc. National Meeting, Mar. 1988.
81. Peters, E.N. (1978). Red phosphorus as a flame retardant, *Flame-retardant polymeric materials, Vol. 5*, (Lewin, M., Atlas, S.M., and Pearce, E.M., eds.), Plenum Press, New York, pp. 113-176.
82. Granzow, A., Ferrillo, R.G., and Wilson, A. (1977). The effect of elemental red phosphorus on the thermal degradation of poly(ethylene terephthalate), *J. Appl. Polym. Sci.*, *21*: 1687.
83. Lyons, J.W. (1970). *The chemistry and use of flame retardants*, Wiley-Interscience, New York, pp. 135, 215.
84. Flame Retardant Buyer's Guide (1985), *Amer. Dyestuff Reporter*, Jan. 1985: 13.
85. Shen, C.Y., Stahlheber, N.E., and Dyroff, D.R. (1969). Preparation and characterization of crystalline long-chain ammonium polyphosphates, *J. Am. Chem. Soc.*, *91*: 62.
86. Scharf, D. (1989). Intumescent flame retardants - a new perspective for plastics, *Fire retardant engineering polymers and alloys*, (papers presented at San Antonio, TX, Mar. 12-15, 1989), Fire Retardant Chemicals Assn., Lancaster, PA, pp. 183-202.
87. Mount, R. (1990). Non-halogenated flame retarded thermoplastics, *International conference on fire safety, papers presented at fire retardant chem. assn.*, New Orleans, March 25-28, 1990, pp. 253-267.
88. Staendeke, H., and Scharf, D. (1988). Intumescent fireproofing compositions for polymers, *Ger. Offen 3,720,094*.
89. Bertelli, G., and Locatelli, R. (1986). Self-extinguishing polyolefinic compositions having improved flame resistance characteristics and a high thermal stability, U.S. Patent 4,*579,894*.
90. Landoni, G., Fontani, S., and Cicchetti, O. (1982). Self-extinguishing polymeric products based on polyolefins, U.S.

Patent 4,*336,182*.
91. Scarso, L. (1988). Self-extinguishing polymeric products based on polyolefins, *U.S. Patent 4,727,102*.
92. Montaudo, G., Scamporrino, E., and Vitalini, D. (1983). Intumescent flame retardants for polymers. The polypropylene-ammonium polyphosphate-polyurea system, *J. Polym. Sci., 21*: 3321.
93. Fontanelli, R., Landoni, G., and Legnani, G. (1985). Self-extinguishing polymeric compositions, *U.S. Patent 4,504,610*.
94. Kay, M., Price, A.F., and Lavery, I. (1979). A review of intumescent materials with emphasis on melamine formulations, *J. Fire Retard. Chem., 6*: 69.
95. Costa, L., Camino, G., and Luda di Cortemiglia, M.P. (1990). Mechanism of thermal degradation of fire-retardant melamine salts, *Fire & polymers*, (Nelson, G., ed.), American Chemical Society Symposium Series 425, Washington, D.C., pp. 211-238.
96. Hull, D.C., and Agett, A.H. (1947). Neutral esters of phosphoric acid, *U.S. Patent 2,430,569*.
97. Hull, D.C., and Snodgrass, J.R. (1946). Neutral esters of phosphoric acid, *U.S. Patent 2,407,279*.
98. Nametz, R. (1967). Self-extinguishing polyester resins, *Ind. Eng. Chem., 59*: 99.
99. Beavon, A.N. (1975). Flame retardant reinforced bonded articles and bonding compositions therefor, *U.S. Patent 3,909,484*.
100. Data Brochure on Disflammoll TOF (1980). Bayer AG, KL Division, D-5090, Leverkusen, Germany.
101. Bonsignore, P.V., and Levendusky, T.L. (1977). Alumina trihydrate as a flame retardant and smoke suppressive filler in rigid high density polyurethane foams, *J. Fire Flamm., 8*: 95.
102. Anderson, J.J. (1963). Retention of flame properties of rigid polyurethane foams, *Ind. Eng. Chem. Prod. Res. Dev., 2*: 260.
103. Anderson, J.J., Camacho, J.G., and Kinney, R.E. (1974). Cyclic phosphonate esters as flame retardants for polymers, *U.S. Patent 3,789,091*.
104. Anderson, J.J., Camacho, V.G., and Kinney, R.E. (1974). Fire retardant polymers containing thermally stable cyclic phosphonate esters, *U.S. Patent 3,849,368*.

105. Halpern, Y., Mott, M., and Niswander, R.H. (1984). Fire retardancy of thermoplastic materials by intumescence, *Ind. Eng. Chem. Prod. Res. Dev., 23*: 233.
106. Termine, E., and Taylor, K.G. (1989). A new intumescent flame retardant additive for thermoplastics and thermosets, *Additive approaches to polymer modification*, SPE RETC Conference Papers, Toronto, Ontario, Sept. 1989.
107. Halpern, Y. (1982). Intumescent flame retardant compositions, *U.S. Patent 4,341,694*.
108. Parr, W.J., Mack, A.G., and Moy, P.Y. (1989). Bicyclic phosphate ether, ester, and carbonate intumescent flame retardant compositions, *U.S. Patent 4,801,625*.
109. Robertson, A.J., and Gallivan, J.B. (1990). 1,4-Disubstituted-2,3,5,6-tetrahydroxy-1,4-diphosphorinanes and their oxides or sulfides, *U.S. Patent 4,929,393*.
110. Robertson, A.J. (1989). Synthesis of 1,4-dialkyl-1,4-diphospha-2,3,5,6-tetrahydrocyclohexanes, Paper presented at the 11th Internation Conference on Phosphorus Chemistry, Tallinn, USSR, July 1989.
111. Mauric, C., and Wolf, R. (1976). Flame resistant regenerated cellulose, *Ger. Offen. 2,532,521*.
112. Wolf, R. (1981). Flame retardant viscose rayon containing a pyrophosphate, *Ind. Eng. Chem. Prod. Res. Dev., 20*: 413.
113. Choudhary, M.S., Fink, J.K., and Lederer, K. (1985). Investigation of the action of flame retardants in cellulose. I. Investigation of the flame retardant action of 2,2'-oxybis-(5,5-dimethyl-1,3,2-dioxaphosphorinane-2,2'-disulfide) in cellulose, *J. Appl. Polym. Sci., 30*: 4345.
114. Smith, A.L. (1963). Chlorinated alkyl phosphates, *U.S. Patent 3,100,220*.
115. Crook, J.W., and Haggis, G.A. (1969). Some aspects of the behaviour of halogen containing phosphates and phosphonates in urethane foams, *J. Cellular Plast.*: 119.
116. Polacek, R. (1962). Tris(1,3-dichloro-2-propyl) phosphate as a flame retardant, *U.S. Patent 3,041,293*.
117. Fesman, G. (1984). Polyurethane foams having low scorch discoloration, *U.S. Patent 4,477,600*.
118. Fesman, G., Jacobs, B., and Williams, B. (1988). Reduction of discoloration in flame retarded polyurethane foams, *U.S. Patent 4,794,126*.
118a. Grace, O.M., Mericle, R.E., Wujcik, S.E., and Smiecinski, T.M. (1987). Improvement in cigarette smoldering resistance

of upholstered furniture, *Proc. polyurethanes world congress*, Sept. 29-Oct. 2, 1987, FSK/SPI, Aachen, Germany.
119. Tesoro, G. (1979). Chemical technology in the "TRIS" experience, *J. Fire Retardant Chem.*, *6*: 239.
120. Smith, T.L., and Whelihan, B.N. (1978). Determination of surface tris(2,3-dibromopropyl) phosphate on FR polyester fabrics, *Text. Chem. Colorist*, *10*: 102.
121. Albright, J.A., and Wilkinson, T.C. (1987). Halogenated alkyl phosphate esters and polymer systems incorporating them, *U.S. Patent 4,696,963*.
122. Turley, R.J. (1972). Tetrakis(haloalkyl) alkylene (or arylene) diphosphates as flame-retarding additives for polyurethane foams, *U.S. Patent 3,707,586*.
123. Babiec, J.S., Pitts, J.J., Ridenour, W.L., and Turley, R.J. (1975). Flame-retarding flexible PU foam, *Plastics Technol.*: 47.
124. Puig, J.E., Natoli, F.S., and Peterson, B.W. (1989). Chlorinated phosphate esters as flame retardants in flexible urethane foam, *Proc. intl. symposium of flame retardants*, Nov. 1989, Academic Publ. (Pergamon), Beijing, China, pp. 139-147.
125. Moshkina, T.M., and Pudovik, A.N. (1962). Synthesis of glycol diphosphates and some derivatives of esters of phosphonic acids, *Zh. Obshch. Khim.*, *32*: 1761.
126. Birum, G.H. (1975). Pentaerythrite esters of halophosphoric acids, *U.S. Patent 3,192,242*.
127. Weil, E.D. (1970). Air filter, *U.S. Patent 3,513,644*.
128. Weil, E.D. (1975). Phosphoric acid ester polymers, *U.S. Patent 3,896,187*.
129. Hardy, T.A., and Jaffe, F. (1984). Polyurethane foam having a flame retardant oligomeric phosphate ester, *U.S. Patent 4,458,035*.
130. Kabachnik, M.I., and Rossiiskaya, P.A. (1947). Reaction of ethylene oxide with phosphorus trichloride, *Izv. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*: 515.
131. Kabachnik, M.I., and Rossiiskaya, P.A. (1946). Transformation of tris(2-chloroethyl) phosphite into compounds of quinquevalent phosphorus, *Izv. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*: 295.
132. Blinova, G.G., Zhukova, I.L., Lavrent'ev, A.N., and Mel'nikova, L.N. (1982). By-product in the preparation of

tris(2-chloroethyl) phosphite and its isomerization to phosphonate, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *52*: 2467.
133. Weil, E.D. (1974). Phosphorus-containing vinyl and allyl monomers in flame retardancy, *J. Fire & Flamm. Fire Retardant Chem.*, *1*: 125.
134. Anderson, J.J., Camacho, V.G., Kinney, R.E., and Seger, F.M. (1979). Phosphonate flame retardant mixture and resinous foams containing same, *U.S. Patent 4,144,387*.
135. Zuhl, E. (1902). *U.S. 700,885*.
136. Krauskopf, L.G. (1988). Plasticizers, *Encyclopedia of PVC, 2nd Ed., Vol. 2*, (Nass, L.I., and Heiberger, C.A., eds.), Marcel Dekker, Inc., New York, pp. 143-261.
137. Lapp, W.T. (1976). *The manufacture and use of selected aryl and alkyl aryl phosphate esters*, Final report prepared for the EPA, Midwest Research Institute, distributed by NTIS as PB-251678.
138. Buszard, D.L. (1978). The development and properties of phosphate plasticizers for polyvinyl chloride, *Chem. Ind. (London)*: 610.
138a. Green, J. (1988). Polyurethane flame retardant, *U.S. Patent 4,746,682*.
139. Lowenheim, F.A., and Moran, M.K. (1975). Tricresyl phosphate, *Faith, Keyes and Clark's industrial chemicals, 4th Ed.*, John Wiley & Sons, Inc., New York, pp. 849-853.
140. Prahl, W. (1957). Manufacture of aryl phosphates, *U.S. Patent 2,805,240*.
141. Segal, J., and Shorr, L.M. (1989). *British 2,215,722*.
142. Nobile, E.R., Page, S.W., and Lombardo, P. (1980). Characterization of four commercial flame retardant aryl phosphates, *Bull. Envir. Contam. Toxicol.*, *25*: 755.
143. Heaps, J.M. (1969). Lightfast triaryl phosphate plasticizers, *Plastics (London)*, *33*: 410.
144. Randell, D.R., and Pickles, W. (1975). Polyvinyl chloride plasticized with mixed phosphate esters, *U.S. Patent 3,919,158*.
145. Hamilton, J.P. (1972). Reducing flammability in PVC plastisols with triaryl phosphate plasticizer, *Modern Plastics*: 86.
146. Duke, A.J. (1978). The significance of isomerism and complexity of composition on the performance of triaryl phosphate plasticizers, *Chimia*, *32*: 457.
147. Darby, J.R., and Sears, J.K. (1975). Plasticizers,

Encyclopedia of polymer science and technology, Wiley-Interscience, New York, pp. 229-306.
148. Abolins, V., Betts, J., Holub, F., and Lee, G. (1989). Crosslinkable flame retardant compositions of polyolefin and polyphenylene ether, U.S. Patent 4,*808,647*.
149. Green, J. (1990). Brominated phosphate ester flame retardants for engineering thermoplastics, *Fire & polymers*, (Nelson, G.L., ed.), American Chemical Society Symposium Series 425, Washington, D.C., pp. 253-265.
150. Green, J., and Chung, J. (1990). Flame retarding polybutylene tertphthalate - properties, processing characteristics and rheology, *J. Fire Sci.*, *8*: 254.
151. Papa, A.J. (1970). Reactive flame retardants for polyurethane foams, *Ind. Eng. Chem. Prod. Res. Dev.*, *9*: 478.
152. Virginia-Carolina Chemical Co. (1964). Flame-retarded polyurethane foams, *British 954,792*.
153. Beck, T.M., and Walsh, E.N. (1966). Bis(hydroxyalkyl)-aminoalkylphosphonic acid diesters, *U.S. Patent 3,235,517*.
154. Wortmann, J., Dany, F., and Kandler, J. (1974). Self-extinguishing polyurethane foams, *U.S. Patent 3,850,859*.
155. Weil, E.D., Fearing, R.B., and Jaffe, F. (1982). Oligomeric phosphorus esters with flame retardant utility, *J. Fire Retard. Chem.*, *9*: 39.
156. Fesman, G., Lin, R.Y., and Raeder, R.A. (1985). Flame-retardant mixture for polyurethane material, *Eur. Pat. Publ. 138,204*.
157. Konkus, D.M., and Kraft, P. (1988). Flame retardant for polyurethane compositions, *Eur. Pat. Appl. 255,381*.
158. Braksmayer, D.P., and Hussain, S.N. (1982). Tris-(3-hydroxyalkyl)phosphine oxide flame retardant compositions, *U.S. Patent 4,341,696*.
159. Braksmayer, D.P. (1984). *S*-Butyl bis(3-hydroxypropyl)-phosphine oxide, *U.S. Patent 4,485,262*.
160. Lee, F.T., Nicholson, P., and Green, J. (1982). New reactive phosphorus flame retardant for rigid polyurethane application: Part 1, *Fire Retardant Chem.*, *9*: 194.
161. Lee, F.T., Green, J., and Gibilisco, R.D. (1984). Recent developments using phosphorus-containing diol as a reactive combustion modifier for rigid polyurethane foams, *J. Fire Sciences*, *2*: 439.
162. Horrocks, A.R. (1986). Flame retardant finishing of textiles, *Rev. Prog. Coloration*, *16*: 62.

163. Vail, S.L., Daigle, D.J., and Frank, A.W. (1982). Chemistry of hydroxymethyl phosphorus compounds. Part I. Introduction, *Text. Res. J.*, *52*: 671.
164. Frank, A.W., Daigle, D.J., and Vail, S.L. (1982). Chemistry of hydroxymethyl phosphorus compounds. Part II. Phosphonium salts, *Text. Res. J.*, *52*: 678.
165. Frank, A.W., Daigle, D.J., and Vail, S.L. (1982). Chemistry of hydroxymethyl phosphorus compounds. Part III. Phosphines, phosphine oxides and phosphonium hydroxides, *Text. Res. J.*, *52*: 738.
166. Daigle, D.J., and Frank, A.W. (1982). Chemistry of hydroxymethyl phosphorus compounds. Part IV. Ammonia, amines, and THPOH, *Text. Res. J.*, *52*: 751.
167. Reeves, W.A., Daigle, D.J., Donaldson, D.J., and Drake, G.L. (1969). Methylol phosphorus polymers used for flame retardancy, *Text. Chem. Color.*, *2*: 283.
168. Vullo, W. (1968). Studies concerning the neutralization of tetrakis(hydroxymethyl)phosphonium chloride and the reaction of tris(hydroxymethyl)phosphine with formaldehyde, *J. Org. Chem.*, *33*: 3665.
169. Cole, R. (1974). Flame-resistant impregnation of cellulose fibers, *Ger. Appl. 2,340,437*.
170. Harper, R.J., and Demorais, M.F. (1985). *Book of papers, national technical conference, AATCC*, Amer. Assoc. Textile Chemists and Colorists, Research Triangle Park, NC, pp. 164-173.
171. Weil, E.D. (1987). Recent progress in flame retardant fabrics for the armed forces, *Amer. Dyestuff Reporter*, Jan. 1987, 41; Feb. 1987, 38, 49.
172. Aenishanslin, R., Guth, C., Hofmann, P., Maeder, A., and Nachbur, H. (1969). New chemical approach to durable flame-retardant cotton fabrics, *Text. Res. J.*, *39*: 375.
173. Aenishanslin, R., and Bigler, N. (1968). Theory and practice of flameproof finishing of cotton, *Textilveredlung*, *3*: 467.
174. Zaske, O., Fintelmann, C.H., and Igdaroff, H.B. (1969). Combustion-resistant and heat-stable polyester resins, *French 1,584,020*.
175. Gallagher, R.E., Goswami, J.C., Kraft, P., and Yu, A. (1980). Internally plasticized vinyl chloride copolymer composition, *U.S. Patent 4,210,739*.
176. Goswami, J.C., and Querido, R. (1979). Internally

plasticized vinyl chloride copolymer, *U.S. Patent 4,147,853.*
177. Kraft, P., and Brunner, R. (1972). Flame retardant vinyl chloride lattices, *U.S. Patent 3,691,127.*
178. Jin, J.I., and Kraft, P. (1975). Flame retardant binder for flammable materials, *U.S. Patent 3,883,463.*
179. Kraft, P., and Yuen, P.S. (1975). Stable, aqueous, flame-resistant polymer latexes, *Ger. Pat. Appl. 2,452,309.*
180. Weil, E.D. (1974). Neutralized polycondensed vinylphosphonates, *U.S. Patent 3,822,327.*
181. Weil, E.D. (1974). Copolycondensed vinylphosphonates, *U.S. Patent 3,855,359.*
182. Weil, E.D. (1977). Textiles fire-retardant treated with copolycondensed vinylphosphonates and process, *U.S. Patent 4,017,257.*
183. Weil, E.D. (1978). Copolycondensed vinylphosphonates and their use as flame retardants, *U.S. Patent 4,067,927.*
184. Reeves, W.A., and Marquette, Y.B. (1979). Lightweight, durable-press cotton and polyester/cotton with ignition resistance, *Text. Res. J., 49*: 163.
185. Endo, S., Kashihara, K., Osako, A., Shizuki, T., and Ikegami, T. (1978). Phosphorus-containing compounds, *U.S. Patent 4,127,590.*
186. Bollert, U., Lohmar, E., and Ohorodnik, A. (1977). Process for the manufacture of flame retarding linear polyesters, *U.S. Patent 4,033,936.*
187. Kleiner, H.J., Finke, M., Bollert, U., and Herwig, W. (1976). Flame retarding linear polyesters and shaped articles thereof, *U.S. Patent 3,941,752.*
188. Allcock, H.R. (1988). Polyphosphazenes, *Encyclopedia of polymer science and engineering, Vol. 13*, (Mark, H., Bikales, N., Overberger, C., and Menges, G., eds.), John Wiley & Sons, Inc., New York pp. 31-41.
189. Singler, R.E., Hagnauer, G.L., and Sicka, R.W. (1982). Polyphosphazene elastomers: synthesis, properties, and applications, *Elastomers, rubber and elasticity*, American Chemical Society Symposium Series 193, Washington, D.C., pp. 229-242.
190. Penton, H.R. (1986). Polyphosphazenes - semi-inorganic elastomers for specialty applications, *Kautsch. Gummi Kunstst., 39*: 301.
191. Godfrey, L.E.A., and Schappel, J.W. (1970). Alkoxy-phosphazenes as flame retardants for rayon, *Ind. Eng.*

Chem. Prod. Res. Dev., *9*: 426.
191a. Muir, D.C.G. (1984). Phosphate esters, *Anthropogenic compounds, handbook of environmental chemistry, Vol. 3, Part C*, (Hutzinger, O., ed.), Springer-Verlag, Berlin, pp. 41-66.
192. Abou-Donia, M.B. (1985). Biochemical toxicology of organophosphorus compounds, *Neurotoxicology*, (Blum, K., and Manzo, L., eds.), Marcel Dekker, Inc., New York, pp. 423-444.
193. Abou-Donia, M.B. (1981). Organophosphorus ester-induced delayed neurotoxicity, *Ann. Rev. Pharmacol. Toxicol.*, *21*: 511.
194. FYREX Material Safety Data Sheet (1989). Akzo Chemicals Inc., Chicago, IL.
195. FYROL DMMP Material Safety Data Sheet (1988). Akzo Chemical Inc., Chicago, IL.
196. Triethyl phosphate Material Safety Data Sheet (1990). Eastman Chemicals, Kingsport, TN.
197. FYROL CEF Material Safety Data Sheet (1989). Akzo Chemicals Inc., Chicago, IL.
198. FYROL PCF Material Safety Data Sheet (1989). Akzo Chemicals Inc., Chicago, IL.
199. FYROL FR-2 Material Safety Data Sheet (1989). Akzo Chamicals Inc., Chicago, IL.
200. PHOSFLEX TPP Material Safety Data Sheet (1985). Akzo Chemicals Inc., Chicago, IL.
201. LINDOL Material Safety Data Sheet (1988). Akzo Chemicals Inc., Chicago, IL.
202. PHOSFLEX 41P Material Safety Data Sheet, Akzo Chemicals Inc., Chicago, IL.
203. PHOSFLEX 51B Material Safety Data Sheet, Akzo Chemicals Inc., Chicago, IL.
204. Holleman, J.W. (1984). *Health effects of haloalkyl phosphate flame retardants and potential metabolic products*, Oak Ridge National Laboratory, DOE/NBM-4006848 (DE84 006848).
205. Ulsamer, A.G., Osterberg, R.E., and McLaughlin, J. (1980). Flame retardant chemicals in textiles, *Clinical Toxicology*, *17*: 103.
206. Hodge, H.C., and Sterner, J.H. (1943). The skin absorption of tri*ortho*cresyl phosphate as shown by radioactive phosphorus, *J. Pharmacol. Exper. Therapeutics*, *79*: 225.

206a. Marzulli, F.N., Callahan, J.F., and Brown, D.J. (1965). *J. Invest. Derm., 39*: 339.
206b. Smith, M., (1930). The pharmacological action of certain phenol esters with special reference to the etiology of so-called ginger jake paralysis, *Pub. Health Rep., 45*: 2509.
206c. Susser, M., and Stein, Z. (1957). An outbreak of tri-*ortho*-cresyl phosphate poisoning in Durban, *Brit. J. Indust. Med., 14*: 111.
206d. Senenayake, N. (1981). Tri-cresyl phosphate neuropathy in Sri Lanka, *J. Neurol. Neurosurg. Psych., 44*: 775.
207. Johnson, M.K. (1975). The delayed neuropathy caused by some organophosphorus esters: mechanism and challenge, *CRC Critical Reviews in Toxicology*: 289.
208. Abou-Donia, M.B., and Lapadula, D.M. (1990). Mechanisms of organophosphorus ester-induced delayed neurotoxicity: Type I and Type II, *Ann. Rev. Pharmacol. Toxicol., 30*: 405.
209. Sprague, G.L., Castles, T.R., and Bickford, A.A. (1984). Assessment of the delayed neurotoxic potential of isopropyl triphenyl phosphate using a nontraditional testing strategy, *J. Toxicol. Environ. Health, 14*: 773.
210. Johnson, M.K. (1990). Organophosphates and delayed neuropathy - is NTE alive and well?, *Toxicol. Appl. Pharmacol., 102*: 385.
211. Katz, A.C., Turnier, J.C., Zwicker, G.M., and Sprague, G.L. (1988). Hepatic changes in rats following subchronic administration of FYROL 6, an organophosphorus ester flame retardant, *J. Toxicol. Environ. Health, 23*: 295.
212. Carlton, B.D., Basaran, A.H., Mezza, L.E., and Smith, M.K. (1987). Examination of the reproductive effects of tricresyl phosphate administered to Long-Evans rats, *Toxicology (Ireland), 46*: 321.
213. Chapin, R.E., George, J.D., and Lamb, J.C. (1988). Reproductive toxicity of tricresyl phosphate in a continuous breeding protocol in Swiss (CD-1) mice, *Fundam. Appl. Toxicol., 10*: 344.
214. Brusick, D., Matheson, D., Jagannath, D.R., Goode, S., Lebowitz, H., Reed, M., Roy, G., and Benson, S. (1980). A comparison of the genotoxic properties of tris(2,3-dibromopropyl) phosphate and tris(1,3-dichloropropyl) phosphate in a battery of short-term bioassays, *J. Envir. Pathol. Toxicol., 3*: 207.

215. Soderland, E.J., Dybing, E., Holme, J.A., Hongslo, J.K., Rivedal, E., Sanner, T., and Nelson, S.D. (1985). Comparative genotoxicity and nephrotoxicity studies of the two halogenated flame retardants tris(1,3-dichloro-2-propyl) phosphate and tris(2,3-dibromopropyl) phosphate, *Acta pharmacol. et toxicol.*, *56*: 20.
216. Sala, M., Moens, G., and Chouroulinkov, I. (1982). *In vivo* and *in vitro* biological effects of the flame retardants tris(2,3-dibromopropyl) phosphate and tris(2-chloroethyl) phosphate, *Eur. J. Cancer Clin. Oncol.*, *18*: 1337.
217. Lynn, R.K., Wong, K., Garvie-Gould, C., and Kennish, J.M. (1981). Disposition of the flame retardant, tris(1,3-dichloro-2-propyl) phosphate, in the rat, *Drug Metab. Disposition*, *9*: 434.
218. Nelson, S.D., Omichinski, J.G., Iyer, L., Gordon, W.P., Soderlund, E.J., and Dybing, E. (1984). Activation mechanism of tris(2,3-dibromopropyl) phosphate to the potent mutagen, 2-bromoacrolein, *Biochem. Biophys. Res. Commun.*, *121*: 213.
219. Weil, E.D., and Aaronson, A.M. (1978). Phosphorus flame retardants - meeting new requirements, *Proc. 1st European conference on flammability and flame retardants*, Brussels, July 1977, Technomic Publishing CO., Westport, CT.
220. Weil, E.D., and Aaronson, A.M. (1976). Phosphorus flame retardants - some effects on smoke and combustion products, lecture presented at Univ. of Detroit Polymer Conf. on Recent Advances in Combustion and Smoke Retardance of Polymers.
221. Herpol, C. (1976). Biological evaluation of the toxicity of products of pyrolysis and combustion, *Fire and Materials*, *1*: 29.
222. Hasegawa, H.K. (1990). *Characterization and toxicity of smoke*, Publication STP 1082, Amer. Assoc. for Testing and Materials, Philadelphia, PA.
223. Paciorek, K.J., Kratzer, R.H., Kaufman, J., Nakahara, J.H., Christos, T., and Hartstein, A.M. (1978). Thermal oxidative degradation studies of phosphate esters, *Amer. Indust. Hygiene Assn. J.*, *39*: 633.
224. Uehara, Y., and Ogawa, Y. (1975). Advances in fire retardants in Japan, *Advances in fire retardant textiles, prog. fire retardancy ser., Vol. 5*, (Bhatnagar, V.M., ed.), Technomic Publishing Co., Westport, CT., pp. 507-599.

225. Einhorn, I.N. (1974). Effects of fire retardants on the nature of smoke, *Flammability characteristics of polymeric materials*, Polymer Conference Series, Univ. of Utah, Salt Lake City.
226. Mathis, T.C., and Hinchen, J.D. (1973). Effect of phosphate ester/filler interactions on the flammability and smoke generation of PVC, *31st Ann. Tech. Conf. SPE, Technical Papers*, *19*: 343.
227. Mathis, T.C., and Morgan, A.W., (1975). Smoke-retardant halogen-containing polymer systems, *U.S. Patent 3,896,420*.
228. Ahrens, V.D., Maylin, G.A., Henion, J.D., St. John, L.E., and Lisk, D.J. (1979). Fabric release, fish toxicity and water stability of the flame retardant FYROL FR-2, *Bull. Env. Contam. Toxicol.*, *21*: 409.
229. Nevins, M.J., and Johnson, W.W. (1978). Acute toxicity of phosphate ester mixtures to invertebrates and fish, *Bull. Env. Contam. Toxicol.*, *7*: 250.
230. ANTIBLAZE 19 (1988). *Handbook of flame retardant chemicals and fire testing*, (Kidder, R., ed.), Technomic Publishing Co., Lancaster, PA, p.79.
231. Cleveland, L., Mayer, F.L., Buckler, D.R., and Palawski, D.U. (1986). Toxicity of five alkyl-aryl phosphate ester chemicals to four species of freshwater fish, *Envir. Tox. Chem.*, *5*: 273.
232. Bengtsson, B.-E., Tarkpea, M., Sletten, T., Carlberg, G.E., Kringstad, A., and Renberg, L. (1986). Bioaccumulation and effects of some technical triaryl phosphate products in fish and *Nicotra Spinipes*, *Envir. Tox. Chem.*, *5*: 853.
233. Mabey, W., and Mill, T. (1978). Critical review of hydrolysis of organic compounds in water under environmental conditions, *J. Phys. Chem. Ref. Data*, *7*: 383.
234. Saeger, V.W., Hicks, O., Kaley, R.G., Michael, P.R., Mieure, J.R., and Tucker, E.S. (1979). Environmental fate of selected phosphate esters, *Envir. Sci. Tech.*, *13*: 840.
235. Boethling, R.S., and Cooper, J.C. (1985). Environmental fate and effects of triaryl and trialkyl/aryl phosphate esters, *Residue Reviews*, *94*: 49.
236. Ghisalba, O., Kuenzi, M., Ramos Tombo, G.M., and Schar, H.-P. (1987). Microbial degradation and utilization of selected organophosphorus compounds - strategies and applications, *Chimia*, *41*: 206.

237. Menn, J.J., and McBain, J.B. (1974). New aspects of organophosphorus pesticides. IV. Newer aspects of the metabolism of phosphonates insecticides, *Residue Review*, *53*: 35.
238. Zeleznick, L.D., Myers, T.C., and Titchener, E.B. (1963). Growth of *Escherichia coli* on methyl- and ethylphosphonic acids, *Biochim. Biophys. Acta*, *78*: 546.
239. Frost & Sullivan market report (1990). *Chem. Week*, Nov. 28: 44.

CHAPTER 15

ALIPHATIC CARBON-PHOSPHORUS COMPOUNDS AS HERBICIDES

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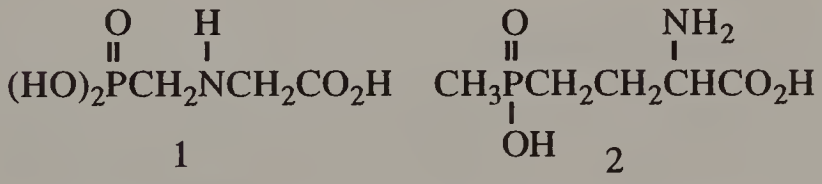
I. Overview

Perhaps no two inventions have had a greater impact on the chemistry of aliphatic phosphonic and phosphinic acid derivatives in the last two decades than the discovery of the herbicidal properties of glyphosate (1) and phosphinothricin (2). As the active ingredient in Monsanto Company's ROUNDUP® herbicide, glyphosate [*N*-(phosphonomethyl)glycine; PMG] has achieved tremendous success as a broad spectrum, non-selective herbicide that controls many of the world's worst weeds while exhibiting very low mammalian toxicity. PMG has achieved worldwide acceptance as an environmentally friendly herbicide. PMG kills plants by specifically inhibiting one enzyme critical for the biosynthesis of plant aromatic amino acids. As such, glyphosate was one of the first commercially successful herbicides to have a primary identified enzyme site of action in plants.



1 2

Similarly, phosphinothricin [L-2-amino-4-(hydroxymethyl-phosphinyl)-butanoic acid; PPT] has its own claim to fame as the first natural product to be introduced as a commercial herbicide. Cultures of various *Streptomyces* species produce PPT as the tripeptide derivative, bialaphos. Meiji Seika Kaisha, Ltd. has introduced bialaphos under the product name herbiace, as a broad spectrum foliarly applied herbicide. Hoechst AG has commercialized PPT under the product name glufosinate as the active ingredient in its BASTA® herbicide. PPT kills plants by inhibiting a specific enzyme critical for ammonia assimilation in plants. As a natural product, PPT has stimulated a multitude of

investigations into the biosynthesis of organophosphorus compounds, particularly those containing a methylphosphinate moiety. Over ten thousand literature references currently exist describing the chemistry, biochemistry, mode of action, application and utility of glyphosate and its derivatives. Virtually every major agrichemical company and nearly every country in the world has published at least one patent related to PMG or its derivatives. Hundreds of references describe similar aspects of phosphinothricin research. Obviously, a comprehensive review of all aspects of these herbicides could easily encompass several volumes. The purpose of this review is to highlight the unique phosphorus chemistry reported for each of these products, with emphasis on synthetic methods involved in carbon-phosphorus bond formation.

At the time of their discovery, few chemical methods were known for the laboratory syntheses of such molecules. Fewer still were appropriate for their industrial scale production. Rapid strides continue to be made since these areas were last reviewed.[1,2]

The literature is covered through 1990. Where possible, representative procedures are drawn from the appropriate patent literature to demonstrate the practical application and specific utility of these methods.

II. Glyphosate Chemistry

A. Introduction

1. General Background

From its initial discovery in 1970 through today, glyphosate represents a major breakthrough in herbicide research and development.[3] When formulated as the monoisopropylamine salt in ROUNDUP® herbicide, PMG controls undesired vegetation by direct post-emergence application to plant leaf tissue while retaining low mammalian toxicity. ROUNDUP® has achieved worldwide success because of its ability to control undesired plant species under a variety of conditions in forestry, vineyard, orchard and residential applications. ROUNDUP® is particularly effective against hard-to-kill perennial weeds, whose growing regions lie hidden below the soil, and are therefore often difficult to control with post-emergence applications.

Glyphosate exhibits low toxicity to birds, fish, insects and most bacteria. In soil, PMG is readily broken down by microbes to aminomethylphosphonic acid. Subsequent degradation then

proceeds to give ammonia, inorganic phosphate, and carbon dioxide.[4] These desirable environmental characteristics are the reason PMG has had a significant impact on worldwide agronomic practices.

The commercial success of ROUNDUP® has stimulated an enormous worldwide research effort over the last two decades to identify novel methods for its synthesis and a search for proprietary derivatives that might be suitable as competitive products. Several hundred patents have been published in this area since 1970, many with novel process chemistry claims. To date no other derivative or analogue product has been identified or commercialized with a significant advantage over the PMG-based products currently in the marketplace.

2. Discovery

The herbicidal properties of glyphosate were discovered at Monsanto Company in 1970 by Dr. John Franz.[5,6] In the 1960's perennial weeds represented a significant and uncontrolled problem which often reduced crop productivity for many farmers. Dr. Phil Hamm, recognizing a potential new commercial opportunity, developed greenhouse screens to uncover new lead structures with herbicidal activity against major perennial weeds in response to this problem.

During this time, a variety of phosphonylated amino acid derivatives were available and tested from another program supporting DEQUEST® (3) detergent builders and other metal sequestering agents. This effort uncovered two leads [(4) and (5)] in the early 1960's with interesting greenhouse activity against quackgrass and johnson grass, but their performance in the field against perennial weeds was not sufficient to warrant commercialization as herbicides.[7]

$5\,Na^+\ [^{2-}O_3PCH_2]_3\overset{+}{N}H$

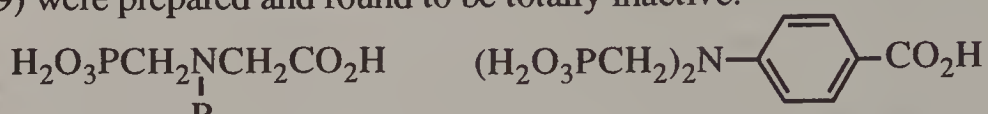
DEQUEST® 2006 3

$H_2O_3PCH_2N(CO_2H)_2$ 4

$(H_2O_3PCH_2)_2NCH_2CO_2H$ 5

A number of structurally related analogues such as the *N*-substituted derivatives (6) and (7) were synthesized and evaluated

to follow-up these leads, but no significant activity improvement was attained through 1969. Many other closely related bis-phosphonomethylamines such as (8) or amino acid homologs such as (9) were prepared and found to be totally inactive.



6 R = CH_3
7 R = C_6H_5

8

$(H_2O_3PCH_2)_2NCH_2CH_2CH_2CO_2H$

9

Dr. Franz began his work on the project in late 1969. While several approaches were attempted simultaneously, one operating hypothesis that he developed ascribed the essentially equivalent herbicide activity observed for (4) and (5) to a common, possibly more active, metabolic intermediate, such as glyphosate. He evaluated several possible synthetic procedures and eventually succeeded in preparing PMG from chloromethylphosphonic acid.[8] By the summer of 1970 this new material had been evaluated. Greenhouse and field testing clearly demonstrated its potential commercial utility. Commercial launch came in 1974.

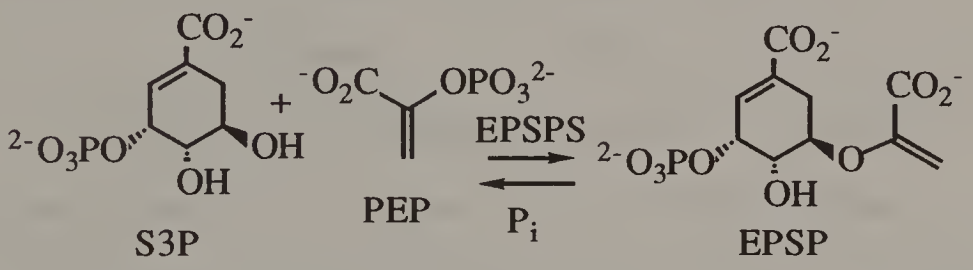
3. Mode of Action

It is widely accepted that PMG kills plants by inhibiting the enzyme EPSPS (5-enolpyruvoylshikimate-3-phosphate synthase).[9-14] EPSPS is a critical enzyme in the biosynthesis of the essential aromatic amino acids and other aromatic compounds. This pathway is present in all plants and micro-organisms, but is completely absent in mammals, birds, fish and insects. The highly specific interaction of PMG with this enzyme accounts for its effective control of plant species while retaining very favorable environmental acceptability. This mode of action is only known for glyphosate-based herbicides. No other commercial herbicides exhibit this mode of action.

Experimental evidence supporting inhibition of EPSPS as the primary mode of action for glyphosate includes the following: (a) The herbicidal effects of glyphosate-treated plant cells can be reversed by aromatic amino acids;[15] (b) Plants treated with glyphosate accumulate shikimate[10] and shikimate-3-phosphate

(S3P);[16] (c) All plant and bacterial EPSPS's isolated and characterized to date are inhibited by glyphosate;[11,17] (d) Plant cells exposed to non-lethal doses of glyphosate can increase their tolerance to this herbicide by overproducing EPSPS;[18] (e) Plants which are genetically engineered with modified EPSPS exhibiting reduced PMG affinity are tolerant to glyphosate applications.[19,20]

EPSPS catalyzes a very unusual transfer reaction of the carboxy vinyl portion of phosphoenolpyruvate (PEP) regiospecifically to the 5-OH of S3P, producing EPSP and inorganic phosphate (P_i) (Scheme 1).[21-23] Each of the EPSPS substrates is a multiply charged anion. For optimum binding, each ionic residue must be fully exposed and available in the substrates. Glyphosate acts as a competitive inhibitor to PEP and an uncompetitive inhibitor to S3P. Neither PEP nor PMG has any significant interaction with EPSPS in the absence of S3P.[24-26] In the presence of S3P glyphosate forms a very stable dead-end ternary complex with EPSPS.[27] Anion recognition at the active site follows a compulsory ordered binding process[28,29] and must therefore be quite specific.

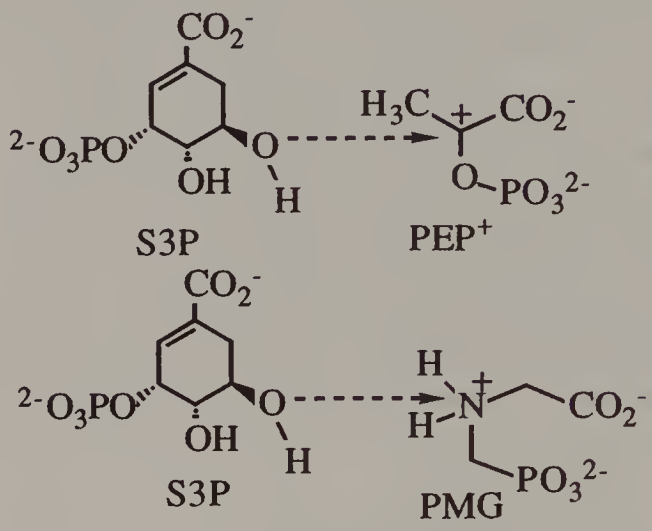


Scheme 1 - EPSPS enzyme reaction

As an enzyme inhibitor glyphosate displays a unique specificity for EPSPS. PMG does not inhibit any other PEP-dependent enzymes. Even minor structural changes in the glyphosate skeleton lead to a significant loss in inhibitor potency and reduced herbicidal activity. These results, coupled with the enzyme mechanism studies supporting protonation of the PEP double bond during catalysis,[14,23] led Amrhein and Steinrucken to propose that glyphosate functions as a transition state analogue which effectively occupies the transient PEP oxonium ion (PEP^+) site (Scheme 2).[24] Since glyphosate does not inhibit any other PEP-dependent enzymes, it can not simply function as a ground state mimic for PEP.

To function as a transition state inhibitor, the glyphosate binding site should overlap fully with that of PEP^+. Although quite

dissimilar in chemical composition, a careful modeling comparison of PMG *vs.* PEP demonstrates that the two molecules are quite similar in three-dimensional structure.[30] The conformational flexibility of PMG will allow it to adopt a low energy orientation that overlaps quite well with PEP when the phosphonic acid of PMG is fitted to the phosphate moiety in PEP and the two carboxyl residues are superimposed.



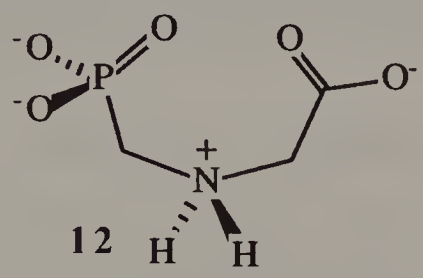
Scheme 2 - Glyphosate as a transition state inhibitor

The ionic and steric requirements of the glyphosate binding site have been characterized and are quite restrictive.[31] PMG and its enzyme-active derivatives form a very narrow chemical class. Only two closely related analogues, *N*-hydroxy-PMG (10)[32] and *N*-amino-PMG (11)[33,34] inhibit EPSPS to about the same extent as glyphosate (Scheme 3).[31]

The structural specificity for PMG analogue binding is apparent from comparison of these *N*-hetero substituted derivatives with their *N*-alkyl counterparts. Similarly, any simple heteroatom substitution for the backbone N-H produces analogues with no significant EPSPS interaction and no observed herbicidal activity. Thus, only certain functional groups can replace the proton in the glyphosate skeleton such that some of the biological activity is retained. No structural modifications of the glyphosate backbone have been identified which exhibit either enhanced *in vitro* or *in vivo* activity.

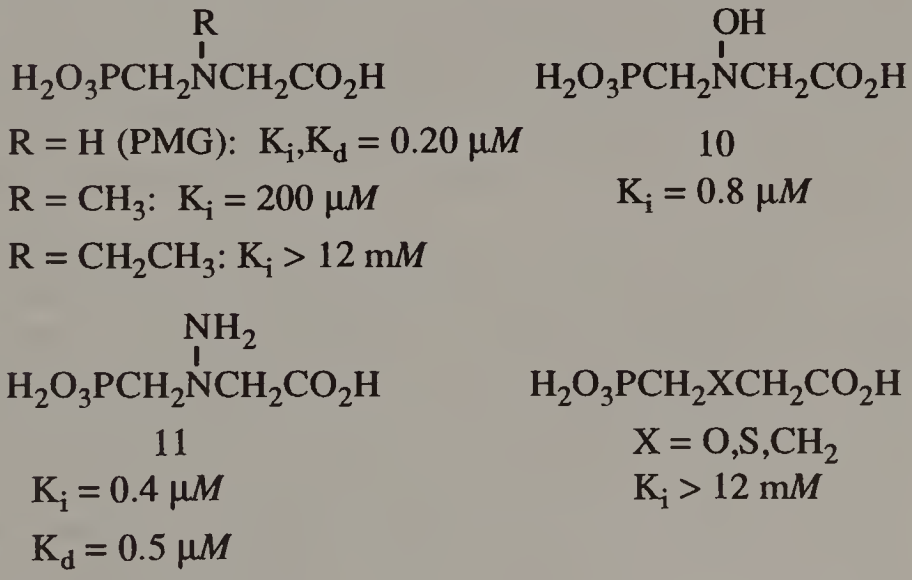
Just as the substrates require all of their ionic functionality for optimum binding to EPSPS, glyphosate also is recognized

optimally in its dianionic form (12).[27] All mono, di or triester derivatives of PMG have dramatically lowered affinities for EPSPS.[31] Even herbicidally active ester or amide derivatives of PMG do not interact strongly with the enzyme. These results coupled with the backbone modification studies described above have led to the following working hypothesis:



12

The anion of N-*phosphonomethylglycine is the herbicidally active component of all PMG-based herbicides* via *EPSPS inhibition. Only those derivatives which readily break down to this anion either on or within the plant will be herbicidally active.*



Scheme 3 - *N*-Substituted glyphosates as EPSPS inhibitors

This hypothesis has guided all PMG-based research over the last decade. Thus, backbone-modified PMG derivatives are relatively rare in the patent literature. The vast majority of patented process work relates directly to the production of glyphosate. This hypothesis has also stimulated research in delivering PMG through

various hydrolytically unstable ester and amide derivatives. Such derivatives form the major portion of the patented glyphosate analogue area.

Unlike many other amino acid derivatives, glyphosate is stable in strong acid or base, even at elevated temperatures. PMG will also tolerate strong reductants and oxidants. This stability accounts for the diversity of synthetic methods which have been explored and developed to prepare PMG and its derivatives over the last twenty years.

B. Syntheses *via* Mannich Procedures

1. With Glycine under Acidic Conditions

The most widely reported synthetic procedure to construct the P-C-N linkage in PMG and its derivatives utilizes an adaptation of the classical Mannich reaction.[35] The first general and direct method for the phosphonomethylation of amines or amino acids using phosphorous acid and formaldehyde was developed by Irani and Moedritzer.[36] The reaction works equally well for ammonia or primary and secondary amines. The "acidic" phosphorus source may be phosphorous or hypophosphorous acid or one of their ester derivatives. Either aliphatic or aromatic aldehydes and ketones can also be used as the carbonyl component.[37] This procedure has been widely applied to make many α-aminomethylphosphonic acids.[38,39]

Typically, improved yields and shorter reaction times are observed at low pH using concentrated hydrochloric acid and elevated temperatures. Normally, aqueous solutions of the amine hydrochloride, phosphorous acid and concentrated hydrochloric acid are heated to reflux. Then, excess aqueous formaldehyde or paraformaldehyde is added over a one to two hour period. The reaction proceeds equally well with primary and secondary amines. However, with primary amines such as glycine, the yield of mono-phosphonomethylated product (PMG) is quite low, even at reduced temperature, and 1:1:1 stoichiometry. PMG reacts faster than glycine so the bis-phosphonomethyl adduct (13) always predominates. With excess phosphorous acid and formaldehyde, good isolated yields of this 2:1 adduct are obtained. While relatively weak as a herbicide, (13) has been commercialized as a plant growth regulator in the sugar cane enhancer, POLARIS®.

N-Methylglyphosate (14) often is formed as a side product

through a reductive alkylation of PMG with formaldehyde, presumably through an Eschweiler-Clarke process.[3]

The propensity for glycine to form the undesired product (13) under acidic Mannich conditions has stimulated a diverse search for suitable alternative routes to PMG that avoids this 2:1 adduct. Modifications of the reaction conditions or a change in substrate to an *N*-substituted glycine lengthen the synthetic sequence, but often result in higher overall isolated yields of PMG.

$(H_2O_3PCH_2)_2NCH_2CO_2H$
13

$H_2O_3PCH_2\underset{\displaystyle CH_3}{\underset{|}{N}}CH_2CO_2H$
14

2. With Glycine under Basic Conditions

The Mannich reaction with glycine can be controlled to give the desired PMG skeleton as the predominant product when the condensation reaction is conducted at a more basic pH.[40] Under these conditions one must substitute an appropriate dialkyl phosphite for the phosphorous acid described above. Consequently, this modification produces various dialkyl phosphonate esters of PMG (15) and necessitates an additional deprotection step in the sequence. Nevertheless, moderate isolated yields of PMG are reported using this two step, one-pot procedure. While these phosphites add significantly to the cost of any commercial process, they are quite convenient for laboratory scale operations.

Alternatively, the reaction can be run at a lower temperature with better pH control under non-aqueous conditions using triethylamine in methanol.[41,42] The milder conditions produce PMG in high purity (97-99%) and improved yield (65-78%). Glycine combines with paraformaldehyde under these conditions to form the bis-hydroxymethylglycine intermediate (16a),[43] which is not isolated, but immediately converted with dimethyl phosphite at reflux to give the reported *N*-hydroxymethyl-PMG-phospho-dimethyl ester (17a). Acidic hydrolysis produces first the PMG phospho-dimethyl ester then PMG. This procedure is the basis of the commercial process utilized by Alkaloida Chemical Works in Hungary for the manufacture of glyphosate.

Suitable precautions should be taken in utilizing this procedure since substantial quantities of bis-chloromethyl ether and methyl chloride are formed under the reaction conditions. It is

worth noting that intermediates such as (17a) have been postulated in a number of publications and patents in this area. However, no experimental evidence has been reported which supports the presence or formation of such species in any significant amount.

Recently, an interesting cyclic intermediate has been characterized for this process.[44] By maintaining the reaction temperature below 60° and carefully monitoring for disappearance of phosphite by ^{31}P NMR, the unusual oxazaphospholidine (18) forms cleanly by ^{31}P NMR (17.7 ppm) and can be isolated in nearly quantitative yield as the triethylamine salt. Acidic hydrolysis of (18) proceeds cleanly to PMG.

The formation of (18) under these conditions from glycine stands in sharp contrast to the *N*-phosphonomethyl oxazolidinone (19) which is distinguishable on the basis of ^{31}P NMR (26.4 ppm) and has been isolated in moderate yield under similar conditions using alkyl glycinate esters.[43]

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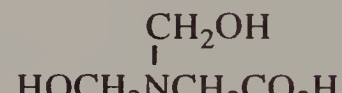
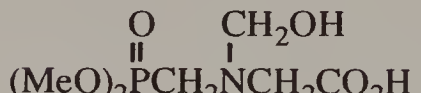
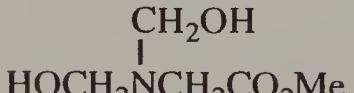


16a



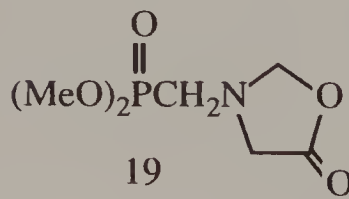
17a

18



16b

17b



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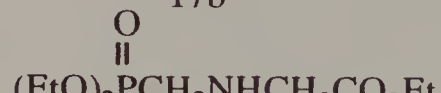

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It is tempting to speculate that the methyl ester in (16b) favors the formation of (19) by activating the carboxyl site for lactone formation. On the other hand, the carboxyl groups in (16a) should be ionized thus retarding reaction at the carboxylate and favoring cyclization at the phosphonate center. No evidence has yet

been reported to substantiate (17a) or (17b) as present in significant amounts in these reactions, though they may be generated transiently.

The corresponding neutral Mannich condensation of glycinate esters with aqueous formalin and dialkyl phosphites produces PMG triester derivatives (20) in reasonable yields after distillation.[45]

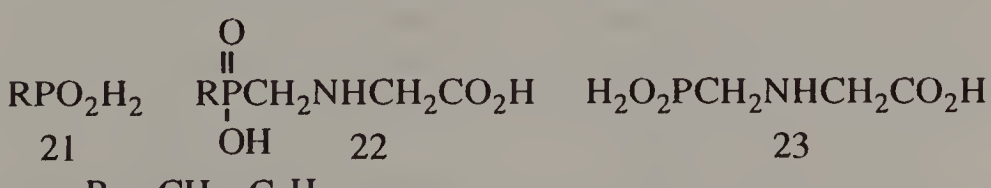
3. *N*-Substituted Glycines

A variety of *N*-substituted glycines have been utilized to prepare PMG *via* acidic Mannich condensations. The most widely reported approach incorporates the *N*-phosphonomethyl derivative of iminodiacetic acid (IDA) (4).[37] This two-carbon carboxymethyl fragment can be conveniently removed as formate and formaldehyde either with hot fuming acid,[46] or, in higher yields, under a variety of oxidative conditions using oxygen with activated carbon catlaysts,[47-52] hydrogen peroxide in sulfuric acid,[47,53] sodium chlorite[47] or by electrolysis.[54]

Consequently, the carboxymethyl moiety in IDA represents a relatively inexpensive protecting group for this conversion. This procedure is the basis of the commercial process utilized by Monsanto Company for the manufacture of glyphosate. Modifications are also reported where phosphorus trichloride is used directly to generate the required phosphorous acid *in situ*.[55,56]

This IDA-based approach is easily adaptable with the appropriate phosphonites (21) to the synthesis of PMG-alkyl and aryl phosphinic acid derivatives (22).[57]

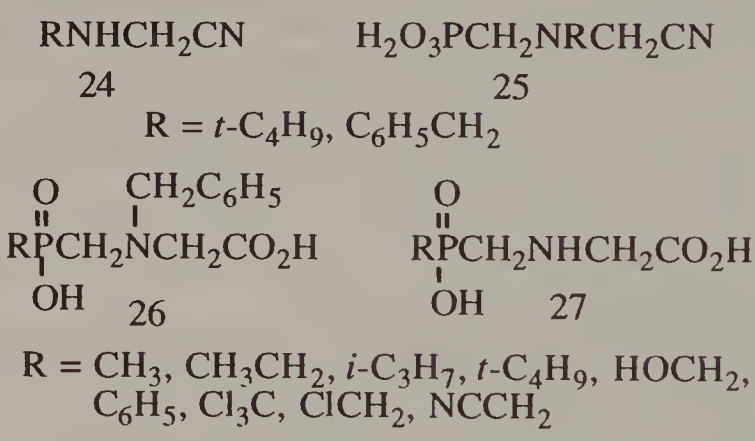
Even the parent member of this series, PMG-phosphinic acid (23), is available in good yield using this sequence, starting with hypophosphorous acid in the Mannich condensation. Oxidative cleavage occurs selectively at the carboxymethyl group with no apparent oxidation at phosphorus.[58] While inactive as a herbicide, (23) is particularly useful for the synthesis of a variety of unusual PMG-thionophosphonate derivatives (Section F).



Essentially any *N*-substituted glycine which is stable to the reaction conditions can also be used. As expected, sarcosine gives *N*-methyl-PMG[8,56] and *N*-hydroxyglycine produces *N*-hydroxy-PMG (10)[32] under acidic conditions. Glycinate esters, containing removable *N*-alkyl protecting groups such as *N*-*t*-butyl-,[59] *N*-allyl-,[54] or *N*-benzyl-[60] have all been utilized in this procedure. Even the corresponding glycinonitriles (24) can be used and successfully hydrolyzed to PMG *via* the *N*-phosphonomethylglycinonitriles (25).[61]

The yield of PMG from *N*-benzylglycine can be improved dramatically over these HCl or HBr cleavage reactions through the nearly quantitative removal of the *N*-benzyl protecting group by hydrogenolysis.[62]

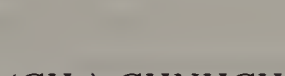
This mild and selective deprotection of the *N*-benzyl substituent has led to the synthesis in moderate to very good yield of a number of unusual PMG-phosphinic acid derivatives [(26) and (27)] using *N*-benzylglycine in combination with various alkyl and aryl phosphonites (21).[57,63,64]



Simple aliphatic phosphonites containing branched chains or chloro substituents are readily accommodated. Cyanomethylphosphonite gives the corresponding carboxymethyl analog under the acidic Mannich conditions. Removal of the benzyl group proceeds in moderate to good yields. Over-reduction was only observed in the case of the trichloromethyl substituent producing some of the dichloro analog. The PMG-phosphinates prepared by this method are summarized in Table 1.

The thermal stability of glyphosate also allows the use of protecting groups that can only be removed under harsher conditions. Consequently, PMG can be synthesized in high yield

from either *N-iso*-propylglycine (28) *via* the *N-iso*-propyl-PMG intermediate (29)[65,66] or in moderate to good yield from *N*-cyanomethylglycines.[67]



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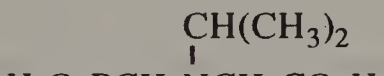

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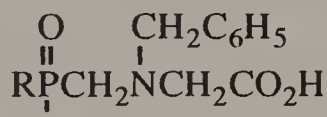
Certain *N*-hydroxyethylamines (30) can also be utilized.[68-71] Oxidation at high temperature produces the required carboxymethyl component which can be manipulated further to give PMG.

30

Table 1 - Glyphosate phosphinic acid derivatives prepared from *N*-benzylglycine[57,62,63]



26

27

R	Yield(%)	R	Yield(%)
CH_3	100	CH_3	57
$HOCH_2$	88	$HOCH_2$	44
Cl_3C	71	Cl_3C	46
$ClCH_2$	61	$ClCH_2$	72
CH_3CH_2	83	CH_3CH_2	75
HO_2CCH_2	39	HO_2CCH_2	71
n-C_3H_7	83	*n*-C_3H_7	71
t-C_4H_9	52	*t*-C_4H_9	64
C_6H_5	63	C_6H_5	83

31

32

33

Labile glycyl-*N*-carbamates[72,73] or glycyl-*N*-sulfonates (31),[74,75] may also serve as PMG starting materials, when the Mannich condensation is run under more neutral conditions *via* intermediate (32).

An interesting sulfur dioxide variation of the Mannich condensation has recently been repoted to provide the first PMG analog (33) containing a sulfonic acid replacement for the phosphonic acid.[76] While no herbicidal activity is reported for (33), these glycinate analogs can be used as intermediates to PMG derivatives by thermal displacement of the SO_3H by alkylphosphites. Similarly, no EPSPS inhibition[31] is observed with (33) and its derivatives.

Another novel approach utilizes ethyl 2-azabicyclo[2.2.1]-hept-5-ene acetate (34) to deliver the glycine aldimine component for the Mannich condensation by a thermal retro Diels-Alder reaction. Further reaction with phosphorous acid or a dialkyl phosphite produces the PMG skeleton in good yield.[77]

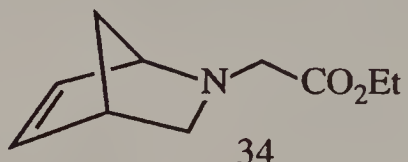


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Table 2 - *N*-Substituted glyphosate derivatives prepared by Mannich methods from *N*-substituted glycines and glycinates

$(RO)_2P(O)CH_2NR'CH_2CO_2R''$

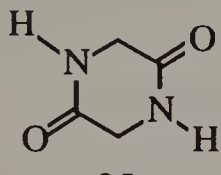
R	R'	R''	Yield(%)	Reference
H	OH	H	30	32
H	*i*-C_3H_7	H	64	65
H	$NCCH_2CH_2$	H	81	67
H	$HO_2CCH_2CH_2$	H	73	67
H	$C_6H_5CH_2$	H	90	62
CH_3CH_2	$NCCH_2CH_2$	H	77	67
CH_3CH_2	$C_6H_5CH_2$	H	74	78
C_6H_5	$C_6H_5CH_2$	H	59	78
CH_3CH_2	*t*-C_4H_9	CH_3CH_2	-	59
C_6H_5	CH_3O_2C	CH_3	70	72

4. With 2,5-Piperazinediones

Alternatively, one can protect glycine as an *N*-acyl derivative using diketopiperazines (35) in these procedures. These heterocycles can be prepared readily by cyclo-dehydration of glycine or its esters and are quite stable.[79] They undergo the typical acidic Mannich condensation. Basic hydrolysis of the cyclic intermediate (36) produces PMG in moderate yield.[80]

Recently, a convenient synthesis of *N*-substituted-2,5-piperazinediones (37) has been reported from *N,N'*-dialkylglycinamides.[81] These derivatives presumably undergo ring opening during the acidic Mannich reaction providing a direct entry into a number of *N*-substituted PMG derivatives (38).[82]

Hydantoin (39) has also been used in a similar process as a protected form of glycine.[83]



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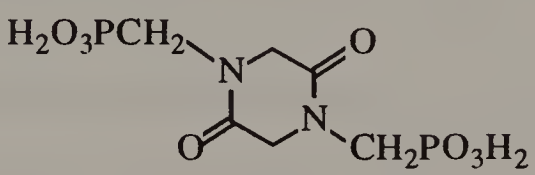

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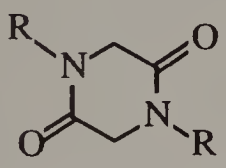
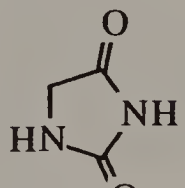


37

$H_2O_3PCH_2NRCH_2CO_2H$

38

R = H, Me, *i*-Pr, Bz



39

These Mannich-based methods therefore constitute an important approach to PMG and many of its derivatives.

5. Procedures

a. Preparation of *N*-Phosphonomethylglycine from Glycine[41]

Glycine (37.5 g, 0.48 mol) is added to a hot solution of anhydrous methanol (500 mL) with triethylamine (47.0 g) and paraformaldehyde (30.0 g). The *N,N*-bishydroxymethylglycine obtained in the reaction mixture is treated without isolation with diethyl phosphite (55.0 g, 0.4 mol) and the mixture is boiled with stirring for 1 hr. To the resulting solution is added conc. hydrochloric acid (200 mL) and the reaction mixture is heated for

1.5 hr at 115° to hydrolyze it to *N*-phosphonomethylglycine. On work-up 66-68 g (78%) of *N*-phosphonomethylglycine is obtained in crystalline form with purity >96% by HPLC.

b. Preparation of the Triethylamine salt of 1,4,2-Oxazaphospholidine-4-acetic acid-2-methoxy-2-oxide[44]

Triethylamine (5.05 g, 0.05 mol) and paraformaldehyde (3.0 g, 0.1 mol) are heated in solution at 55° in methanol (50 mL). Glycine (3.75 g, 0.05 mol) is aded in one portion and the mixture is heated at reflux for 1 hr. The solution is cooled to room temperature and dimethyl phosphite (5.5 g, 0.05 mol) is added in one portion. The solution is heated at reflux for 40 min, at which time the ^{31}P NMR spectra shows the absence of dimethyl phosphite. The methanol is removed on a rotary evaporator at 35° and reduced pressure (25 Torr) to yield the desired compound (15.4 g, 100%).

c. Preparation of *N*-Phosphonomethylglycine from *N*-Benzylglycine[62]

In a reactor equipped with a stirrer and a reflux condenser *N*-benzylglycine hydrochloride (101.0 g, 0.5 mol) and phosphorous acid (41.0 g) are dissolved in conc. hydrochloric acid (500 mL) and water (100 mL). The mixture is heated to reflux and 35% aqueous formalin (160 mL) is added dropwise while stirring for 30 min, and the stirring is continued for 4 hr while heating at reflux. The cloudy solution is filtered and evaporated until dry on a rotary evaporator. The residue is crystallized from water (1 L), filtered, and the filtrate evaporated under vacuum with crystallization of the residue from water to yield *N*-benzyl-*N*-phosphonomethylglycine of mp 203-206° (combined yield 116.8 g, 90.1%). A solution of this material (51.8 g, 0.2 mol) in water (500 mL) is treated with hydrogen at room temperature in an agitated hydrogenation vessel after adding 5% palladium on carbon (5.0 g). Hydrogen is absorbed (4.89 L) over a period of 45 hr. The catalyst is removed by filtration and decocted with water (2 x 500 mL). The combined filtrates are evaporated under vacuum to give the desired material (33.5 g, 99%) as a white powder of mp 309-312°.

d. Preparation of *N*-Phosphonomethylglycine from *N*-Isopropylglycine[65]

To a 3-necked flask (5 L) fitted with a mechanical stirrer, thermometer, addition funnel, and condenser is added *N*-isopro-

pylglycine hydrochloride (363 g, 2.37 mol), phosphorous acid (205 g, 2.50 mol), and 20% hydrochloric acid (1.7 L). The mixture is heated at 108° giving a solution. From the addition funnel 37% aqueous formaldehyde solution (231 g, 2.84 mol) is added to the hot reaction mixture over 2 hr. The resulting yellow solution is refluxed for 8.5 hr. All volatiles are removed by vacuum distillation to leave a yellow oil. The oil is dissolved in water (300 mL) and diluted with ethanol (500 mL) to cause precipitation of the product. The crystals are collected by filtration, washed with ethanol, and air-dried to give *N*-isopropyl-*N*-phosphonomethylglycine (322 g, 64%) as a white solid of mp 205-208°.

To a pressure reactor (100 mL) constructed of Monel is added *N*-isopropyl-*N*-phosphonomethylglycine (21.1 g, 0.10 mol), 50% aqueous sodium hydroxide solution (26.2 g, 0.33 mol), and water (8 mL). The reactor is closed and flushed with nitrogen for 20 min. The reactor is then sealed and heated to 300° for 3 hr. The excess pressure generated by the liberation of propene during the reaction is released, but the overall reactor pressure is controlled so as to retain water in the reaction mixture. After cooling and releasing the residual pressure the viscous solution is removed from the reactor and diluted with water (24 mL). The solution is neutralized with conc. hydrochloric acid (27.2 mL). The *N*-phosphonomethylglycine precipitates from solution as white crystals and is collected by filtration and air-dried. The mother liquors are purified by ion-exchange chromatography to provide additional material (16.43 g, 97%) of 95.2% purity.

e. Preparation of *N*-Phosphinomethylglycine from Iminodiacetic Acid[58]

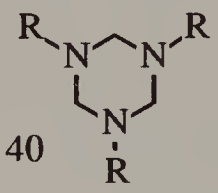
A solution of iminodiacetic acid (53.2 g, 0.40 mol), aqueous 37% formalin (32.4 g, 0.40 mol), and aqueous 50% hypophosphorous acid (159 g, 1.2 mol) in water (150 mL) is heated at reflux for 2 hr and then cooled to room temperature. A voluminous white precipitate forms which is collected by filtration, washed with water, and air-dried to give *N*-phosphinomethyliminodiacetic acid (55 g, 65%) as a white solid of mp 195-197°. A solution of this product (2.1 g) and solid NaOH (0.8 g) in water (50 mL) containing charcoal (2 g) (Norite A) is pressurized with oxygen to 30 lb/in^2, bled, repressurized, and agitated at room temperature in a Parr shaker for 24 hr. The mixture is filtered to remove the catalyst and the water is removed under reduced pressure at room temperature. The resulting semi-solid is washed with ether and

ethanol and then air-dried to give the target material (1.3 g, 85%) as a white crystalline solid identical to authentic material.[84]

C. Syntheses *via* Hexahydrotriazines

1. Introduction

An extremely versatile and complementary method to these Mannich-based procedures utilizes a symmetrical hexahydro-1,3,5-triazine (HHT) as an intermediate. In this case the aldimine product normally produced *in situ* between formaldehyde and glycine is pre-formed as a trimer prior to the reaction with the secondary phosphite component. The resulting 1,3,5-trialkylhexahydro-1,3,5-triazines (40) readily hydrolyze in acid or revert to the parent amine and aldehyde upon heating in water.[85] Under acid catalysis, HHT's will undergo ring opening with compounds containing either reactive O-H or S-H groups to produce the corresponding amino-methylated adducts (41).[86,87]



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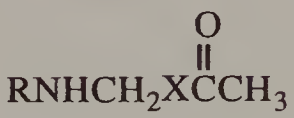


X = O, S 41

2. With Aliphatic Dialkyl Phosphites

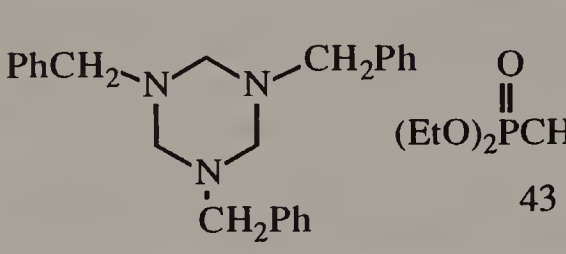
The first reported reaction of HHT's with dialkyl phosphites was developed as a convenient route to α-aminomethylphosphonic acids (43) from tribenzyl-1,3,5-hexahydrotriazine (42) by Ratcliffe and Christensen.[88] This reaction requires neat conditions and heating for six hours at 100°. No comparable reaction is observed in solvents such as benzene, toluene, or acetonitrile.[89]

Like the analogous reaction described above with reactive S-H functionalities, the condensation between HHT's and phosphites is believed to occur by a stepwise process following activation of the HHT ring by protonation through intermediates (44)-(47).[90] A thermal reversal to a transient aldimine is also possible, but all attempts to observe a free aldimine intermediate during such reactions from thermal cracking of these trimers have been unsuccessful.[89]

Glycines and glycinates also form trimeric HHT derivatives with formaldehyde. The first reported use of a glycine based HHT as an intermediate to PMG utilized *N*-methyleneglycinonitrile (48)

which is commercially available or easily synthesized from glycinonitrile.[91] This HHT reacts with neat aliphatic dialkyl phosphites under acid catalysis at 40° to provide *N*-diethylphosphonomethylglycinonitrile (49) in very low yield (6%).[92]

Dr. Gerard A. Dutra and co-workers at Monsanto Company have studied these reactions extensively and have provided the following details.[89] No such reaction is observed in the absence of an acid catalyst at 40°. Raising the temperature to 100° for 24 hr either neat or using solvents such as chloroform or acetonitrile at reflux gives tars with no detectable product. Like many α-aminoacetonitrile derivatives, (49) is sensitive to the second base step and readily decomposes upon heating. Thus (49) is present in 30-35% yield as the crude product, but most is lost upon work-up and attempted distillation. At higher temperatures (48) becomes unstable to the reaction conditions and no product is observed.



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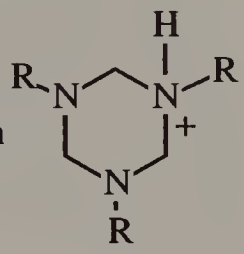

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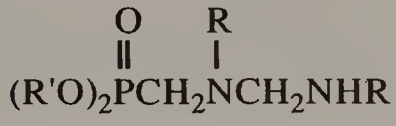

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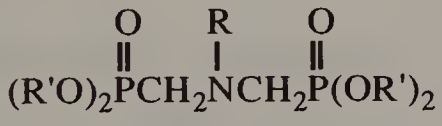

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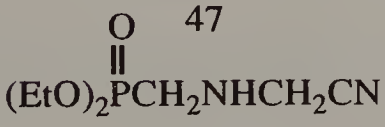

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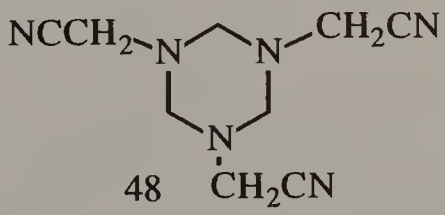


48

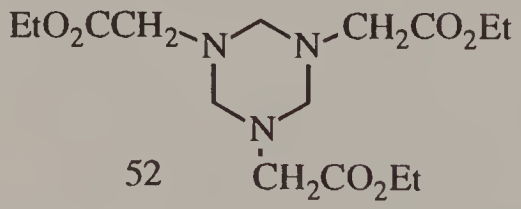
However, if one carefully maintains the temperature at 40°, the crude precipitate can be isolated and characterized by ^{1}H and ^{31}P NMR as a mixture of aminoacetonitrile hydrochloride and the expected hydrochloride salt of (49). The remaining liquid layer

contained excess diethyl phosphite and unexpectedly significant quantities of bis-phosphonomethylglycinonitrile (50) as the major product of the reaction. Pure neutral (49) can be obtained by filtration and neutralization with triethylamine, while pure (50) can be isolated easily in analytically pure form and high yield by simply removing the excess diethylphosphite by a bulb-to-bulb vacuum distillation. This is the method of choice for the preparation of (50) and it analogs. It is interesting that under these conditions (50), as an analog of (47), predominates, while no products corresponding to (45) and (46) are detected. It is possible that a change in reaction mechanism may be occurring under these conditions.

Alternatively, (48) can be used under acidic Mannich conditions with phosphorus trichloride in acetic acid to provide *N*-phosphonomethylglycinonitrile (51) as its hydrochloride salt which can be hydrolyzed to PMG under basic conditions in somewhat better yield.[93]

In contrast, the more stable HHT of ethyl glycinate (52) reacts smoothly and cleanly with neat diethyl phosphite at 100° in 3 hr to give quantitative conversion to the triethyl ester of PMG, (20), which is identical in all respects to the normal Mannich product.[104] The corresponding reaction with diethyl thiophosphite[94] is slower, requiring about 9 hr, to yield a complex mixture containing about 20% of the desired triester and a multitude of other unidentified products.[89]

Good overall yields of PMG can also be obtained using dialkyl phosphites in a similar procedure with the more stable HHT derivative of sodium glycinate (53) in place of (48).[95]



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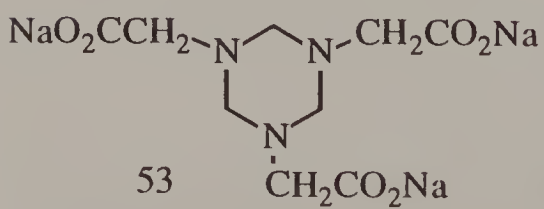


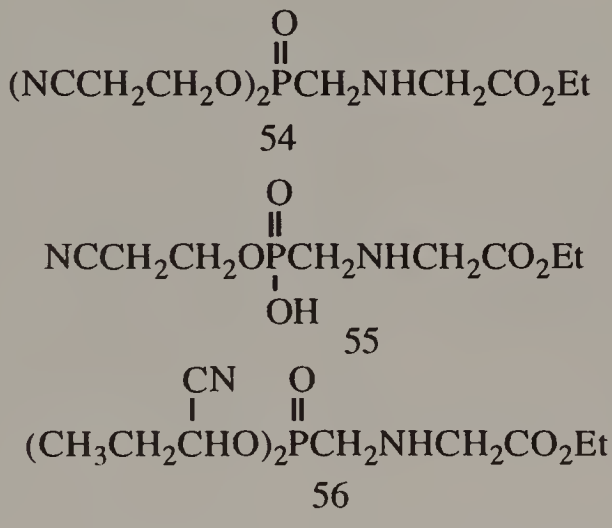
53

51

Dialkyl phosphites bearing β-hetero substituents generally undergo comparable reactions with (52) in lower yield. Usually the

resulting triester product is either hydrolytically or thermally unstable, resulting in decreased amounts of isolated product. For example, bis(β-cyanoethyl) phosphite reacts with (52) at 100° for 30 min to give a crude form of the desired triester (54).[96] Subsequent hydrolysis to the corresponding diester (55) proceeds in about 25% overall yield.[89]

Similarly, poor yields (8-16%) of these triesters are also observed with various β-sulfur substituted dialkyl phosphites.[97] However, a very good yield of triester product (56) is obtained using dialkyl phosphites containing α-cyanoalkyl groups.[98] In this case isolation of the hydrolytically unstable product (56) was facilitated by column chromatography using microcrystalline cellulose.



54

55

56

3. With Hetero-substituted Trialkyl Phosphites

Dramatically improved yields of such hetero-substituted phosphonate triesters can be obtained using a three component, one pot solventless procedure with the corresponding trialkyl phosphites (57).[99] With this method, one equivalent of (57) and (52) are combined with one equivalent of water and stirred for 1-12 hr. Tris(cyanoalkyl) phosphites generally react smoothly at 10-20°, while other substituted phosphites require heating for 1-3 hr at 100-110°. When the reaction is complete the displaced alcohol is removed by a bulb to bulb vacuum distillation, and the resulting residues are usually purified by column chromatography on cellulose. Using this procedure a variety of hetero-substituted phosphonate analogs of (58) have been prepared and isolated in

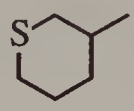
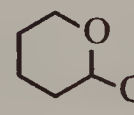
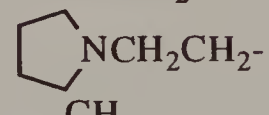
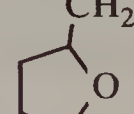
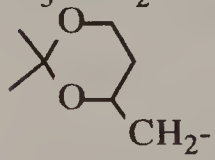
moderate to excellent yields as summarized in Table 3. While simple aliphatic PMG-triesters generally lack significant herbicide activity themselves, these activated analogs of (58) are patented with reasonable herbicide activity.[99]

$(EtO_2CCH_2O)_3P$ (57)

$(EtO_2CCH_2O)_2P(=O)CH_2NHCH_2CO_2Et$ (58)

Table 3 - Glyphosate triesters containing hetero-alkyl substitutents within the phospho-diester from (52) and the corresponding trialkyl phosphite[99]

$(RO)_2P(=O)CH_2NHCH_2CO_2Et$

R	Yield(%)	R	Yield(%)
$NCCH_2CH_2$-	45		40
$Me_2C(CN)$-	94		
EtO_2CCH_2-	62		57
$EtO_2CCH_2CH_2$-	84		
$EtO_2CSCH_2CH_2$-	52		41
$EtO_2CCH_2CH(CO_2Et)$-	13		
$EtO_2CCH_2CH(CH_3)$-	61		37
$ClCH_2CH_2$-	97		
Cl_3CCH_2-	15		
	35		

The exact mechanism of this transformation is unknown. It is believed to proceed analogously to the known reaction between *N*-methylol-sulfonamides (59) and trialkyl phosphites with elimination of one equivalent of alcohol.[100] The proposed path for this transformation involves first thermal loss of water to form the formaldimine (60) which adds trialkyl phosphite to give the zwitterionic intermediate (61) which then hydrolyzes with loss of alcohol to the phosphonomethylated adduct (62).

These HHT reactions with trialkyl phosphites, likewise, are presumed to proceed *via* the zwitterionic intermediate (63).[101]

RSO_2NHCH_2OH (59) $RSO_2N{=}CH_2$ (60) $RSO_2\overset{-}{N}CH_2\overset{+}{P}(OR)_3$ (61)

$RSO_2NHCH_2PO_3R_2$ (62) $EtO_2CCH_2\overset{-}{N}CH_2\overset{+}{P}(OR)_3$ (63)

4. With Diaryl and Dibenzyl Phosphites

A significant methodological breakthrough has also been reported using diaryl phosphites. While fairly rigorous conditions requiring high temperatures, neat conditions and/or an acid catalyst are needed in reactions between simple aliphatic dialkyl phosphites and HHT's, a nearly quantitative conversion to the desired products is observed in solution with common aprotic solvents using aromatic phosphites.[102]

Essentially any non-reactive aprotic solvent can be used. Benzene, toluene, chloroform and acetonitrile have all been widely reported. This provides an extremely versatile and general method for the synthesis of a number of patented herbicidal PMG-triester derivatives (64) and diester derivatives (65).

Presumably, electron withdrawing substituents make the phosphite more acidic. These phosphites can thus act as internal catalysts to facilitate the overall reaction. Dibenzyl phosphites also give comparable yields of triester products. Neither bis(trimethylsilyl) phosphite nor bis(*t*-butyl) phosphite give any detectable product under similar conditions.[89]

The diaryl (66) and dibenzyl phosphites required for this procedure can be conveniently synthesized by known methods in 60-98% purity.[103]

$(ArO)_2P(=O)H$ (66)

However, extreme caution should be used in attempting purification of these materials since rapid and occasionally violent decomposition has been observed in vacuum distillations of diaryl phosphites bearing strong electron-withdrawing substituents.[89] Analogs of (66) containing nitro or halogen functionality are especially prone to decomposition. These materials can often be used directly without further purification following careful quantitation by ^1H and ^{31}P NMR to determine the relative amounts of

phenol and triaryl phosphite present in the sample.[89]

Reaction of diphenyl phosphite and the HHT of ethyl glycinate proceeds cleanly and quantitatively within two hours using benzene at reflux to give the phospho-diphenylester analog of (64). The corresponding reaction with diphenyl thiophosphite[94] gives an 80% yield of the desired diphenyl thiophosphonate analog under similar conditions.[89]

The ready availability of these adducts provides access to a wide variety of PMG-monoaryl esters. Like aryl carboxylate esters, these phospho-diarylesters (64) can be hydrolyzed under extremely mild conditions, either stepwise in aqueous acetone to the zwitterionic monoaryl esters (65) which readily precipitate[102] or simultaneously under acidic or basic conditions to provide PMG in good yield and purity.[104] Analogs of (64) and (65) prepared by this method are summarized in Table 4.

Table 4 - Diaryl and monoaryl phosphonomethyl glycinate ethyl esters prepared from hexahydrotriazines[89,102]

64

Ar	Yield(%)
C_6H_5	70
p-F-C_6H_4	----
m-Cl-C_6H_4	----
o-CH_3-C_6H_4	>99
p-CH_3O-C_6H_4	>99
m-NO_2-C_6H_4	----
p-CH_3-C_6H_4	>99
m-CF_3-C_6H_4	----
o-CH_3O-C_6H_4	57
3,4-Cl_2-C_6H_3	53
3,4-$(CH_3)_2$-C_6H_3	----
2,4,6-$(CH_3)_3$-C_6H_2	70
p-NO_2-$C_6H_4CH_2$	>99
p-Cl-$C_6H_4CH_2$	>99

65

Ar	Yield(%)
C_6H_5	75
p-F-C_6H_4	42
m-Cl-C_6H_4	70
o-CH_3-C_6H_4	14
p-CH_3O-C_6H_4	----
m-NO_2-C_6H_4	31
p-CH_3-C_6H_4	20
m-CF_3-C_6H_4	47
o-CH_3O-C_6H_4	10
3-CH_3-4-NO_2-C_6H_3	33
3,4-$(CH_3)_2$-C_6H_3	13
3,4-Cl_2-C_6H_3	53
p-CH_3-$C_6H_4CH_2$	7
p-Cl-$C_6H_4CH_2$	----
2,4-Cl_2-C_6H_3	65
p-$C_6H_5CH_2OC_6H_4$	41

A major advantage in these diaryl phosphite procedures is that the reaction can often be run conveniently in common aprotic organic solvents, and, if necessary, under anhydrous conditions. This allows many functional groups to be accommodated during the reaction. In particular, more sensitive functional groups can be incorporated into the procedure which would normally decompose under the typical Mannich conditions or which may be more difficult to isolate.

For example, similar methods have been used starting with (48) and diaryl phosphites to prepare a variety of analogous PMG-glycinonitrile derivatives (67) which are also widely patented as herbicides. In contrast to the very poor reaction described above with diethyl phosphite, nearly quantitative conversions are observed with diaryl phosphites. For example, diphenyl phosphite reacts with (48) in refluxing acetonitrile giving 94% conversion to produce diphenyl phosphonomethylglycinonitrile (67) in 75% isolated yield after chromatography.[105]

Hydrolysis of (67) again occurs under very mild conditions in acetone at room temperature providing the insoluble monoaryl ester products (68) in moderate to high yield.[105] A direct hydrolysis of diphenyl phosphonomethylglycinonitrile with 2*N* HCl for 8-16 hours at 100° easily provides PMG in 79% yield and 96% assay.[89] Similarly, direct hydrolysis with tetrabutylammonium hydroxide produces the tetrabutylammonium salt of PMG in high purity and 71% yield.[106] Analogs of (67) and (68) prepared by this method are summarized in Table 5.

Interestingly, representative examples of these herbicidal diarylphosphono PMG-ester [(64), (65)] and PMG-nitrile [(67), (68)] derivatives have each been evaluated as potential inhibitors of EPSPS and display no significant activity against this enzyme *in vitro*.[31] Presumably, *in vivo* activity arises as a result of extensive and facile hydrolysis to PMG, either on the plant surface, or within the plant following uptake.

By carefully monitoring these HHT reactions by ^{31}P NMR it is possible to detect the presence of 5-15% of the herbicidal symmetrical PMG aminal derivative (69) under the reaction conditions, particularly when HHT is used in excess.[107,108] Like many aminals, (69) is acid sensitive and will convert quantitatively to the strong acid salts (70) corresponding to (64) or (67) upon treatment with methanesulfonic acid or hydrochloric acid. Thus, any yield loss due to this aminal side reaction can be averted using an acid workup to give the desired product as a strong acid salt.[89]

Table 5 - Diaryl and monoaryl phosphonomethyl-glycinonitriles prepared from hexahydrotriazines[89,105]

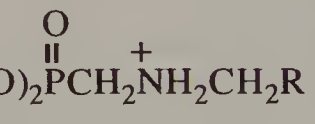
67

Ar	Yield (%)
C_6H_5	90
p-F-C_6H_4	92
m-Cl-C_6H_4	92
p-Cl-C_6H_4	100
p-CH_3O-C_6H_4	82
m-NO_2-C_6H_4	>99
m-CH_3-C_6H_4	14
m-CF_3-C_6H_4	40
p-CH_3S-C_6H_4	45
3,4-Cl_2-C_6H_3	53
3,4-$(CH_3)_2$-C_6H_3	40
2,4,6-$(CH_3)_3$-C_6H_2	14

68

Ar	Yield (%)
C_6H_5	75
p-F-C_6H_4	98
m-Cl-C_6H_4	60
p-Cl-C_6H_4	51
p-CH_3O-C_6H_4	---
m-NO_2-C_6H_4	51
m-CH_3-C_6H_4	53
m-CF_3-C_6H_4	40
p-CH_3S-C_6H_4	66
3-CH_3-4-NO_2-C_6H_3	30
o-Cl-C_6H_4	82

69 R = CN, CO_2Et

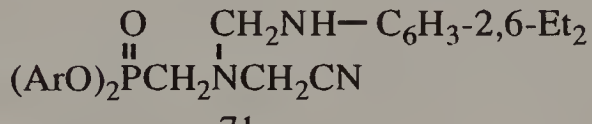


70 R = CN, CO_2Et

Such aminals are analogous to (45). Careful monitoring by ^{31}P NMR suggests that other products may also be produced in small amounts under the reaction conditions. However, it is interesting that in these diaryl phosphite reactions with HHT's, no bisphosphonomethyl analogs corresponding to (47) and (50) or unsymmetrical aminals (46) have ever been isolated.[89]

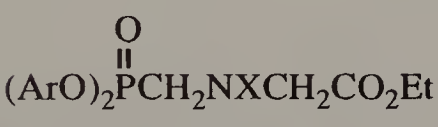
The aminal nitriles (69) can be produced in high yield using an azomethine transfer reaction between (67) and a hindered aryl azomethine.[107] The reaction proceeds first through the diethyl aniline adduct (71) which has been isolated in low yield following chromatography and characterized spectroscopically.[89] Vacuum distillation of the reaction mixture removes the aniline, driving the equilibrium toward aminal product.

Another advantage related to these diaryl phosphite reactions with HHT's has also been widely exploited. The resulting products conveniently provide herbicidally active derivatives of PMG which are soluble in common organic solvents and readily derivatized at nitrogen under anhydrous conditions. This has led to the synthesis of several series of patented and herbicidally active *N*-substituted PMG phospho-diarylester derivatives (72), particularly with novel *N*-hetero substituents as summarized in Table 6.

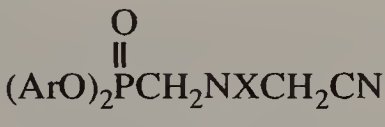


71

Table 6 - Herbicidal *N*-hetero substituted diaryl *N*-phosphonomethylglycinate ethyl esters and *N*-phosphonomethylglycinonitriles



72a



72b

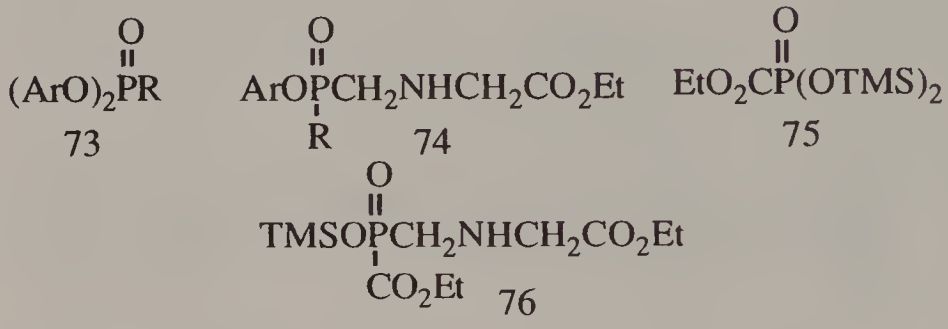
X	Reference	X	Reference
ON-	109	ON-	110
Alkyl-S-	111	Alkyl-S-	112
Aryl-S-	113	Aryl-S-	114
Alkyl-S-S-	115	Alkyl-S-S-	116
R_2N-S-	117	R_2N-S-	118
Aryl-SO-	119	Aryl-SO-	120
R_2N-SO-	121	R_2N-SO-	122
		Cl-S-	123
		Cl-	124

Formation of the analogous PMG *N*-substituted derivatives would normally take place under aqueous conditions. Therefore, many of these substituents could not tolerate such conditions and would not normally be incorporated into PMG directly because of their hydrolytic lability.

Diaryl phosphonates (73) also react with HHT's in the presence of one equivalent of water to produce aryl esters of PMG-

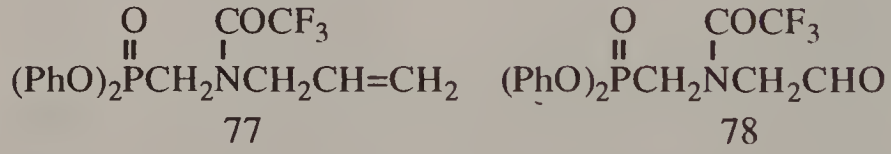
phosphinic acids (74) in high yield. Unlike the reaction of HHT's with trialkyl phosphites, this reaction can be run conveniently in dioxane with a variety of diaryl phosphonites.[125,126]

Whereas bistrimethylsilyl phosphite produces no observed product with (52) in solution,[89] the bissilyl ester of ethoxycarbonylphosphonate (75) will react similarly in ethanol and dioxane producing the PMG-phosphinate triesters (76) in very high yield.[127]



4. Miscellaneous Methods

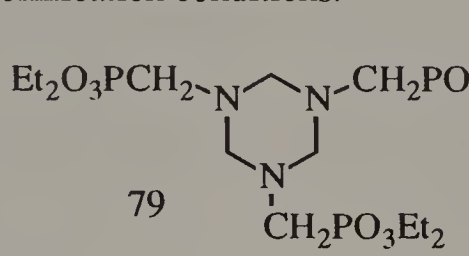
These HHT procedures can also be used to synthesize conveniently a wide range of interesting synthetic intermediates. For example, the HHT of allyl amine reacts with diphenyl phosphite to give the *N*-allyl aminomethylphosphonate. This is protected at nitrogen as the trifluoroacetamide (77) and then ozonolyzed to produce the unusual PMG-glycinal derivative (78), which is patented as a herbicide.[128]



HHT's will also undergo ring opening reactions with simple acid chlorides to produce the corresponding *N*-chloromethylamides. These are extremely versatile synthetic intermediates. For example, the HHT of diethyl aminomethylphosphonate (79) reacts cleanly with acetyl chloride to give the *N*-chloromethyl amide (80). Further reaction with powdered potassium cyanide gives the desired PMG-glycinonitrile (81). Subsequent acid hydrolysis produces PMG in good yield.[129]

Another clever twist to these HHT procedures uses an analogous reaction between aliphatic phosphites and benzoxazine

(82), which gives a protected *N*-benzyl PMG derivative (83) directly.[130] These benzoxazines can be prepared from either ethyl or sodium glycinate and formaldehyde using a base-catalyzed condensation with *p*-cresol or other phenol derivatives. Ring opening with alkyl phosphites proceeds cleanly to (83) which can be deprotected further to PMG under standard hydrogenolysis and saponification conditions.



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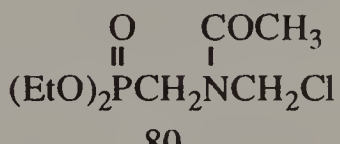

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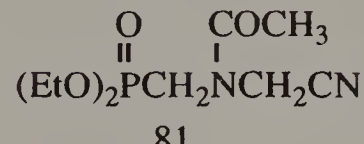

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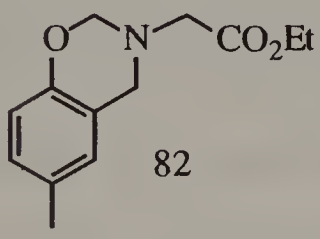

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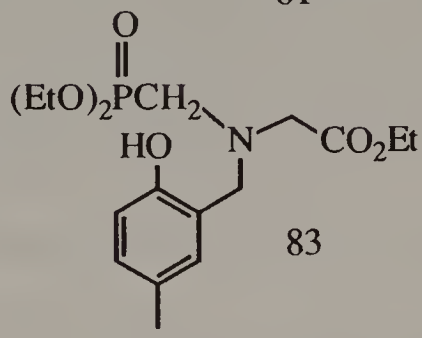
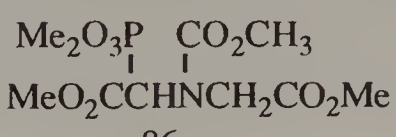


83

An interesting related reaction has been reported using trialkyl phosphites to trap activated carbomethoxyiminium ions (85). These transient species are generated by Lewis acid reaction with the corresponding α-methoxyurethanes (84) which are available using an electrochemical methanolysis procedure.[131] Subsequent reaction with trimethyl phosphite produces a novel α-carbomethoxy-PMG triester (86) in good yield.[132]

84 85



86

No biological activity or deprotection studies have been reported for these PMG derivatives.

5. Procedures

a. Preparation of *N,N*-bis(Diethylphosphonomethyl)-glycinonitrile[89]

Anhydrous hydrogen chloride is slowly added to a solution of diethyl phosphite (40.0 g, 0.3 mol) and 1,3,5-tris(cyanomethyl)-hexahydrotriazine (10 g, 0.05 mol) at such a rate as to maintain a temperature between 30-40°. External cooling with ice is necessary after the initial extremely exothermic reaction. *CAUTION*: Slow addition of hydrogen chloride is necessary to control the reaction. A white solid precipitates from the solution. After 1 hr the reaction mixture is cooled to 5° in an ice bath, ether is added, and the precipitate is collected and washed with ether to give a white solid characterized as a 70:30 mixture of (49) and aminoacetonitrile hydrochloride. The ether filtrate is concentrated and the excess diethyl phosphite is removed by a bulb-to-bulb vacuum distillation to give pure target material as a clear oil (15 g, 84%).

b. Preparation of Diphenoxyphosphinylmethylglycino-nitrile[105]

A solution of 1,3,5-tris(cyanomethyl)hexahydrotriazine (13.6 g, 0.066 mol) and diphenyl phosphite (46.8 g, 0.2 mol) in acetonitrile (100 mL) is heated at 55° for 48 hr. The acetonitrile is removed *in vacuo* to give a viscous black oil, which is subjected to chromatographic purification on silica gel eluting with chloroform. The eluents are concentrated, dissolved in methylene chloride, washed twice with cold aq. KOH (5%) and water, dried over magnesium sulfate, filtered and evaporated to give a light yellow oil which crystallizes on standing and is recrystallized from carbon tetrachloride using activated charcoal to give the pure target material (37.9 g, 75%) of mp 66-68°.

c. Preparation of *N,N'*-Methylenebis(*O,O*-diphenyl-*N*-phosphonomethylglycinonitrile)[107]

A mixture of diphenoxyphosphinylmethylglycinonitrile (78.0 g, 0.26 mol) and 2,6-diethylphenylazomethine (21.1 g, 0.13 mol)[133] is placed in a kugelrohr distillation apparatus with a catalytic amount (10 mg) of sodium methoxide. The mixture is

heated at 65-75° under vacuum (0.02-0.07 Torr) for 1 hr. Distillation of 2,6-diethylaniline begins almost at once, and continues for almost 1 hr. The vacuum is released and 500 mL of carbon tetrachloride is added until the oil crystallizes. The hot solution is filtered and allowed to cool to room temperature. Solids are collected and washed with cold carbon tetrachloride. The mother liquor is concentrated to yield additional material which is combined with the first product to yield the pure target material (72.5 g, 90%) as an off white solid of mp 100-100.5°.

d. Preparation of Glycine *N*-bis(ethoxycarbonylmethoxyphosphinylmethyl)-, ethyl ester[99]

A mixture of tri(ethoxycarbonylmethyl) phosphite (15.0 g, 0.044 mol), water (0.79 g, 0.044 mol), and 1,3,5-tri(ethoxycarbonylmethyl)hexahydrotriazine (5.08 g, 0.0147 mol) is heated at 100-110° for 3 hr with agitation. An alcohol co-product, ethyl glycolate, is removed by bulb-to-bulb distillation of the reaction mixture at 75°/0.1 Torr. The distillation residue is chromatographed on microcrystalline cellulose with an eluent of ethyl acetate to give pure target material (10.1 g, 62%) as a viscous yellow oil.

D. Syntheses *via* Michaelis-Arbuzov Reactions

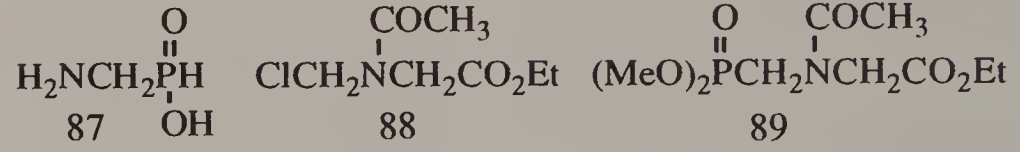
1. With α-Halomethyl Amides

The Michaelis-Arbuzov reaction of trialkyl phosphites with alkyl halides is one of the more common synthetic procedures for P-C bond formation.[134] These reactions typically are run using the phosphite in excess as solvent at temperatures that frequently exceed 100°. The method has limited application for preparing α-aminomethylphosphonates and -phosphinates, presumably due to the lack of suitably stable α-halomethylamides that can tolerate the fairly high temperatures required for reaction.

Certain *N*-halomethylphthalimides have been utilized successfully in this procedure to provide good yields of the desired α-aminomethylphosphonates[135] and -phosphinates. A recent report describes a facile preparation of aminomethylphosphonous acid (87) from *N*-bromomethylphthalimide.[136]

Halomethylacetamides have also been applied successfully in this procedure. For example, as noted earlier with intermediate (80), the HHT (52) will also undergo ring opening with acetyl

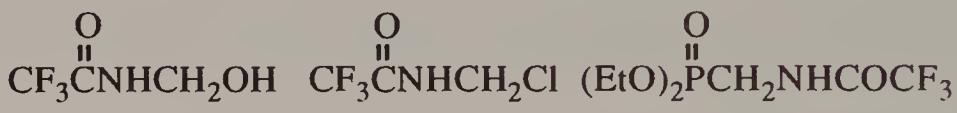
chloride. The resulting chloromethylamide (88) will react similarly with trimethyl phosphite to produce the *N*-acetyl-PMG-triester (89), which can be hydrolyzed to PMG.[137]



87 88 89

The glycinonitrile HHT (48) is stable to these conditions and can also be converted in a similar process to the analogous *N*-acetyl-PMG-glycinonitrile derivative.[138]

Alternatively, the PMG backbone can be constructed in a stepwise process starting with the *N*-methylol derivative of trifluoroacetamide (90) *via* the chloromethyl amide (91). Conversion the the trifluoroacetyl-aminomethylphosphonate (92) and alkylation with methyl chloroacetate completes this process.[139]



90 91 92

2. Preparation of *O,O*-Dimethyl *N*-Cyanomethyl-*N*-acetylaminomethylphosphonate[138]

1,3,5-Tricyanomethylhexahydro-1,3,5-triazine (17 g, 0.0835 mol) is slurried in a round-bottomed flask with 1,2-dichloroethane (150 mL). Acetyl chloride (40 mL) is added all at once and the reaction is refluxed for 3 hr and then stripped under reduced pressure to give the intermediate amide. This material is dissolved in methylene chloride (75 mL) and trimethyl phosphite (25.5 g, 0.206 mol) is added and the mixture is stirred at room temperature overnight, refluxed for 0.5 hr, and stripped under reduced pressure to give the pure target material (34.9 g, 79%).

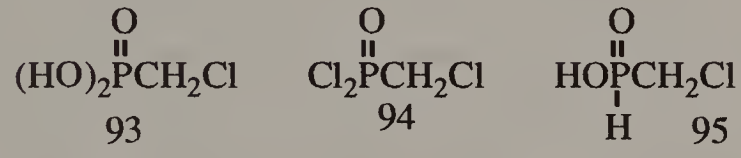
E. Substitutions *alpha* to Phosphonates

1. With α-Halomethylphosphonates

Conceptually, one of the easiest and most direct routes to envision to PMG and its derivatives would involve a simple displacement reaction with substituted methylphosphonates bearing an appropriate leaving group. These electrophilic reagents are

conveniently prepared starting from the readily available α-hydroxymethylphosphonates. With the more reactive sulfur[140] and selenium[141] nucleophiles good yields of the desired α-substituted-methylphosphonates can be obtained from α-chloromethylphosphonate esters. The weaker nitrogen and oxygen nucleophiles tend to give very poor yields or no conversion under comparable conditions.

PMG can be prepared in moderate yields from the reaction of sodium glycinate with α-chloromethylphosphonic acid (93) in aqueous base at reflux.[5] Alternatively, one can start with α-chloromethylphosphonic dichloride (94) to generate (93) *in situ*. Subsequent reaction with sodium glycinate produces PMG in 31% yield.[142] This yield can be improved to about 40% using a polyamine catalyst.[143] Higher yields are obtained using the more reactive α-chloromethylphosphinic acid (95) followed by mercuric chloride oxidation of the intermediate PMG-phosphinic acid to the required phosphonic acid.[5,84]



93 94 95

2. With Phosphonomethyl Mesylates, Tosylates, and Triflates

Over the last two decades a variety of solvolysis studies have clearly established the greater reactivity of mesylate, tosylate, and triflate reagents in these substitution reactions *alpha* to phosphonates.[144-146] Indeed, dramatic yield improvements have been realized using these intermediates. For example, various 5'-nucleosides can be phosphonomethylated in excellent yield using phosphonomethyl mesylate or tosylate.[147] These reagents also react with various primary and secondary amines to give the corresponding phosphonomethyl amines in very good yields.[148]

The phosphonomethyl triflate (96) has been developed as an even more efficient electrophile to introduce the phosphonomethyl group to weaker nucleophiles. For example, the diethyl ester analog reacts cleanly with ammonia within five minutes at 0° and will even alkylate the highly hindered 2,6-di-*t*-butyl-4-methylphenol within 1

hr at 0°.[149]

$$(R'O)_2P(O)CH_2OSO_2CF_3$$

96

Both highly hindered and hydrolytically sensitive ester analogs of (96) have been prepared by this method. The reaction easily tolerates acid labile bis(*t*-butyl) phosphonates or diaryl phosphonates. All react with glycine or alkyl glycinates to produce the corresponding PMG derivatives in good yield. Indeed, this is the preferred method for synthesizing PMG-bis(*t*-butyl) phosphodiester analogs.[150]

3. Preparation of Diethyl Phosphonomethyl Triflate[150]

Trifluoromethanesulfonyl chloride (60.25 g, 0.356 mol) is added in a single portion to a mixture of 99% granular sodium hydride (9.28 g, 0.386 mol) in diethyl ether (500 mL) at -20°, and is followed immediately by the rapid dropwise addition of a solution of diethyl hydroxymethylphosphonate (50.0 g, 0.297 mol) in diethyl ether (100 mL), maintaining an internal temperature between -20° and -15°. After the reaction is stirred for 1 hr at -20°, hydrogen evolution has almost ceased and the mixture is filtered rapidly through Celite and then diluted with methylene chloride (1 L) and thoroughly extracted with aqueous sodium bicrabonate (3 x 35 mL). The organic solution is dried over magnesium sulfate and concentrated to afford the pure target material (71.36 g, 80%) as a colorless oil.

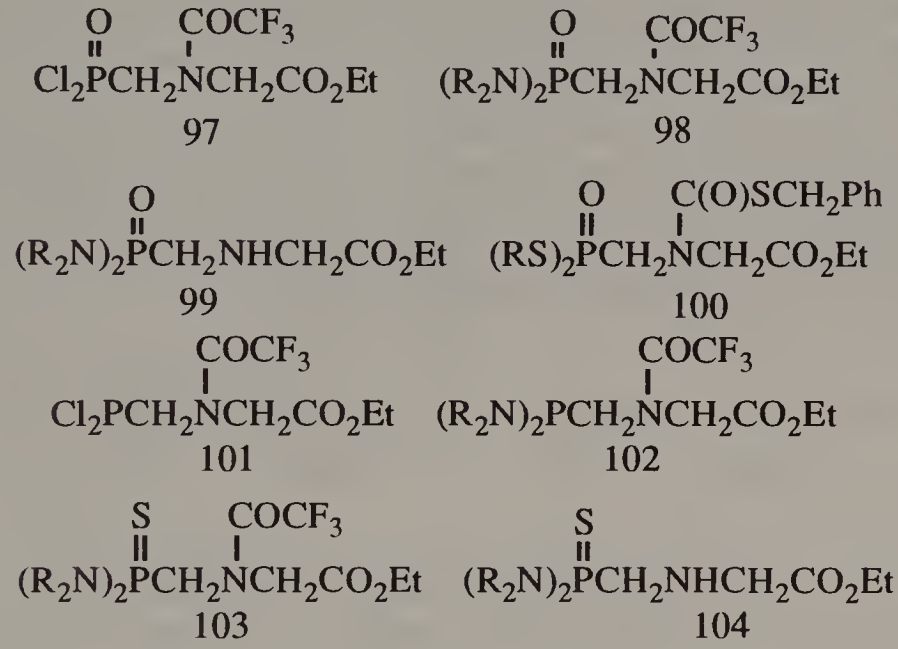
F. Phosphorus-substituted Derivatives

A wide variety of herbicidal PMG ester derivatives have been patented which contain amide or hydrazide substitutents on the phosphonate moiety. In the oxophosphonate series, most of these analogs can be prepared from a single common intermediate, the N-protected phosphonic dichloride (97). Treatment of (97) with excess amine or hydrazine produces the N-protected phosphonamide (98) in good yield.[151] Removal of the trifluoroacetyl group can be accomplished using sodium borohydride to produce the desired deprotected phosphonamide or hydrazide (99) in low to moderate yields.[152]

A similar sequence has been used to prepare analogous N-protected thiolphosphonates (100) which are patented as

herbicides.[153]

A somewhat different strategy has been used to accomplish the synthesis of the corresponding thionophosphonate derivatives. Tretament of N-protected PMG-phosphinic acid with phosphorus trichloride readily provides the dichloro phosphine intermediate (101).[154] Reaction with excess amine or hydrazine gives the corresponding diamino phosphine (102), which is not isolated but converted directly to the thionophosphonate (103) in good yield with elemental sulfur. Removal of the trifluoroacetyl protecting group again proceeds in fair to moderate yield to give the PMG-thionophosphonamide (104).[155]



97 98 99 100 101 102 103 104

G. Summary

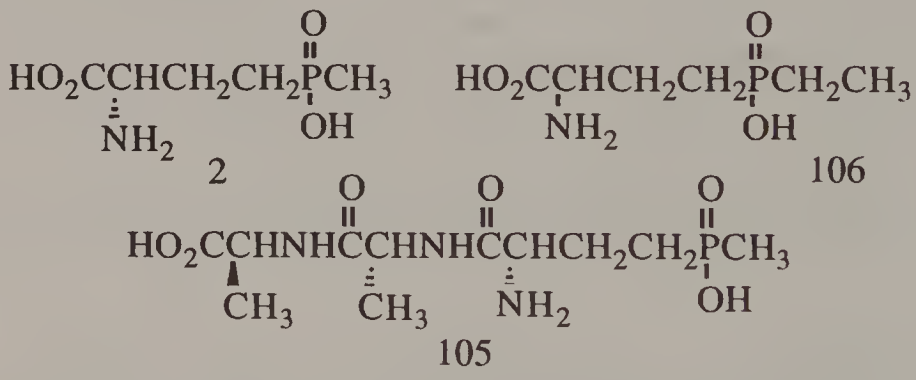
Since its discovery in 1970 the tremendous commercial success of glyphosate has stimulated an enormous world-wide effort to expand the repertoire of synthetic methodology available to prepare α-aminomethylphosphonates and their derivatives. From a limited beginning a variety of improved conditions, new reactions and new reagents have been developed over the last two decades. The well-exemplified Mannich reaction now provides access to many new water soluble derivatives. Hexahydrotriazines are versatile intermediates for the preparation of many new and complementary soluble organic derivatives. Phosphonomethyl tosylates and triflates have opened new avenues for electrophilic

phosphono- methylations. These advances have greatly expanded the field of organophosphorus chemistry and have significantly contributed to our knowledge of the biological activity of glyphosate and its derivatives.

III. Phosphinothricin Chemistry

A. Introduction

Phosphinothricin (2), PPT, is a methylphosphinic acid mimic of L-glutamic acid which is produced by various streptomycete species as a component of excreted antibacterial peptides.[156-159] These peptides were discovered independently in the early 1970's in the research laboratories of Meiji Seika Kaisha, Ltd. in Japan and at the University of Tubingen in Germany. PPT was commercialized in the mid-1980's by Hoechst A.-G. as a broad-spectrum postemergence herbicide in the racemic form under the product name glufosinate and, more recently, in the enantiomerically pure L-form. In a competitive development, Meiji Seika has commercialized the fermentation-derived phosphinothricyl-alanyl-alanine tripeptide (105) under the product name bialaphos.



Phosphinothricin bears the distinction of being the first microbial natural product to be commercialized as a herbicide on a large scale. Its combination of broad-spectrum phytotoxicity, animal safety, and environmental nonpersistence is strongly reminiscent of the advantageous characteristics of glyphosate, and would appear to favor its widespread acceptance in agriculture.

Phosphinothricin chemistry and synthesis have given rise to a voluminous patent literature and have been the subject of numerous publications in refereed journals, with significant contributions being made by Meiji Seika, Hoechst, Monsanto, CIBA-GEIGY, Fisons, Chevron, and other agricultural companies.

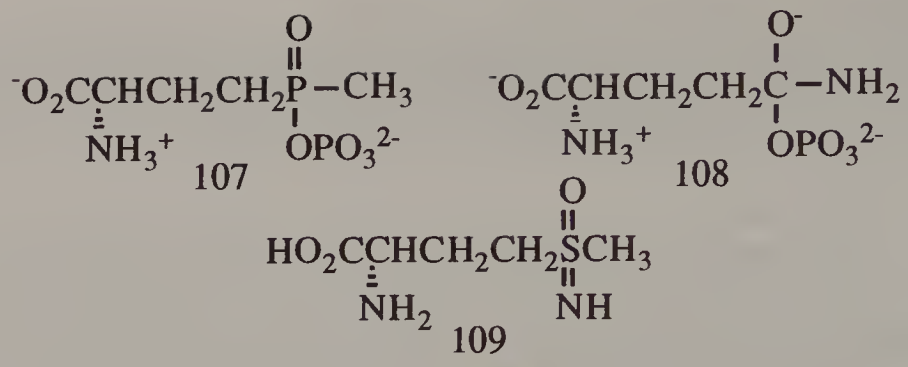
This review focuses attention primarily on the synthetic aspects of PPT chemistry, with an emphasis on the main reaction types encountered for carbon-phosphorus bond formation. A limited overview of biological activity is also provided.

1. Discovery

As would be expected for a natural product, the remarkable biological properties of PPT appear to have been discovered by way of microbiological culture screens. The first characteristics of PPT and its peptide conjugates were accompanied by descriptions of its antibacterial and antifungal activities.[156,157] While PPT was immediately identified as being a glutamine antimetabolite and an inhibitor of the enzyme glutamine synthetase, its potent phytotoxic activity does not appear to have been recognized initially, which may account in part for a relatively long delay in efforts at commercialization. The tripeptide (105) is not by itself active, and breakdown to PPT is required for glutamine synthetase inhibition and biological activity. Such breakdown appears to occur readily in plants, accounting for the potent herbicidal activity of (105). It is interesting to note that the racemic P-ethyl analog (106) of PPT was synthesized some 15 years before the discovery of PPT, and was shown with remarkable prescience to inhibit glutamine synthetase.[160,161]

2. Mode of Action

Phosphinothricin is a potent inhibitor in all plant species tested of the enzyme glutamine synthetase (GS; EC 6.3.1.2), displaying K_i values of competitive inhibition *vs.* L-glutamate in the low (<10) micromolar range.[162,163] PPT also inactivates GS in a time-dependent manner, serving as a substrate for ATP-mediated phosphorylation of the terminal methylphosphinate group, by analogy with phosphorylation of the enzyme's natural substrate, L-glutamate.[164] The resulting phosphorylated inhibitor (107) bonds tightly to the enzyme, apparently acting as a transition-state analog inhibitor by virtue of its close resemblance to the catalytic reaction intermediate (108).



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GS catalyzes a reaction of central importance in plant metabolism, the conversion of L-glutamate to L-glutamine. In plants the amide functionality of L-glutamine is the ultimate source of nitrogen for the biosynthesis of amino acids *via* transaminase-catalyzed reactions, and for nucleic acid biosynthesis *via* carbamoyl phosphate utilizing enzymes. Exposure to PPT and the resulting inactivation of GS causes accumulation of toxic ammonia in plant tissues, and also blocks recycling of carbon from the photorespiratory pathway to the Calvin cycle.[165,166] These physiological effects account for the potent herbicidal activity of PPT.

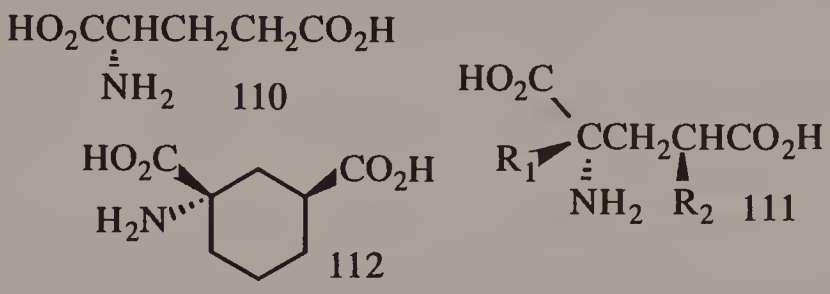
However, glutamine synthetase is found in all organisms, and PPT inhibits the enzyme from all species to a similar extent.[164,167] Other GS inhibitors are known to cause neurological damage in mammals, apparently by upsetting the balance of glutamine and glutamate, which is an excitatory neurotransmitter. The failure of PPT to exhibit mammalian toxicity is therefore somewhat puzzling, and may reflect an inability of the compound to cross the blood-brain barrier. This inference is supported by the potent neurotoxic activity of another GS amino acid inhibitor and herbicide, methionine sulfoximine (109).[168] A more thorough understanding of the toxicological properties of PPT must await the appearance of detailed animal metabolism studies.

Studies on the soil metabolism of PPT have been published and demonstrate rapid degradation (half-life < 11 days) accompanied by extensive mineralization of the central methylene carbon atoms.[169,170]

3. Analog Chemistry

While L-glutamate (110) is the natural substrate for glutamine synthetase, the classic investigations of Meister, *et al.* documented the ability of various substituted glutamic acids to function as substrates.[171] Of particular importance are the α- and γ-substituted

analogs of type (111), exemplified by cyclohexaneglutamic acid (112).



Considerations of GS substrate structural variability have led to the design and synthesis of α- and γ-substituted phosphinothricins[172-174] which are potent GS inhibitors and effective herbicides.[167,175-177] The synthesis of both active and inactive analogs of PPT illustrates the types of carbon-phosphorus bond-forming reactions encountered in phosphinothricin chemistry, and such syntheses will be highlighted as appropriate in the following discussion.

B. Phosphinothricin Synthesis: General Considerations

PPT is a molecule of some complexity, particularly by comparison with other organophosphorus agricultural chemicals, and its synthesis presents considerable challenges from an industrial standpoint. These may be divided conceptually into three distinct goals: 1) substitution of a methyl group for a hydroxyl moiety in a phosphorous acid equivalent, generating a methylphosphinic acid equivalent; 2) attachment of the latter to a three- or four-carbon aliphatic chain bearing a suitably functionalized terminus, with generation of a corresponding alkylmethylphosphinic acid; and 3) elaboration of the aliphatic chain chirality so as to generate the biologically active L-enantiomer.

Goals 1 and 2 necessarily require carbon-phosphorus bond-forming reactions, and are the main subject matter of this review; goal 3, while not involving carbon-phosphorus bond attachement *per se*, is briefly highlighted with reference to the various types of aliphatic chain used for phosphorus attachment. Biological syntheses of L-phosphinothricin have also been reported, drawing on an extensive understanding of PPT biosynthesis and employing modern recombinant DNA techniques. These efforts have been described in numerous patents and publications and are not discussed in this review. Carbon-phosphorus bond-forming

reactions used in phosphinothricin chemistry are exemplified by specific experimental procedures drawn from the patent and refereed literature. The reported yields of virtually all reactions cited in this section are quite good, proceeding in >80% isolated yield.

C. Methyl-Phosphorus Attachment

1. Approaches

Although methyl group replacement to generate the methylphosphinic acid moiety of PPT could follow an initial phosphorous acid attachment to an α-aminobutyric acid equivalent, such an approach has not been reported to date. Virtually all syntheses of PPT described in the literature, in fact, rely on methyl group attachment to phosphorus as a first step, generating a methylphosphinic acid equivalent which is subsequently attached to an appropriate precursor of α-aminobutyric acid.

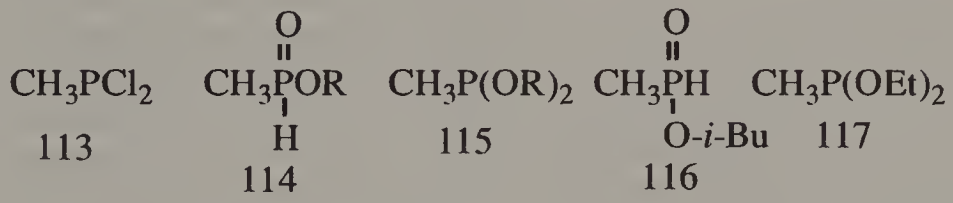
The most common realization of the carbon-phosphorus bond-forming reaction is achieved by synthesis of methyldichlorophosphine (113), a compound first reported in 1958.[178] Higher alkyldichlorophosphines have been known for many years, and have been extensively reviewed.[179,180] A convenient laboratory-scale preparation of (113) involves the aluminum chloride-catalyzed reaction of phosphorus trichloride with methyl chloride.[181]

Methyldichlorophosphine (113) is manufactured and sold on an industrial scale by Hoechst A.-G. The industrial synthesis of (113) is based on a previously described gas-phase, continuous flow, high-temperature reaction between methane and phosphorus trichloride in the presence of a suitable radical generator, for example carbon tetrachloride.[182]

The Hoechst manufacturing process achieves good conversion and high throughput with ingenious solutions to problems such as reactor design, recycling of unreacted starting material, product separation from volatile co-products, and fouling of the distillation tower by polymeric solid deposits. Extensive details are provided in patents.[183-186] Besides serving as a basic phosphinothricin building block, (113) is a versatile starting material for many other uses. A review of phosphorus chemistry based on transformations of methyldichlorophosphine has appeared.[187]

Although (113) can be used directly in Michaelis-Arbuzov reactions with suitable alkyl halides, published routes to phosphin-

othricin and analogues generally rely on formation of alkylmethylphosphinates (114) or the related dialkyl methylphosphonites (115) as nucleophilic reagents for carbon-phosphorus bond formation.

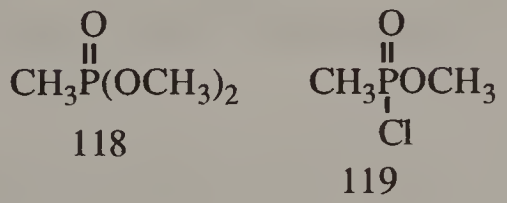


CH_3PCl_2 (113); $CH_3P(O)(H)OR$ (114); $CH_3P(OR)_2$ (115); $CH_3P(O)(O\text{-}i\text{-}Bu)H$ (116); $CH_3P(OEt)_2$ (117)

The monoesters (114) are readily obtained by reaction of (113) with an excess of alcohol.[188,189] For example, the commercially available isobutyl ester (116) is prepared industrially using isobutyl alcohol and (113), with nitrogen purging of by-product HCl to prevent complete acidolysis of the ester.[190] A convenient laboratory-scale preparation employs one mole-equivalent of triethylamine for partial neutralization of HCl as described below.

Dialkyl methylphosphonites (115) are generally prepared *via* reaction of (113) with an alcohol in the presence of excess base, as exemplified by the preparation of the widely used diethyl methylphosphonite (117).[191,192]

In addition to free radical and nucleophilic processes, aliphatic chain attachment to phosphorus has also been carried out in a reverse sense, *i.e.* using electrophilic alkyl methylphosphonyl halides as acceptors for organometallic reagents. Such an approach to dialkylphosphinate synthesis is a relatively recent addition to the organic phosphorus chemical literature. For example, the phosphonyl chloride (119) is readily prepared by Arbuzov rearrangement of dimethyl methylphosphonate (118) using phosphorus pentachloride.[193]



$CH_3P(O)(OCH_3)_2$ (118); $CH_3P(O)(Cl)OCH_3$ (119)

2. Procedures

a. Preparation of Methyldichlorophosphine[181]

Methyl chloride (70 g, 1.39 mol) is added dropwise to a mixture of aluminum chloride (370 g, 2.7 mol) and phosphorus trichloride (191 g, 1.39 mol) in a reaction flask fitted with a low

temperature reflux condenser. After the addition of aluminum turnings (25 g, 0.93 g-atom) the reaction is warmed to 10° and heating is withdrawn. The reaction temperature gradually rises to 180° and is air-cooled if necessary. After all of the solid aluminum is consumed the reaction is cooled to room temperature and sodium chloride (325 g, 5.56 mol) is added and the mixture is distilled under vacuum to give the target material (141 g, 87% yield) of bp 81.5°. *Caution*: Methyldichlorophosphine is toxic, corrosive, flammable, and highly moisture-sensitive. All reactions with methyldichlorophosphine must be conducted in a well-ventilated fume hood with proper safety precautions.

b. Preparation of Isobutyl Methylphosphinate[190]

A solution of methyldichlorophosphine (58.5 g, 0.5 mol) in anhydrous ether (300 mL) is admixed under nitrogen, with agitation and while cooling, with isobutyl alcohol (88.8 g, 1.2 mol) and triethylamine (50.5 g, 0.5 mol) in anhydrous ether (100 mL). The mixture is heated at reflux for 30 min, cooled to 5°, and filtered. The filtrate is concentrated and vacuum distilled under nitrogen to give the target material (59.8 g, 88% yield).

c. Preparation of Diethyl Methylphosphonite[192]

Methyldichlorophosphine (425 g, 4 mol) is added dropwise over 1.5 hr to a mixture of ethanol (400 g, 8.7 mol), *N,N*-diethylaniline (1030 g, 8.7 mol) and pentane (2.8 L) with rapid stirring at 0° under a static nitrogen atmosphere. After the addition is complete, stirring is continued for 0.5 hr. The heavy white precipitate is filtered and the filter cake rinsed thoroughly with pentane. The nearly clear filtrate is concentrated at 0° and 50-100 Torr. The concentrate is then distilled at < 10° and 0.3 Torr, collecting the target material in a receiver cooled to -78° (496 g, 91% yield).

d. Preparation of Methyl Methylphosphonyl Chloride[193]

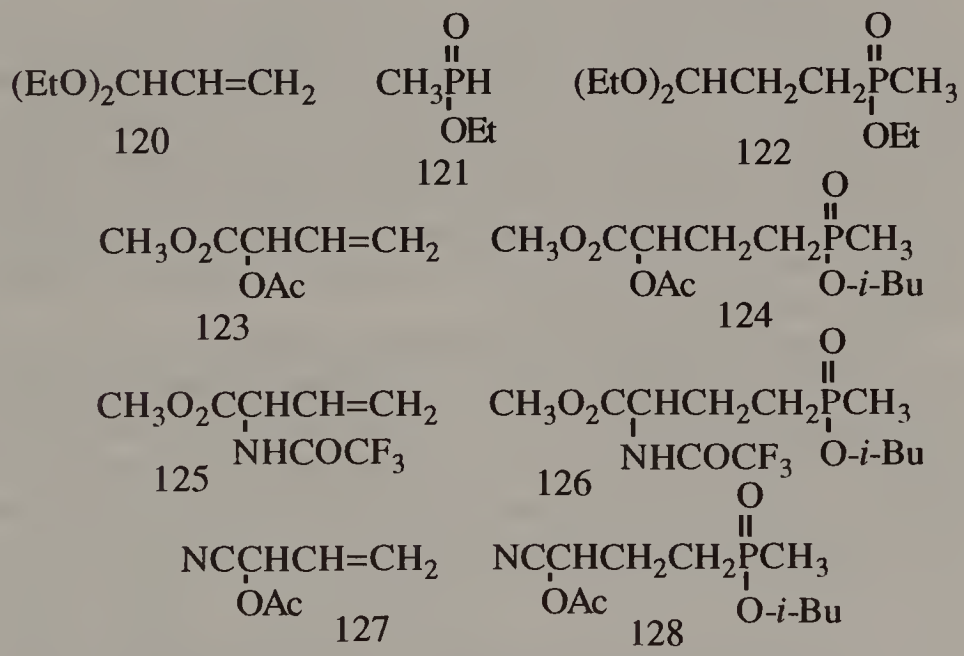
Dimethyl methylphosphonate (80 g, 0.64 mol) in benzene (160 mL) is cooled to 0° and phosphorus pentachloride (153.7 g, 0.737 mol) is added without allowing the temperature to exceed 10°. After 1 hr of stirring the solvent and phosphorus oxychloride are removed under vacuum and the residue is distilled (64°/15 Torr) to give the target material (75 g, 92% yield).

D. Free Radical Additions of Alkylmethylphosphinates to Unactivated Olefins

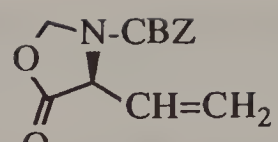
1. Approaches

Free radical additions of H-bonded alkylphosphinates to olefins are well known.[194-196] In the case of singly substituted double bonds such additions proceed at the unsubstituted position, apparently for steric reasons. The earliest example of such addition in PPT synthesis is the benzoyl peroxide-catalyzed reaction of ethyl methylphosphinate (121) with neat acrolein diethylacetal (120).[197] The reaction product (122) is readily converted to PPT by Strecker synthesis. Similar radical additions to more highly elaborated PPT precursors such as (123) and (125) have been reported leading to species (124) and (126) respectively.[198]

The radical addition reaction has also been adapted to industrial-scale synthesis by Hoechst A.G. In this case the isobutyl ester (116) is used as the phosphorus component and acrolein hydrate diacetate or cyanohydrin acetate (127) serves as the phosphorus acceptor to produce (128).[199-201]



A recent example of the free radical addition process employs a chiral oxazolidinone vinylglycine equivalent (129), leading to the direct preparation of L-PPT after acid hydrolysis of the intermediate adduct (130).[202]



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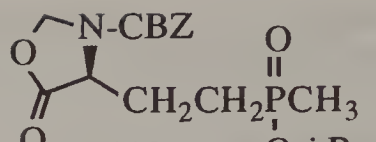

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2. Free Radical Addition of Isobutyl Methylphosphinate to Acrolein Cyanohydrin Acetate[200]

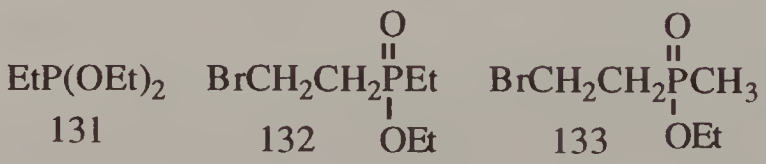
Methanephosphonous acid monoisobutyl ester (914 g, 6.7 mol) is heated to 115° under nitrogen. Acrolein cyanohydrin acetate (250 g, 2.0 mol) containing *t*-butyl peroctoate (8 g, 0.036 mol) is added dropwise over 2 hr with vigorous agitation. Agitation is continued for a further 15 min at 120° and the excess starting material is distilled off under reduced pressure at a bath temperature of up to 175°. The residue is distilled in a thin-layer evaporator (0.66 mbar) to give the target material (513 g, 98% yield).

E. Michaelis-Arbuzov Reaction of Dialkyl Methylphosphonites with Alkyl Halides

1. The Approach

The Michaelis-Arbuzov reaction is perhaps the most familiar of all carbon-phosphorus bond-forming reactions, and has been widely employed in laboratory-scale syntheses of phosphinothricin.[203] The chief drawbacks of the Michaelis-Arbuzov reaction, *i.e.* the need for elevated reaction temperatures and the attendant formation of ester-derived phosphinate by-products, have tended to limit the competitiveness of this approach as compared with other phosphorus addition processes.

The earliest recorded syntheses of PPT and the P-ethyl analog (106) featured the reaction of 1,2-dibromoethane with either diethyl ethylphosphonite (131) or diethyl methylphosphonite (117).[160,204] The resulting 2-bromoethylphosphinate esters (132) and (133) were converted to amino acids through a displacement reaction with diethyl acetamidomalonate.



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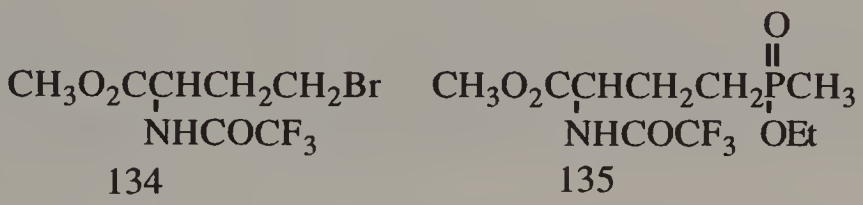
The Tubingen group reported a synthesis of PPT in their

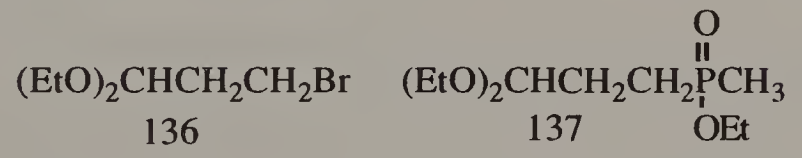
landmark paper that employed the reaction of diethyl methylphosphonite with the protected bromoester (134) to produce (135).



134 135

Other Michaelis-Arbuzov approaches have included reaction of phosphonite (117) with acetal (136) and bromoester (138).[205,206] The corresponding reaction products (137) and (139) were converted to PPT *via* Strecker synthesis and α-bromination/ammonolysis, respectively.

A more recent approach to PPT synthesis *via* the Michaelis-Arbuzov reaction has utilized the bromoester (140), a versatile starting material useful for the synthesis of other glutamine synthetase inhibitors as well.[207-210]



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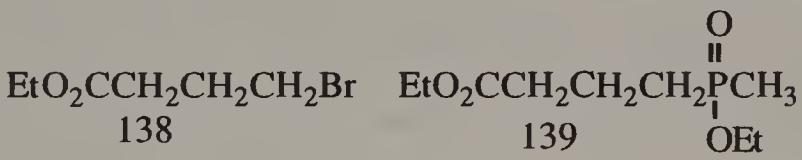

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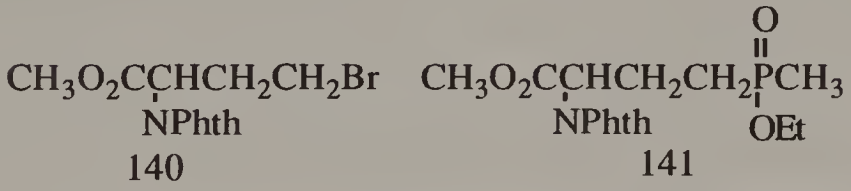

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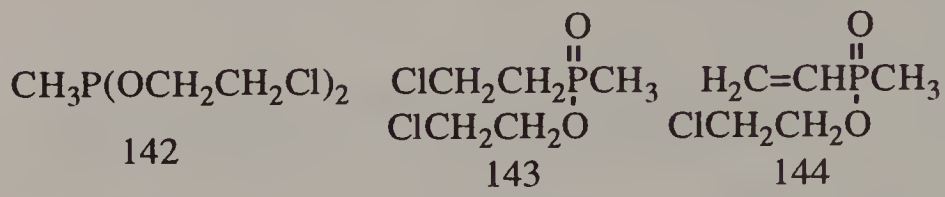
An interesting variant of the Michaelis-Arbuzov reaction for PPT synthesis involves the direct use of (113) rather than its ester equivalents.[211] In this instance (113) was subjected to reaction with ethylene oxide leading to the formation of the intermediate phosphonite ester (142).[212] Heating of (142) results in Arbuzov rearrangement *via* oxygen-to-phosphorus alkyl migration affording the phosphinate ester (143).[213,195] The latter undergoes facile elimination with triethylamine to provide the vinylphosphinate (144) which serves as a Michael acceptor for diethyl acetamidomal-

onate in an early example of PPT construction *via* conjugate addition of a glycine carbanion equivalent (see section H).



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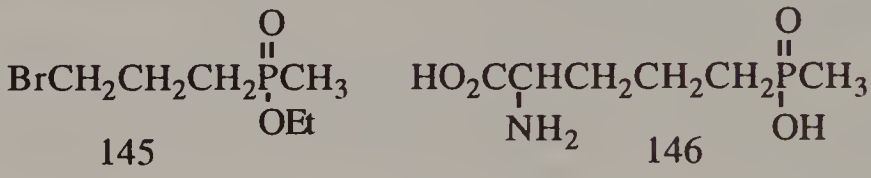
The Arbuzov reaction has also been employed for the synthesis of the PPT analog D,L-homophosphinothricin (146).[173] The bromophosphinate (145) was used to alkylate diethyl acetamidomalonate and the resulting product was hydrolyzed to give (146).



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2. Preparation of Methyl D,L-2-Phthalimido-4-(ethoxymethylphosphinyl)butanoate[208]

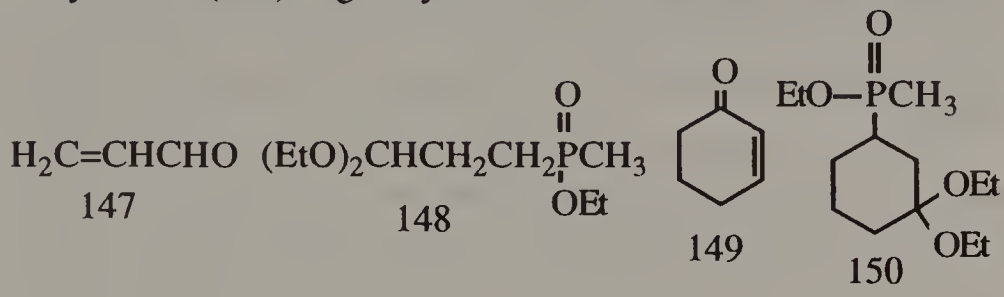
A solution of methyl 2-phthalimido-4-bromobutanoate (6.52 g, 20 mmol) and diethyl methylphosphonite (5.44 g, 40 mmol) in dry toluene (30 mL) is heated at reflux in an atmosphere of dry nitrogen for 16 hr. The toluene is evaporated under vacuum and the residue is heated at 80° and 1 Torr to remove volatile phosphinates. Chromatography of the crude product using 4/1 ethyl acetate/2-propanol gives the pure target material (4.87 g, 97% based on recovered starting material) as a colorless syrup.

F. Addition of Dialkyl Methylphosphonites to Unsaturated and Saturated Carbonyl Systems

1. The Approach

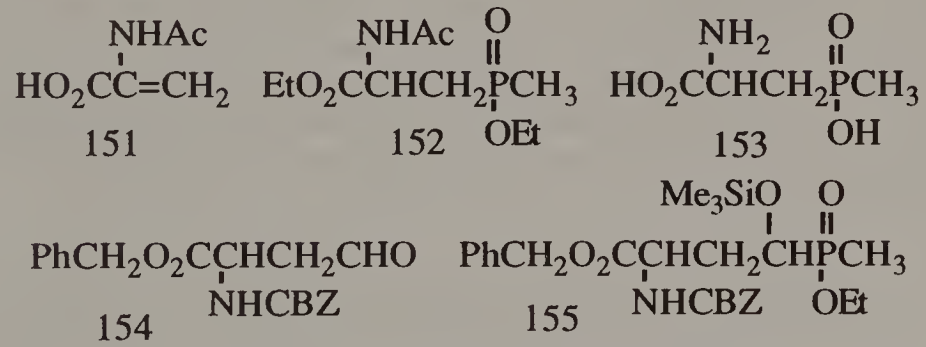
The 1,4- and 1,2-addition of trivalent phosphorus esters to unsaturated and saturated carbonyl systems, *i.e.* the Abramov reaction, has been used for the synthesis of both PPT and a variety of biologically active analogs.[214,216] A direct 1,4-addition of dialkyl methylphosphonite (117) to acrolein (147) was reported by Meiji Seika chemists, although yields of the resulting acetal (148) were modest.[197,217] The acetal (148) was converted to racemic PPT by Strecker synthesis.

The phosphonite conjugate addition reaction has also been used advantageously in 1,4-additions to substituted acroleins and unsaturated ketones, leading to the synthesis of α- and γ-substituted phosphinothricins *via* subsequent Bucherer-Bergs amino acid synthesis.[173] An example of this approach is provided by the reaction of phosphonite (117) with cyclohexenone (149) giving the diethyl acetal (150) in good yield.



A final example of carbon-phosphorus bond formation *via* conjugate addition is provided by the reaction of (117) with 2-acetamidoacrylic acid (151) which gives the ester (152) in good yield.[218,219] The latter was readily converted to the PPT analog D,L-norphosphinothricin (153) by acid hydrolysis.

An example of phosphonite 1,2-addition in PPT chemistry is provided by the reaction of protected amino acid aldehyde (154) with ethyl trimethylsilyl methylphosphonite, which affords in high yield the O-silylated adduct (155).[172,174] The silylated phosphonite reagent is readily obtained from ethyl methylphosphonite (121).



2. Preparation of Ethyl 3,3-Diethoxypropylmethylphosphinate[216]

Into a 100 mL red flask is introduced acrolein (12.5 g, 0.22 mol), hydroquinone (15 mg), and anhydrous ethyl alcohol (45 mL). The resulting mixture is stirred at -10° in a stream of nitrogen

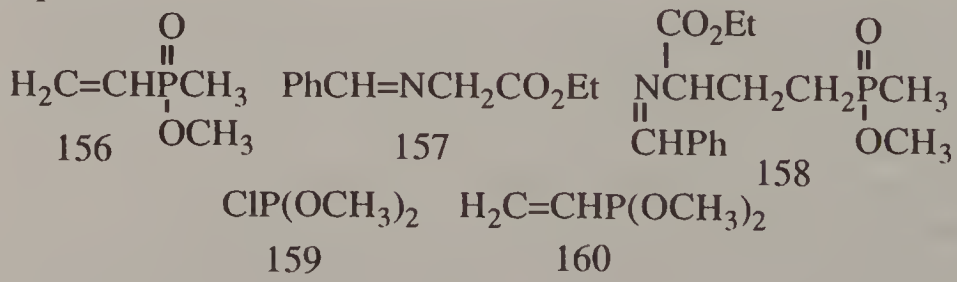
and diethyl methylphosphonite (13.6 g, 0.1 mol) is added dropwise thereto over 20 min. After stirring further for 30 min at -10°, the mixture is stirred for 2 hr at 0° and subsequently for 4 hr at room temperature, followed by further reaction at 70° for 12 hr. After the reaction mixture thus obtained is concentrated by evaporation of the ethanol under reduced pressure, the residue is subjected to distillation under reduced pressure to give the pure target material (12.2 g, 51.2% yield) as a fraction (85-91°/0.17 Torr).

G. Organometallic Addition to Alkyl Methylphosphonyl Halides

The carbon-phosphorus bond-forming reactions described in the previous two sections involve the use of phosphorus reagents as nucleophiles. A particularly fruitful alternative route to PPT synthesis has employed methylphosphonyl halides as electrophilic acceptors in reactions with vinylic organometallic reagents. The resulting vinylmethylphosphinates are well suited for conjugate additions of glycine enolate equivalents in a direct construction of the α-amino acid functionality of PPT.

The first example of this approach is provided by the additon of vinylmagnesium bromide to methyl methylphosphonyl chloride (119) which gives the vinylphosphinate (156).[219] Conjugate addition to (156) of the deprotonated benzaldehyde imine (157) results in the formation of (158), which is readily hydrolyzed to give D,L-PPT.

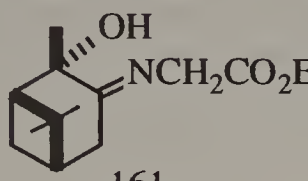
The same communication also describes an alternative preparation of (156) from the reaction of dimethyl chlorophosphite (159) with vinylmagnesium bromide, followed by thermal rearrangement of the resulting vinylphosphonite (160) *via* oxygen-to-phosphorus alkyl migration, which gives (156). The latter reaction appears to be the sole example in PPT chemistry of methyl-phosphorus bond formation following aliphatic chain attachment to phosphorus.



The vinylphosphinate (156) has been employed in chiral

syntheses of L-PPT *via* conjugate addition of chiral glycine Schiff base (161).[220] Another approach involves the conjugate addition of metalated 2,5-dialkoxy-3,6-dihydropyrazines (164) as a chiral glycine enolate equivalent.[221]

An innovative application of conjugate addition reactions with the vinylphosphinate (144) involves transition metal-catalyzed oxocarbonylation or amidocarbonylation with carbon monoxide and the appropriate nucleophile.[222] The use of alcohols with this method leads to acetals of type (166), while the inclusion of a primary amide and hydrogen gas in the reaction mixture leads directly to amino acid esters of type (167).



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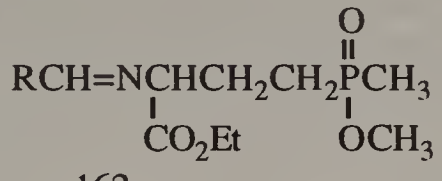

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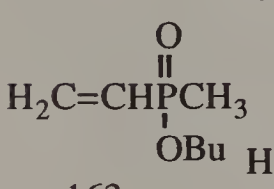

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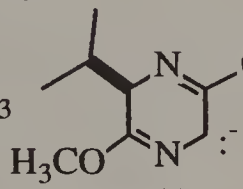

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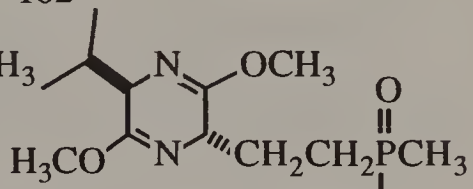
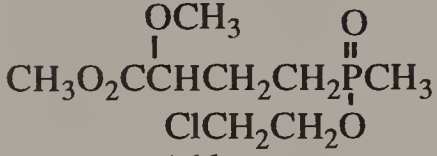
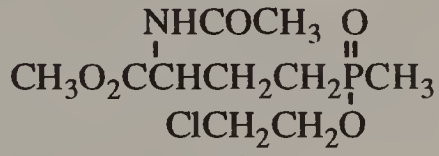


165



166



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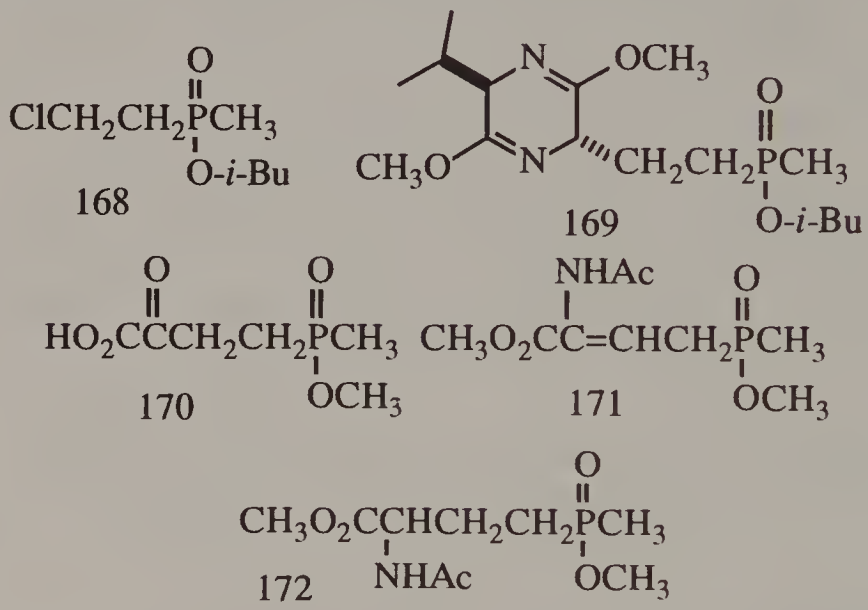
H. Formation of the α-Amino Acid Terminus of Phosphinothricin

Conceptually, the final strategic goal to be addressed in most PPT syntheses is formation of the α-amino acid functionality. Most of the methods used for this task have already been mentioned in the previous three sections. The most common approach has involved the conversion of a carbonyl group or acetal to an amino acid *via* Strecker or Bucherer-Bergs reaction. Another strategy has called for alkylation of a glycine enolate equivalent with a methylphosphinate-bearing electrophile, as in alkylation of diethyl acetamidomalonate with bromoesters (132) and (133).

A more recent variant of the latter approach involves the use of chiral glycine equivalents for alkylation, as in the conversion of (156) to (162). Chiral glycinate alkylation *via* bislactim ethers has also been performed using the 2-chloroethylphosphinate (168).[223,224]

The final approach to PPT synthesis considered here involves the amination/catalytic hydrogenation of 2-aminoacrylate precursors. Such aminoacrylates are obtained by addition of amines or ammonia to 2-ketoacids of type (170).[225] Reduction with Raney nickel affords D,L-PPT.[226]

More recently, catalytic hydrogenation of α-aminoacrylate (171) with chiral rhodium-phosphine complexes has been found to lead to production of enantiomerically pure D- and L-PPT in good yields.[227,228]



IV. Summary

The synthesis of phosphinothricin, both on laboratory and industrial scales, has provided considerable impetus for the development of new synthetic methods in organophosphorus chemistry. The construction of the α-amino moiety of PPT presents a challenge in its own right, but the key obstacle in PPT synthesis remains the satisfactory formation of two carbon-phosphorus bonds. While much progress has been made in this area, the synthesis of phosphinothricin continues to stimulate much new chemistry and is likely to continue to do so for the foreseeable future.

V. Dedication

This work is dedicated to Dr. John E. Franz and to the late Drs. Phillip Hamm and V. Russell Gaertner as well as their many colleagues and collaborators at Monsanto Company.

VI. Acknowledgements

The authors would like to acknowledge the following Monsanto Company colleagues for their assistance. We are grateful to Mr. Ross Hakes for his kind and thorough help in gathering patent citations. We would like to thank Drs. Terry Balthazor, Gerard Dutra, John Franz, Raymond Grabiak, Kurt Moedritzer, Mark Peterson, Peter Rogers, Lowell Smith, and Jimmy Worley for their thoughtful comments and critique in reviewing this work. The authors are also particularly grateful to Drs. Gerard A. Dutra, John E. Franz, Wm. H. Miller, Wm. R. Purdum, and Messrs. Donald. L. Fields and Joel E. Ream for their willingness to share unpublished material.

VII. Bibliography

1. Redmore, D. (1976). The chemistry of P-C-N systems, *Topics in phosphorus chemistry, Vol. 8*, (Griffith, E.J., and Grayson, M., eds.), John Wiley and Sons, Inc., New York, pp 515-585.
2. Maier, L. (1983). Advances in the chemistry of aminophosphinic acids, *Phosphorus Sulfur*, *14*: 295.
3. Franz, J.E. (1985). Discovery, development and chemistry of glyphosate, *The herbicide glyphosate*, (Grossbard, E., and Atkinson, D., eds.), Butterworth, Boston, MA, pp 1-17.
4. Rueppel, M.L., Brightwell, B.B., Schaefer, J., and Marvel, J.T. (1977). Metabolism and degradation of glyphosate in soil and water, *J. Agric. Food Chem.*, *25*: 517.
5. Franz, J.E. (1974). *N*-Phosphonomethyl-glycine phytotoxicant compositions, *U.S. Patent 3,799,758*.
6. Franz, J.E. (1983). Salts of *N*-phosphonomethylglycine, *U.S. Patent 4,450,531*.
7. Irani, R.R. (1969). Aminophosphonate herbicides, *U.S. Patent 3,455,675*.
8. Franz, J.E. (1979). Glyphosate and related chemistry, *Advances in Pesticide Science, Part 2*, (Geissbuhler, H., ed.), Pergamon Press, New York, pp 139-147.

9. Steinrucken, H.C., and Amrhein, N. (1980). The herbicide glyphosate is a potent inhibitor of EPSPS, *Biochem. Biophys. Res. Commun.*, *94*: 1207.
10. Amrhein, N., Deus, B., Gehrke, P., and Steinrucken, H.C. (1980). The site of the inhibition of the shikimate pathway by glyphosate. II, *Plant Physiol.*, *66*: 830.
11. Amrhein, N. (1985). Specific inhibitors as probes into the biosynthesis and metabolism of aromatic amino acids, *Recent Adv. Phytochem.*, *20*: 83.
12. Duke, S.O. (1988). *Herbicides: chemistry, degradation and mode of action*, (Kearney, P.C., and Kaufman, D.D., eds.), M. Dekker, New York, pp 20-34.
13. Kishore, G.M., and Shah, D.M. (1988). Amino acid biosynthesis inhibitors as herbicides, *Ann. Rev. Biochem.*, *57*: 627.
14. Sikorski, J.A., Anderson, K.S., Cleary, D.G., Miller, M.J., Pansegrau, P.D., Ream, J.E., Sammons, R.D., and Johnson, K.A. (1991). An enzyme-targeted herbicide discovery program based on EPSP synthase: chemical mechanism and glyphosate inhibition studies, *Chemical aspects of enzyme biotechnology: fundamentals*, (Scott, A.I., Raushel, F.M., and Baldwin, T.O., eds.), Plenum Press, New York, pp 23-39.
15. Jaworski, E. (1972). The mode of action of *N*-phosphonomethylglycine. Inhibition of aromatic amino acid biosynthesis, *J. Agric. Food Chem.*, *20*: 1195.
16. Rubin, J.L., Gaines, C.G., and Jensen, R.A. (1982). Enzymological basis for the herbicidal action of glyphosate, *Plant Physiol.*, *70*: 833.
17. Amrhein, N., Schab, J., and Steinrucken, H.C. (1980). The mode of action of the herbicide, glyphosate, *Naturwis.*, *67*: 356.
18. Smart, C.C., Johanning, D., Muller, G., and Amrhein, N. (1985). Selective overproduction of EPSPS in a plant cell culture which tolerated high doses of the herbicide glyphosate, *J. Biol. Chem.*, *260*: 16338.
19. Kishore, G.M., and Shah, D.M. (1987). Glyphosate tolerant EPSPS synthase, *Eur. Patent 293,358*.
20. Comai, L. (1988). Inhibition resistant 5-enolpyruvyl-3-phosphoshikimate synthase, production and use, *U.S. Patent 4,769,061*.
21. Haslam, E. (1974). *The shikimate pathway*, Wiley, New

York.
22. Levin, J.G., and Sprinson, B.J. (1964). Enzymic formation and isolation of EPSP, *J. Biol. Chem.*, *239*: 1142.
23. Bodinell, W.E., Vnek, J., Knowles, P.F., Sprecher, M., and Sprinson, D.B. (1971). Mechanism of EPSPS, *J. Biol. Chem.*, *246*: 6191.
24. Steinrucken, H.C., and Amrhein, N. (1984). EPSPS of *Klebsiella pneumoniae*. 2. Inhibition by glyphosate, *Eur. J. Biochem.*, *143*: 351.
25. Boocock, M.R., and Coggins, J.R. (1983). Kinetics of EPSPS inhibition by glyphosate, *FEBS Lett.*, *154*: 127.
26. Anderson, K.S., Sikorski, J.A., and Johnson, K.A. (1988). An evaluation of EPSPS binding by stopped flow and equilibrium fluorescence measurements, *Biochemistry*, *27*: 1604.
27. Castellino, S., Leo, G.C., Sammons, R.D., and Sikorski, J.A. (1988). The ^{31}P, ^{15}N and ^{13}C NMR of glyphosate: comparison of pH titrations to the herbicidal dead-end complex with EPSPS, *Biochemistry*, *28*: 3856.
28. Duncan, K., Lewendon, A., and Coggins, J.R. (1984). The purification of EPSPS from an overproducing strain of *Escherichia coli*, *FEBS Lett.*, *165*: 121.
29. Anderson, K.S., Sikorski, J.A., and Johnson, K.A. (1988). A tetrahedral intermediate in the EPSPS reaction observed by rapid quench kinetics, *Biochemistry*, *27*: 7395.
30. Anderson, D.K., Duewer, D.L., and Sikorski, J.A. unpublished results.
31. Ream, J.E., Anderson, K.S., Sammons, R.D., and Sikorski, J.A. (1988). A rapid, sensitive binding assay for studying the interaction of glyphosate chemistry with EPSPS synthase, *Plant Physiol., Supplement 91*: 377.
32. Franz, J.E. (1978). *N*-Hydroxy-*N*-phosphonomethylglycines and the herbicide use thereof, *U.S. Patent 4,084,953*.
33. Diehl, P., and Maier, L. (1988). Organic phosphorus compounds. 85. Preparation, properties and biological effects of *N*-aminoglyphosate and azaglyphosate, *Phosphorus Sulfur*, *39*: 159.
34. Ream, J.E., Anderson, K.S., Andrew, S.S., Phillion, D.P., Knowles, W.S., Snyder, K.R., and Sikorski, J.A. (1990). Biochemical and biological characterization of the potent EPSPS inhibitor *N*-aminoglyphosate, *Plant Physiol., Supplement 93*: 60.

35. Kosalapoff, G.M. (1951). The synthesis of phosphonic and phosphinic acids, *Org. React.*, *6*: 273.
36. Moedritzer, K., and Irani, R. (1966). The direct synthesis of α-aminomethylphosphonic acids. Mannich-type reactions with orthophosphorous acid, *J. Org. Chem.*, *31*: 1603.
37. Irani, R.R., and Moedritzer, K., (1966). Process for preparing organo phosphonic acids, *U.S. Patent 3,288,846.*
38. Agababyan, A.G., Gevorgyan, G.A., and Mndzhoyan, O.L. (1982). Amino acids as the amine component in the Mannich reaction, *Russ. Chem. Rev.*, *51*: 678.
39. Balthazor, T.M., and Pulwer, M.J. (1986). α-Substituted *N*-phosphonomethyliminodiacetic acid, *U.S. Patent 4,617,415.*
40. Pfliegel, T., Seres, J., Gajory, A., Daroczy, K., and Nagy, L.T. (1977). Process for the preparation of *N*-phosphonomethyl-glycine, *U.S. Patent 4,065,491.*
41. Brendel, M., Hajinoczki, M.B., Gulyas, I., Gyoker, I., Zsupan, K., Csorvassy, I., Salamon, Z., Somogyi, G., Szentiralyi, I., Timar, T., Czapary, E.B., Fodor, I., and Repasi, J. (1984). Process for the preparation of *N*-phosphonomethyl-glycine, *U.S. Patent 4,486,359.*
42. Ehrat, R. (1980). Process for the preparation of *N*-phosphonomethyl glycine, *U.S. Patent 4,237,065.*
43. Gaertner, V.R. (1975). Oxazolidinonemethylene phosphonates, *U.K. 1,482,377.*
44. Fields, D.L., and Grabiak, R.C. (1989). Amine salts of 1,4,2-oxazaphospholidine-4-acetic acid, 2-alkoxy-2-oxides, *U.S. Patent 4,889,906.*
45. Gaertner, V.R., unpublished results.
46. Smith, L.R. (1977). Process for producing *N*-phosphonomethyl glycine, *U.S. Patent 4,002,672.*
47. Franz, J.E. (1976). Process for producing *N*-phosphonomethyl glycine, *U.S. Patent 3,950,402.*
48. Hershman, A. (1976). Process for producing *N*-phosphonomethyl glycine, *U.S. Patent 3,969,398.*
49. Felthouse, T.R. (1986). Oxidation with encapsulated co-catalyst, *U.S. Patent 4,582,650.*
50. Chou, S.K. (1987). Amine oxidation using carbon catalyst having oxides removed from surface, *U.S. Patent 4,696,772.*
51. Fields, D.L., Grabiak, R.C., and Riley, D.P. (1990).

Process for producing *N*-phosphonomethylglycine, *U.S. Patent 4,898,972*.
52. Fields, D.L., Grabiak, R.C., and Riley, D.P. (1990). Process for producing *N*-phosphonomethylglycine, *U.S. Patent 4,937,376*.
53. Franz, J.E. (1976). Process for producing *N*-phosphonomethyl glycine, *U.S. Patent 3,954,848*.
54. Frazier, H.W., Smith, L.R., and Wagenknecht, J.H. (1974). Electrolytic process for producing *N*-phosphonomethyl glycine, *U.S. Patent 3,835,000*.
55. Gentilcore, M.J. (1988). Process for preparing *N,N*-diacetic acid aminomethylenephosphonic acid, *U.S. Patent 4,775,498*.
56. Balint, S., Kolonics, Z., Gaal, A., Farkas, J., Dufek, L., Horvath, S., and Karasonyi, B. (1979). *N*-Phosphonomethylglycine and its derivatives. *Belg. 875,501*.
57. Maier, L. (1981). Organic phosphorus compounds. 73. Preparation and properties of [*N*-(hydroxycarbonylmethyl)-aminomethyl] alkyl and aryl phosphinic acids and derivatives, *Phosphorus Sulfur*, *11*: 139.
58. Franz, J.E., Kaufman, R.J., and Klemm, G., unpublished results.
59. Gaertner, V.R. (1975). Process for producing *N*-phosphonomethyl glycine, *U.S. Patent 3,927,080*.
60. Parry, D.R., and Tomlin, C.D.S. (1976). Preparation of *N*-phosphonomethylglycine, *U.S. Patent 3,956,370*.
61. Felix, R.A. (1985). *O,O*-Dialkyl-*N*-(benzyl or *t*-butyl)-*N*-cyanomethyl aminomethylphosphonates, *U.S. Patent 4,525,311*.
62. Maier, L. (1982). *N*-Phosphonomethylglycine. *Eur. Pat. 55,695*.
63. Maier, L. (1981). Organic phosphorus compounds. 74. Study on the reaction of cyanomethyldichlorophosphine and 2-chloroethyldichlorophosphine with benzyl glycine and formaldehyde in acidic solution, *Phosphorus Sulfur*, *11*: 149.
64. Maier, L. (1980). Novel glycylmethylphosphinic acid derivatives, process for their production and use thereof, *U.S. Patent 4,233,056*.
65. Balthazor, T.M., and Miller, W.H. (1986). Thermal dealkylation of *N*-alkyl-*N*-phosphonomethylglycine. *Eur. Pat. 187,633*.

66. Miller, W.H., Reitz, D.B., and Pulwer, M.J. (1987). Process for the preparation of *N*-substituted aminomethylphosphonic acids. *U.S. Patent 4,657,705.*
67. Pulwer, M.J., and Gaertner, V.R. (1987). Process for preparing *N*-phosphonomethylglycine and derivatives, *U.S. Patent 4,650,613.*
68. Subramanian, N. (1984). Method for preparation of *N*-phosphonomethylglycine, *U.S. Patent 4,442,041.*
69. Muller, W.D. (1989). Process for the preparation of *N*-phosphonomethylglycine, *U.S. Patent 4,847,013.*
70. Wong, R., and Bunker, N.S. (1985). Method for preparation of *N*-phosphonomethylglycine, *U.S. Patent 4,547,324.*
71. Miller, W.H., and Neumann, T.E. (1986). Oxidative ring cleavage process, *U.S. Patent 4,587,061.*
72. Nagubandi, S. (1985). Process for preparing phosphonomethylated amino acids, *U.S. Patent 4,491,548.*
73. Nagubandi, S. (1985). Process for preparing phosphonomethylated amino acids, *U.S. Patent 4,548,760.*
74. Nagubandi, S. (1985). Preparation of phosphonomethylated amino acids, *U.S. Patent 4,548,758.*
75. Nagubandi, S. (1985). Preparation of phosphonomethylated amino acids, *U.S. Patent 4,548,759.*
76. Clavel, J.P., Corbet, J.-P., and Mulhauser, M. (1990). *N*-Sulfonomethylglycinates, process for their preparation and their use in the preparation of glyphosate-type herbicides, *Eur. Pat. 356,353.*
77. Cortes, D.A. (1990). 2-Azabicyclo[2.2.1]hept-5-ene acetic acid, derivatives thereof, and related compounds, process for the preparation of said compounds and the use of said compounds for the manufacture of *N*-phosphonomethylglycine, *U.S. Patent 4,946,993.*
78. LaCroix, G. (1985). Esters of the family of *N*-phosphonomethylglycine and their use in the preparation of known herbicides, *U.K. 2,155,476.*
79. Svetkin, Y.V., Abdrakhmanov, I.B., and Augstin, M. (1973). Cyclization of 2-chloroacetamides to 2,5-diketopiperazine and hydrolysis of these heterocyclic compounds, *Naturwiss. Reihe., 22*: 7.
80. Wong, R.Y., and Bunker, N.S. (1983). Method for preparation of *N*-phosphonomethylglycine, *U.S. Patent 4,400,330.*

81. Miller, W.H., and Taylor, W.D. (1987). Process to prepare 2,5-diketopiperazines, *U.S. Patent 4,694,081.*
82. Miller, W.H., Reitz, D.B., and Pulwer, M.J. (1989). Process for the preparation of *N*-substituted aminomethylphosphonic acids, *U.S. Patent 4,804,499.*
83. Bayer, A.C., Robbins, J.D., and Bowler, D.J. (1986). Method for preparation of salts of *N*-phosphonomethylglycine, *U.S. Patent 4,578,224.*
84. Toy, A., and Uhing, E.H. (1964). Aminomethylenephosphinic acids, salts thereof, and process for their production, *U.S. Patent 3,160,632.*
85. Smolin, E., and Rapport, L. (1959). *s-Triazines and derivatives*, Interscience, New York, pp 473-544.
86. Reynolds, D.D., and Cossar, B.C. (1971). 1,3,5-Trisubstituted hexahydrotriazines as Mannich reagents. I. Preparation of secondary aminomethyl sulfide hydrochlorides, *J. Heterocycl. Chem., 8*: 597.
87. Reynolds, D.D., and Cossar, B.C. (1971). 1,3,5-Trisubstituted hexahydrotriazines as Mannich reagents. II. Preparation of *p*-secondary aminomethyl phenols, *J. Heterocycl. Chem., 8*: 605.
88. Ratcliffe, R.W., and Christensen, B.G. (1973). Total synthesis of β-lactam antibiotics. I. α-Thioformamidodiethylphosphonoacetates, *Tetrahedron Lett.*: 4645.
89. Dutra, G.A., unpublished results.
90. Soroka, M. (1987). Selected problems of chemistry of aminophosphonic acids, *Pr. Nauk Inst. Chem. Org. Fiz. Politech. Wroclaw*: 3-92.
91. Adams, R., and Langley, W.D. (1970). Methyleneaminoacetonitrile, *Org, Syn. Coll. Vol. 1*: 355.
92. Barton, J.E.D. (1975). Preparation of *N*-phosphonomethyl glycine, *U.S. Patent 3,923,877.*
93. Robbins, J.D. (1983). Method for preparation of *N*-phosphonomethylglycine, *U.S. Patent 4,415,503.*
94. Krawiecki, C., and Michalski, J. (1960). Organophosphorus compounds of sulfur and selenium. XIII. Action of hydrogen sulfide on dialkyl and diaryl phosphorochloridites, *J. Chem. Soc.*: 881.
95. Issleib, K., Balszuweit, A., Wetzke, G., Moegelin, W., Kochmann, W., and Guenther, E. (1980). *N*-Phosphonomethylglycine and its diesters, *E. Ger. Pat. 141,929.*

96. Leber, J.-P. (1977). *N*-[*O*-(β-Cyanoethyl)phosphonomethyl]glycines and derivatives, *U.S. Patent 4,025,331.*
97. Purdum, W.R. (1983). Mono and diesters of *N*-phosphonomethylglycinates as herbicides, *U.S. Patent 4,395,275.*
98. Purdum, W.R. (1983). Diesters of *N*-alkyl substituted amino methyl phosphonic acid useful as herbicides, *U.S. Patent 4,391,625.*
99. Purdum, W.R. (1984). Process for preparing monoesters and diesters of *N*-alkyl substituted amino methyl phosphonic acid, *U.S. Patent 4,442,044.*
100. Scharf, D.J. (1976). Mechanism in organophosphorus chemistry. II. Reaction of trialkyl phosphite esters with *N*-methylol carboxamides and sulfonamides, *J. Org. Chem., 41*: 28.
101. Purdum, W.R., private communication.
102. Dutra, G.A. (1978). Benzyl and aryl esters of *N*-phosphonomethyl glycines, herbicidal compositions and use thereof, *U.S. Patent 4,120,689.*
103. Myers, H. (1967). Lubricating oils containing phosphorus products, *U.S. Patent 3,329,742.*
104. Dutra, G.A. (1977). Preparation of *N*-phosphonomethyl glycine, *U.S. Patent 4,053,505.*
105. Dutra, G.A. (1978). *O*-Aryl-*N*-phosphonomethylglycinonitriles and the herbicidal use thereof, *U.S. Patent 4,067,719.*
106. Dutra, G.A. (1978). Process for preparing *O*-aryl-*N*-phosphonomethylglycinonitriles, *U.S. Patent 4,083,898.*
107. Dutra, G.A. (1978). *N,N'*-Methylene-bis-[*O,O*-diaryl-*N*-phosphonomethylglycinonitriles], *U.S. Patent 4,089,671.*
108. Sikorski, J.A., Mischke, D., and Dutra, G.A. (1986). Esters of *N,N'*-methylene-bis-[*N*-(diaryloxy-phosphinylmethyl)-glycine] as herbicides, *U.S. Patent 4,601,744.*
109. Dutra, G.A., and Sikorski, J.A. (1982). *N*-Nitroso-*N*-phosphonomethylglycine esters and the herbicidal use thereof, *U.S. Patent 4,322,239.*
110. Dutra, G.A., and Sikorski, J.A. (1982). *N*-Nitroso-*N*-phosphonomethylglycinonitrile esters and the herbicidal use thereof, *U.S. Patent 4,322,238.*
111. Dutra, G.A., and Sikorski, J.A. (1987). Alkyl *N*-arylsulfenyl-*N*-diaryloxy-phosphinylmethylglycinates, *U.S. Patent 4,666,500.*
112. Sikorski, J.A., and Hoobler, M.A. (1984). Herbicidal ester

derivatives of *N*-alkylthio and *N*-cycloalkylthio-*N*-phosphonomethylglycinonitrile, *U.S. Patent 4,445,929.*

113. Dutra, G.A., and Sikorski, J.A. (1983). Alkyl *N*-arylsulfenyl-*N*-diaryloxy-phosphinylmethylglycinates, *U.S. Patent 4,395,374.*
114. Dutra, G.A., and Sikorski, J.A. (1981). Ester derivatives of *N*-arylthio-*N*-phosphonomethylglycinonitrile, *U.S. Patent 4,300,943.*
115. Sikorski, J.A., and Curtis, T.G. (1984). Thiosulfenamide derivatives of *N*-phosphonomethylglycine triesters as herbicides, *U.S. Patent 4,428,765.*
116. Sikorski, J.A., and Curtis, T.G. (1983). Thiosulfenamide derivatives of *N*-phosphonomethylglycinonitriles as herbicides, *U.S. Patent 4,395,276.*
117. Sikorski, J.A., and Hoobler, M.A. (1984). Herbicidal aminosulfenamide derivatives of *N*-phosphonomethylglycine triesters, *U.S. Patent 4,445,928.*
118. Sikorski, J.A., and Hoobler, M.A. (1984). Aminosulfenamide derivatives of *N*-phosphonomethylglycinonitriles as herbicides, *U.S. Patent 4,433,996.*
119. Sikorski, J.A., and Hoobler, M.A. (1983). Esters of *N*-arylsulfinyl-*N*-phosphonomethylglycinates as herbicides, *U.S. Patent 4,405,356.*
120. Sikorski, J.A., and Hoobler, M.A. (1983). *N*-Arylsulfinyl-*N*-phosphonomethylglycinonitriles, *U.S. Patent 4,407,764.*
121. Sikorski, J.A., and Hoobler, M.A. (1985). Unsymmetrical aminosulfinamide derivatives of *N*-phosphonomethylglycine triesters, herbicidal compositions and use, *U.S. Patent 4,519,832.*
122. Sikorski, J.A., and Hoobler, M.A. (1984). Unsymmetrical aminosulfinamide derivatives of *N*-phosphonomethylglycinonitrile, herbicidal compositions and use, *U.S. Patent 4,488,894.*
123. Sikorski, J.A., and Hoobler, M.A. (1985). Process for preparing thiosulfenamide derivatives of *N*-phosphonomethylglycinonitriles, *U.S. Patent 4,508,663.*
124. Singh, R.K. (1984). *N*-Halo phosphonomethylamine derivatives as herbicides, *U.S. Patent 4,461,639.*
125. Issleib, K., Moegelin, W., Balszuweit, A., Thust, U., Guenther, E., and Pallas, M. (1983). Process for synthesizing *N*-substituted aminomethylalkyl and aryl phosphinic acids and their derivatives, *E. Ger. Pat. 205,167.*

126. Issleib, K., and Moegelin, W. (1986). *N*-(Phosphinomethyl)amino acids and *N*-bis-(phosphinomethyl)amino acids and their esters, *Synth. React. Met.-Org. Chem.*, *16*: 645.
127. Issleib, K., Moegelin, W., and Balszuweit, A. (1985). *N*-(Carboxyphosphinomethyl) amino acids as herbicides and plant growth regulators. *E. Ger. Pat. 228,263.*
128. Singh, R.K. (1984). *N*-Substituted *N*-(phosphonomethyl) aminoethanal derivatives as herbicides, *U.S. Patent 4,444,580.*
129. Felix, R.A. (1984). Method for preparation of *N*-phosphonomethylglycine, *U.S. Patent 4,429,124.*
130. Corbet, J.-P. (1988). Preparation of herbicides containing a phosphonate group from intermediate benzoxazines, *U.S. Patent 4,755,614.*
131. Shono, T., Matsumura, Y., and Hamaguchi, H. (1975). Electroorganic chemistry. XX. Anodic oxidation of carbamates, *J. Am. Chem. Soc.*, *97*: 4264.
132. Shono, T., Matsumura, Y., and Tsubata, K. (1981). A new carbon-phosphorus bond forming reaction and synthesis of aminoalkylphosphonic acid derivatives, *Tetrahedron Lett.*, *22*: 3249.
133. Chupp, J.P., Olin, J.F., and Landwehr, H.K. (1969). Structural effects influencing rotational isomerism and alkylation properties in some α-haloacetanilides, *J. Org. Chem.*, *34*: 1192.
134. Engel, R. (1988). *Synthesis of carbon-phosphorus bonds*, CRC Press, Boca Raton, FL.
135. Seyferth, D., and Marmor, R.S. (1970). Dimethyl diazomethylphosphonate its preparation and reactions, *Tetrahedron Lett.*: 2493.
136. Grobelny, D. (1989). A convenient synthesis of aminomethylphosphonous acid, *Synth. Commun.*, *19*: 1177.
137. Felix, R.A. (1984). Method for preparation of *N*-phosphonomethylglycine, *U.S. Patent 4,425,284.*
138. Felix, R.A. (1984). Method for preparation of *N*-phosphonomethylglycine, *U.S. Patent 4,427,599.*
139. Felix, R.A. (1986). Method for preparation of *N*-phosphonomethylglycine, *U.S. Patent 4,569,802.*
140. Arbuzov, B.A., and Bogonostseva, N.P. (1957). Syntheses of some phosphone sulfides and phosphone sulfones, *J. Gen. Chem. U.S.S.R., Engl. Transl.*, *27*: 2419.
141. Comasseto, J.V., and Petragnani, N. (1978). The reaction of

selenophosphonates with carbonyl compounds. Vinyl selenides, *J. Organomet. Chem.*, *152*: 295.
142. Stauffer Chemical Co. (1985). Manufacture of phosphonomethylated amino acid, *Jpn. 85 58,996.*
143. Mirviss, S.B., and Weil, E.D. (1987). Process for the formation of phosphonoalkylated amino acids, *U.S. Patent 4,661,298.*
144. Noyce, D.S., and Virgilio, J.A. (1972). The synthesis and solvolysis of 1-phenylethyl disubstituted phosphinates, *J.Org. Chem.*, *37*: 2643.
145. Creary, X., Geiger, C.C., and Hilton, K. (1983). Mesylate derivatives of α-hydroxy phosphonates. Formation of carbocations adjacent to the diethylphosphonate group, *J. Am. Chem. Soc.*, *105*: 2851.
146. Creary, X., Geiger, C.C., and Hilton, K. (1983). Carbocation formation adjacent to the diethylphosphonate group, *Prepr.- Am. Chem. Soc., Div. Pet. Chem.*, *28*: 119.
147. Holy, A., and Rosenberg, I. (1982). Preparation of 5'-*O*-phosphonomethyl analogs of nucleoside-5'-phosphates, 5'-diphosphates and 5'-triphosphates, *Collect. Czech. Chem. Commun.*, *47*: 3447.
148. Petrov, K.A., Treschchalina, L.V., and Chizhov, V.M. (1977). Synthesis and properties of α-substituted methyl phosphonates, *Zh. Obshch. Khim.*, *47*: 2741.
149. Phillion, D.P., and Andrew, S.S. (1986). Synthesis and reactivity of diethyl phosphonomethyl triflate, *Tetrahedron Lett.*, *27*: 1477.
150. Phillion, D.P. (1988). (Phosphonomethyl)trifluoromethyl sulfonates, *U.S. Patent 4,740,608.*
151. Franz, J.E., and Kaufman, R.J. (1985). Amide derivatives of *N*-trifluoroacetyl-*N*-phosphonomethylglycine, herbicidal compositions and use, *U.S. Patent 4,496,389.*
152. Franz, J.E., and Kaufman, R.J. (1985). *N*-(Aminophosphinylmethyl) glycine derivatives, *U.S. Patent 4,545,804.*
153. Kaufman, R.J. (1981). *N*-(Substituted carbonyl) derivatives of *N*-phosphinylmethylglycinates and the herbicidal use thereof, *U.S. Patent 4,300,942.*
154. Franz, J.E., and Kaufman, R.J. (1983). Amido and hydrazido derivatives of *N*-trifluoroacetyl-*N*-phosphinothioylmethylglycine esters, *U.S. Patent 4,421,549.*
155. Franz, J.E., and Kaufman, R.J. (1987). Hydrazido

derivatives of *N*-phosphinothioylmethylglycine esters, *U.S. Patent 4,652,297.*
156. Bayer, E., Gugel, K.H., Haegele, K., Hagenmeier, H., Jessipow, S., Koenig, W.A., and Zahner, H. (1972). Stoffwechselprodukte von Mikroorganismen. Phosphinothricin und Phosphinothricyl-Alanyl-Alanin, *Helv. Chim. Acta*, *55*: 224.
157. Kondo, Y., Shomura, T., Ogawa, Y., Tsuruoka, T., Watanabe, H., Tetsukawa, K., Suzuki, T., Moriya, C., Yoshida, J., Inoue, S., and Niida, T. (1973). New antibiotic SF-1293. I. Isolation and physiochemical and biological characteristization of SF-1293 substance, *Meiji Seika Kenkyu Nempo*, *13*: 34.
158. Ogawa, Y., Tsuruoka, T., Inoue, S., and Niida, T. (1973). New antibiotic SF-1293. II. Chemical structure of antibiotic SF-1293, *Meiji Seika Kenkyu Nempo*, *13*: 42.
159. Omura, S., Hinotozawa, K., Imamura, N., and Murata, M. (1984). The structure of phosalacine, a new herbicidal antibiotic containing phosphinothricin, *J. Antibiotics*, *37*: 939.
160. Mastalerz, P. (1959). Synthesis of phosphinic acids related structurally to glutamic acid, *Rocz. Chem.*, *33*: 985.
161. Mastalerz, P. (1959). Inhibition of glutamine synthetase by phosphonic analogs of glutamic acid, *Arch. Immunol. Exp. Therapy*, *7*: 201.
162. Acaster, M.A., and Weitzman, P.D.J. (1985). Kinetic analysis of glutamine synthetases from various plants, *FEBS Lett.*, *189*: 241.
163. Ridley, S.M., and McNally, S.F. (1985). Effects of phosphinothricin on the isoenzymes of glutamine synthetase isolated from plant species which exhibit varying degrees of susceptibility to the herbicide, *Plant Science*, *39*: 31.
164. Colanduoni, J.A., and Villafranca, J.J. (1986). Inhibition of *Escherichia coli* glutamine synthetase by phosphinothricin, *Bioorg. Chem.*, *14*: 163.
165. Wild, A., Sauer, H., and Ruhle, W. (1987). The effect of phosphinothricin (Glufosinate) on photosynthesis. I. Inhibition of photosynthesis and accumulation of ammonia, *Z. Naturforsch.*, *42C*: 263.
166. Sauer, H., Wild, A., and Ruhle, W. (1987). The effect of phosphinothricin (Glufosinate) on photosynthesis. II. The causes of the inhibition of photosynthesis, *Z. Naturforsch.*,

42C: 270.

167. Logusch, E.W., Walker, D.M., McDonald, J.F., and Franz, J.E. (1989). Substrate variability as a factor in enzyme inhibitor design: inhibition of ovine brain glutamine synthetase by α- and γ-substituted phosphinothricins, *Biochemistry*, *28*: 3043.
168. Meister, A. (1978). Inhibition of glutamine synthetase and γ-glutamylcysteine by methionine sulfoximine and related compounds, *Enzyme-activated irreversible inhibitors*, (Seiler, N., Jung, M.J., and Koch-Weser, J., eds.), Elsevier, New York, pp 187-210.
169. Smith, A.E. (1988). Persistence and transformation of the herbicide [^{14}C]glufosinate-ammonium in prairie soils under laboratory conditions, *J. Ag. Food Chem.*, *36*: 393.
170. Smith, A.E. (1989). Transformation of the herbicide [^{14}C]glufosinate in soils, *J. Ag. Food Chem.*, *37*: 267.
171. Meister, A. (1968). The specificity of glutamine synthetase and its relationship to substrate conformation at the active site, *Advan. Enzymol.*, *31*: 183.
172. Walker, D.M., McDonald, J.F., and Logusch, E.W. (1987). Synthesis of D,L-γ-hydroxyphosphinothricin, a potent new inhibitor of glutamine synthetase, *J. Chem. Soc., Chem. Commun.*: 1710.
173. Logusch, E.W., Walker, D.M., McDonald, J.F., Leo, G.C., and Franz, J.E. (1988). Synthesis of α- and γ-substituted phosphinothricins: potent new inhibitors of glutamine synthetase, *J. Org. Chem.*, *53*: 4069.
174. Walker, D.M., McDonald, J.F., Franz, J.E., and Logusch, E.W. (1990). Design and synthesis of γ-oxygenated phosphinothricins as inhibitors of glutamine synthetase, *J. Chem. Soc., Perkin Trans. I*: 659.
175. Logusch, E.W., Walker, D.M., McDonald, J.F., Franz, J.E., Villafranca, J.J., DiIanni, C.L., Colanduoni, J.I., Li, B., and Schineller, J.B. (1990). Inhibition of *Escherichia coli* glutamine synthetase by α- and β-substituted phosphinothricins, *Biochemistry*, *29*: 366.
176. Johnson, C.R., Boettcher, B.R., Cherpeck, R.E., and Dolson, M.G. (1990). Design and synthesis of potent inhibitors of glutamine synthetase, *Bioorg. Chem.*, *18*: 154.

177. Logusch, E.W., Walker, D.M., McDonald, J.F., and Franz, J.E. (1991), Inhibition of plant glutamine synthetases by substituted phosphinothricins, *Plant Physiol., 95*: 1057.
178. Komkov, I.P., Karavanov, K.V., and Ivin, S.Z. (1959). New methods of preparation of alkyldichlorophosphines and dialkylchlorophosphines, *Zh. Obshch. Khim., 28*: 2963.
179. *Methoden der Organischen Chemie, Vol. XII/1* (1964) (Houben-Weyl), (Muller, E., ed.), Georg Theime Verlag, Stuttgart, p 302.
180. Fild, M., and Schmutzler, R. (1972). *Halo- and pseudo-halophosphosphines. Organic Phosphorus Compounds, Vol. 4*, (Kosolapoff, G.M., and Maier, L., eds.), Wiley, NewYork, pp 75-154.
181. Schliebs, R., and Kaiser, H. (1959). Verfahren zur Herstellung von Methyldichlorophosphin, *Ger. Appl. 1,119,860.*
182. Pianfetti, J.A., and Quin, L.D. (1962). Formation of phosphonous dichlorides by alkylation of phosphorus trichloride with methane or ethane, *J. Am. Chem. Soc., 84*: 851.
183. Schafer, S., Gehrmann, K., Ohorodnik, A., Steil, K.-H., Reichmann, W., and Bylsma, F. (1978). Production of methyldichlorophosphane, *U.S. Patent 4,104,304.*
184. Gehrmann, K., Ohorodnik, A., Steil, K.-H., and Schafer, S. (1978). Production of methyldichlorophosphane, *U.S. Patent 4,101,573.*
185. Ohorodnik, A., Gehrmann, K., Schafer, S., and Mainski, A. (1978). Production of pure methyldichlorophosphane, *U.S. Patent 4,104,299.*
186. Gehrmann, K., Ohorodnik, A., Rosenthal, J., and Schafer, S. (1978). Process for making methyldichlorophosphane, *U.S. Patent 4,518,538.*
187. Weissermel, K., Kleiner, H.-J., Finke, M., and Felcht, U.-H. (1981). Advances in organophosphorus chemistry based on dichloro(methyl)phosphane, *Angew. Chem., Int. Ed. Engl., 20*: 223.
188. *Methoden der Organischen Chemie, Vol. XII/1* (1964) (Houben-Weyl), (Muller, E., ed.), Georg Theime Verlag, Stuttgart, pp 318-319.
189. *Methoden der Organischen Chemie, Vol. XII/1* (1964) (Houben-Weyl), (Muller, E., ed.), Georg Theime Verlag, Stuttgart, pp 320-323.
190. Lohmar, E., Ohorodnik, A., Gehrmann, K., Stutzke, P., and Staendeke, H. (1977). Production of phosphorus-con-

taining esters, *Brit. Pat. 1,461,376.*
191. *Methoden der Organischen Chemie, Vol. XII/1* (1964) (Houben-Weyl), (Muller, E., ed.), Georg Theime Verlag, Stuttgart, pp 324-331.
192. Miles, J.A., Balthazor, T.M., Nufer, H.L., and Beeney, M.T. (1979). Improved, reproducible procedures for the preparation of diethyl methylphosphonite, *Org. Prep. Proced. Int., 11*: 11.
193. Balthazor, T.M., and Flores, R.A. (1979). Dipolar cycloadditions of an acetylenic phosphinate, *J. Org. Chem., 45*: 529.
194. *Methoden der Organischen Chemie, Vol. XII/1* (1964) (Houben-Weyl), (Muller, E., ed.), Georg Theime Verlag, Stuttgart, pp 258-259.
195. Crofts, P.C. (1973). *Phosphinic acids and derivatives. Organic phosphorus compounds, Vol. 6*, (Kosolapoff, G.M., and Maier, L., eds.), Wiley, New York, pp 1-211.
196. Kirby, A.J., and Warren, S.G. (1967). Free radical reactions at phosphorus, *The organic chemistry of phosphorus*, Elsevier, New York, pp 158-183.
197. Gruszecka, E., Soroka, M., and Mastalerz, P. (1979). Preparation of D,L-phosphinothricin by Strecker reaction, *Pol. J. Chem., 53*: 937.
198. Suzuki, A., Tsuruoka, T., Mizutani, K., and Inoue, S. (1981). New synthesis of 2-amino-4-hydroxy-4-(methyl-phosphinoyl)butyric acid and some analogs, *Meiji Seika Kenkyu Nempo, 20*: 33.
199. Zeiss, H.-J., and Mildenberger, H. (1986). Phosphorus-containing α-aminonitriles and a process for their preparation, *Ger. Appl. DE 3,508,573 A1.*
200. Finke, M., and Mundnich, R. (1985). Phosphorus-containing cyanohydrin derivatives, *U.S. Patent 4,521,348.*
201. Lachhein, S., and Mildenberger, H. (1986). Process for the preparation of phosphorus-containing cyanohydrin derivatives, *U.S. Patent 4,599,207.*
202. Zeiss, H.-J. (1989). Verfahren zur Herstellung Phosphorhaltige L-Aminosauren sowie ihrer Ester und *N*-Derivative, *Eur. Pat. Appl. 346,658.*
203. Engel, R. (1987). Nucleophilic displacement at carbon by phosphorus, *Synthesis of carbon-phosphorus bonds*, CRC Press, Boca Raton, FL, pp 7-75.
204. Ogawa, Y., Yoshida, H., Inoue, S., and Niida, T. (1973).

New antibiotic SF-1293. III. Synthesis of a new phosphorus-containing amino acid, a component of antibiotic SF-1293, *Meiji Seika Kenkyu Nempo*, *13*: 49.

205. Gruszecka, E., Mastalerz, P., and Soroka, M. (1975). New synthesis of phosphinothricin and analogues, *Rocz. Chem.*, *49*: 2127.
206. Wasielewski, C., and Antczak, K. (1981). Aminophosphonic acids. XVI. A new and facile synthesis of phosphinothricin and 2-amino-4-phosphonobutanoic acid, *Synthesis*: 540.
207. Logusch, E.W. (1986). Facile synthesis of D,L-phosphinothricin from methyl 4-bromo-2-phthalimidobutyrate, *Tetrahedron Lett.*, *27*: 5935.
208. Logusch, E.W. (1988). 4-Phosphorus-2-phthalimidobutyrate intermediates, *U.S. Patent 4,764,620*.
209. Logusch, E.W. (1988). Preparation of 2-amino-4-phosphinylbutanoic acids, including herbicidal phosphinothricin, *Eur. Pat. Appl. 265,412*.
210. Logusch, E.W. (1988). A simple preparation of *S*-alkyl homocysteine derivatives: *S*-phosphonomethyl homocysteines as inhibitors of glutamine synthetase, *Tetrahedron Lett.*, *29*: 6055.
211. Gross, H., and Gnauk, T. (1976). Eine einfache Synthese fur D,L-Phosphinothricin, *J. prakt. Chem.*, *318*: 157.
212. Ivin, S.Z., and Karavanov, K.V. (1959). Method of preparation of 2-chloroalkyl alkylphosphinates, *Zh. Obshch. Khim.*, *29*: 3456.
213. *Methoden der Organischen Chemie, Vol. XII/1* (1964) (Houben-Weyl), (Muller, E., ed.), Georg Theime Verlag, Stuttgart, pp 247-262.
214. Engel, R. (1987). Trivalent phosphorus addition to carbonyl carbons, *Synthesis of carbon-phosphorus bonds*, CRC Press, Boca Raton, FL, pp 77-136.
215. Engel, R. (1987). Conjugate addition reactions of trivalent phosphorus reagents, *Synthesis of carbon-phosphorus bonds*, CRC Press, Boca Raton, FL, pp 137-164.
216. Tsuruoka, T., Suzuki, A., Tachibana, K., Mizutani, K., Sekizawa, Y., Inouye, S., and Takematsu, T. (1981). Process for preparing D,L-2-amino-4-methylphosphinobutyric acid, *U.S. Patent 4,264,532*.
217. Maier, L., and Rist, G. (1983). Organic phosphorus compounds. 77. Synthesis and properties of phosphinothricin homologs and analogs, *Phosphorus Sulfur*, *17*: 21.

218. Soroka, M., and Mastalerz, P. (1976). The synthesis of phosphonic and phosphinic analogs of aspartic acid and asparagine, *Rocz. Chem.*, *50*: 661.
219. Minowa, N., Fukatsu, S., Niida, T., Takada, M., and Sato, K. (1983). A practical synthesis of (+)-phosphinothricin, *Tetrahedron Lett.*, *24*: 2391.
220. Minowa, N., Hirayama, M., and Fukatsu, S. (1984). Asymmetric synthesis of (+)-phosphinothricin and (+)-2-amino-4-phosphonobutyric acid, *Tetrahedron Lett.*, *25*: 1147.
221. Schollkopf, U., Busse, U., Acker, R.-D., and Meyer, (1986). Verfahren zur Herstellung von weitgehend reinen Enantiomeren von (3-Amino-3-carboxy-propyl)-alkyl-phosphinsaurederivativen, neue Pyrazinderivative und ihre Verwendung als Herbicide und Bioregulatoren, *Ger. Pat. Appl. DE 3,525,267 A1*.
222. Tanaka, M., Sakakura, T., and Takigawa, S. (1989). Novel organic phosphorus derivatives and manufacturing processes therefore, *Eur. Pat. Appl. 336,558*.
223. Zeiss, H.-J. (1987). An efficient asymmetric synthesis of both enantiomers of phosphinothricin, *Tetrahedron Lett.*, *28*: 1255.
224. Zeiss, H.-J. (1987). Process for the preparation of L-homoalanin-4-yl(methyl)-phosphinic acid and its alkyl esters, *U.S. Patent 4,777,279*.
225. Baillie, A.C., Wright, B.J., Wright, K., and Earnshaw, C.G. (1983). Phosphinic acid derivatives, *U.S. Patent 4,399,287*.
226. Mildenberger, H., and Tammer, T. (1984). Verfahren zur Herstellung von Phosphinothricin, *Eur. Pat. Appl. 121,226*.
227. Zeiss, H.-J. (1990). Process for the preparation of L-phosphinothricin (derivatives) and also of their alkyl esters, *U.S. Patent 4,992,006*.
228. Zeiss, H.-J. (1991). Enantioselective synthesis of both enantiomers of phosphinothricin *via* asymmetric hydrogenation of α-acylamido acrylates, *J. Org. Chem.*, *56*: 1783.

CHAPTER 16

PHOSPHORUS CONTAINING INSECTICIDES

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I. Introduction

Since Schrader's finding of insecticidal organophosphorus (OP) compounds in the 1930's, a large number of phosphorus containing insecticides have been developed and used all over the world, because of their high efficiency and low persistency in the natural environment in comparison with organochlorine insecticides. In addition to insecticides, a variety of bioactive OP compounds are known as acaricides, nematicides, fungicides, bactericides, herbicides, rodenticides, antiviral agents, plant growth regulators, insect chemosterilants, and insecticide synergists. They are chemically classified into several types of phosphorus compounds as exemplified in Table I. All the insecticides and many other agrochemicals are neutral ester or amide derivatives of phosphorus acids having a phosphoryl or thiophosphoryl group. Some acids, phosphonium salts, and trivalent phosphorus compounds are also utilized for miscellaneous agrochemicals, particularly herbicides and plant growth regulators. It is interesting to note that the combination of three or four groups or atoms attached to a phosphorus atom yield such a variety of biological activities.

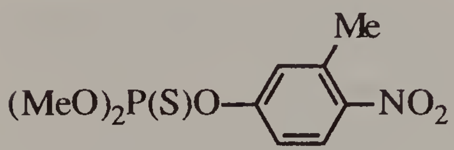
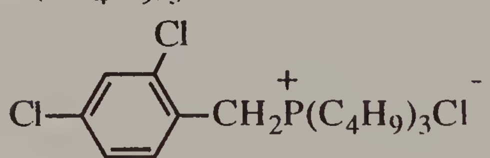
This Chapter deals mainly with OP insecticides and also refers briefly to some other OP agrochemicals. Some monographs on the chemistry and biochemistry of OP pesticides have been published.[1-3] Comprehensive texts and a dictionary on OP compounds have also been published.[4-6]

II. Syntheses of Phosphorus(V) Oxyacid Derivatives

Almost all phosphorus compounds utilized as agrochemicals, particularly insecticides, are esters, amides, or anhydrides of P(V) oxyacids including phosphoric, phosphonic, and phosphinic acids and a variety of their sulfur analogs. A great number of phosphorus acid derivatives have been synthesized and more than one hundred of them have been utilized as agrochemicals. The combinations of four groups or atoms attached to a phosphorus are extremely large. Very general reactions important for the syntheses of phosphorus

pesticides are briefly described here. For details, readers are referred to more comprehensive treatments.[1-5]

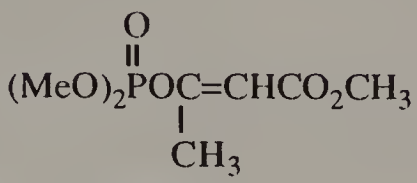
Table 1. Examples of useful organophosphorus compounds I = insecticide; F = fungicide; H = herbicide; PGR = plant growth regulator

Structure	Name	Use
$(MeO)_2P(O)OCH{=}CCl_2$	dichlorvos	I
	fenitrothion	I
$(MeO)_2P(S)SCHCO_2Et$ (with CH_2CO_2Et on the CH)	malathion	I
$(i\text{-}PrO)_2P(O)SBz$	iprobenfos	F
$MeOP(O)NHCOCH_3$ (with SMe on P)	acephate	I
$(MeO)_2P(O)CH(OH)CCl_3$	trichlorfon	I
$H_2O_3PCH_2NHCH_2CO_2H$	glyphosate	H
$MeP(O)CH_2CH_2CH(NH_2)CO_2H$ (with OH on P)	glufosinate	H
$P(SC_4H_9)_3$	merphos	PGR
	chlorphonium	PGR

A. Orthophosphate Esters

Vinyl phosphates are most important in this class. They are readily prepared by the Perkow reaction. The insecticide mevinphos (1) is synthesized by the Perkow reaction from trimethyl phosphite and methyl α-chloroacetoacetate. The *E*-isomer, which has more potent insecticidal activity than the *Z*-isomer, is preferentially obtained.[7] On the other hand the sodium enolate of methyl acetoacetate reacts with dimethyl phosphorochloridate to give almost exclusively the *Z*-isomer.[8] The rearrangement reactions of

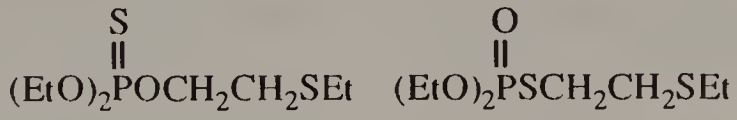
α-hydroxyalkyl phosphonates are also utilized to form vinyl phosphates as exemplified by the production of dichlorvos from trichlorfon.[9]



mevinphos (1)

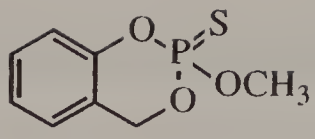
B. Phosphorothionate Esters

A phosphorothionate triester is generally prepared from an appropriate phosphorochloridothionate and a hydroxy compound in the presence of a dehydrochlorinating agent in an organic solvent. The *O*-methyl ester bond is relatively unstable, readily causing thermal rearrangement into the *S*-methyl ester and then demethylation by tertiary amines occurs. Since the thiono-thiolo isomerization occurs more readily in phosphorothionates having a sulfide group at the β-position, the ordinary preparation of demeton is a mixture (7:3) of the thiono form (demeton-O) (2) and thiolo form (demeton-S) (3). This isomerization may proceed through a cyclic sulfonium intermediate.[10]

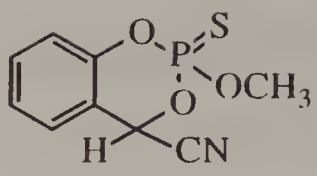


demeton-O (2) demeton-S (3)

In certain cases an aqueous alkaline solution is more effective than a base-organic solvent system for the condensation. Salathion (4) is smoothly prepared by this procedure.[11a,b] Salathion is also synthesized from methyl *o*-formylphenyl phosphorochloridothionate by reduction with sodium borohydride and subsequent intramolecular cyclization in an aqueous alkaline solution.[12] When potassium cyanide is used in place of sodium borohydride, the 4-cyano derivative (5) is produced.[12]



salithion (4)



(5)

C. Phosphorothiolate Esters

Several methods are available for the synthesis of phosphorothiolates:

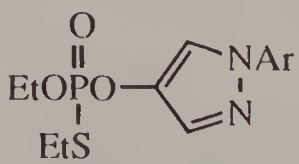
1. Reaction of phosphorochloridates and mercaptans: Since alkylation also occurs, this method is rarely used for phosphorothiolate synthesis. Edifenphos (6), however, is prepared by this reaction from ethyl phosphorodichloridate and thiophenol.[13]

2. Alkylation of dialkyl phosphorothioate ions: Ambident anions having O and S react with haloalkanes selectively at the soft base S. Iprobenfos is prepared by this method without formation of the phosphorothionate isomer.[14]

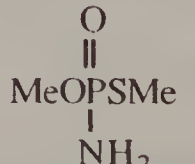
3. Reaction between phosphites and sulfenyl chlorides: Pyraclofos (7) is prepared by the Michaelis-Arbuzov reaction.[15]

4. Isomerization of phosphorothionates: The Pistschimuka reaction of phosphorothionates and haloalkanes can be used for preparation of methamidophos (8).[16] However, realkylation after dealkylation of the phosphorothionate gives a better result as exemplified by the preparation of MTBO (9) from salithion.[17] For the dealkylation soft nucleophiles such as NaI, NaSCN, NaSR, Na_2S, and $KS_2CN(CH_3)_2$ can be used. Since iodide often causes further reactions with the resultant alkyl iodide, sulfur nucleophiles are preferable.

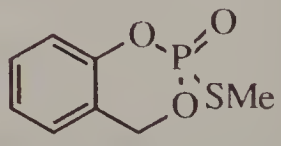
edifenphos (6)



Ar = *p*-Cl-C_6H_5
pyraclofos (7)



methamidophos (8)



MTBO (9)

Besides these methods, oxidations of phosphorothiolate esters and thiophosphites and the addition of phosphorylsulfenyl chloride to unsaturated hydrocarbons are possible.

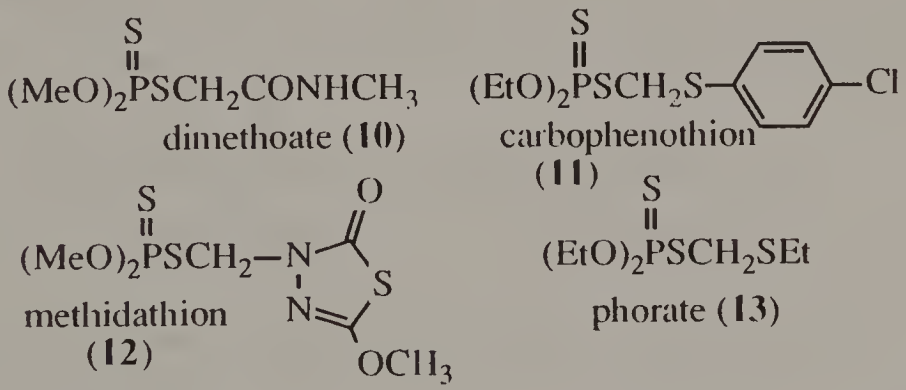
D. Phosphorothiolothionate Esters

Phosphorothiolothionates are generally synthesized from *O,O*-dialkyl hydrogen phosphorodithioates through the formation of a PS-C bond by: 1) alkylation with haloalkanes; 2) addition to aldehydes; 3) addition to alkenes. In addition they are also synthesized by P-S bond formation.

1. Alkylation of *O,O*-dialkyl phosphorodithioates: An example is the synthesis of dimethoate (**10**). *N*- or *S*-Halomethyl compounds are used as intermediates to prepare P-S-C-N (or S) type compounds as exemplified by the synthesis of carbophenothion (**11**). The intermediates are prepared by the addition of an appropriate NH or SH compound to formaldehyde, followed by chlorination of the addition product methylol. However, the final ester product methidathion (**12**), for example, can be prepared not only from the chloromethyl intermediate, but also from the methylol without the isolation of any intermediates.[18]

2. Addition of *O,O*-dialkyl phosphorodithioate to aldehydes: The addition product of an *O,O*-dialkyl hydrogen phosphorodithioate to a carbonyl compound may condense with a mercaptan to form a methylene bridge between two sulfur atoms as exemplified by phorate (**13**)[19]

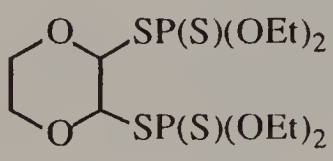
3. Addition of *O,O*-dialkyl phosphorodithioates to alkenes: A typical example of this reaction is the synthesis of malathion from diethyl maleate.[1] A small amount of base is used as a catalyst and hydroquinone is added to the reaction mixture to prevent the polymerization of the maleate.



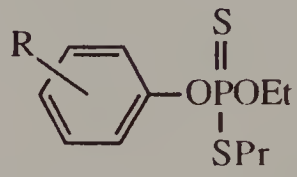
Pure diethyl hydrogen phosphorodithioate adds to unsymmetric alkenes contrary to Markovnikov's rule because of the presence of small amounts of peroxides in ordinary alkene preparations. Crude diethyl hydrogen phosphorodithioate prepared from P_2S_5 and ethanol gives normal addition product because

crude preparations contain a reducing agent, P_4S_3, which destroys the peroxides.[20] It should be noted that crude preparations of diethyl hydrogen phosphorodithioate may also contain toxic phosphorus compounds such as *O,S,S*-trimethyl phosphorodithiolate.[21] In an analogous way bis(diethoxyphosphonothioyl) disulfide adds to *p*-dioxene by a catalytic action of iodine to give the insecticide dioxathion (**14**) as a mixture of *cis* and *trans* isomers in a 2:3 ratio.[22]

4. Formation of P-S bond: The direct esterification of mercaptide with dialkyl phosphorochloridothionate often causes dealkylation. However, some unsymmetric OP insecticides as prothiofos (**15b**) and sulprofos (**15a**) are synthesized by the direct esterification of a mercaptide.[23]

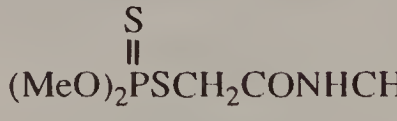


dioxathion (**14**)



sulprofos (R=*p*-MeS) (**15a**)
prothiofos (R=2,4-Cl_2) (**15b**)

The reaction of dialkyl phosphorothioites with sulfenyl chlorides is particularly useful for P-S bond formation in *S*-aryl esters. Alkyl thiosulfate monoesters and thiocyanates undergo similar reactions and can be applied as alternative methods to synthesize dimethoate (**16**) and disulfoton (**17**).[1]



dimethoate (**16**)

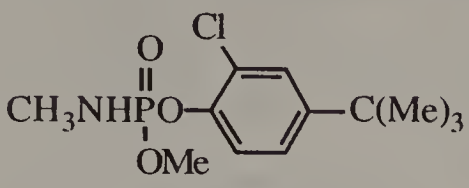
disulfoton (**17**)

E. Phosphoramidic Acid Derivatives

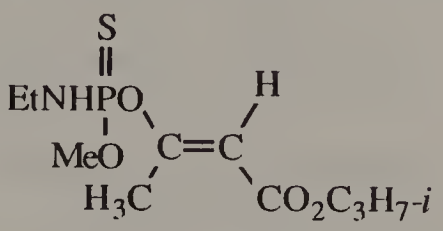
The P-N bond is generally synthesized by the reactions of amines with phosphoryl chlorides or trivalent phosphorus compounds.

1. Reaction of phosphoryl chlorides with amines: From phosphoramid(othio)ic chlorides prepared from amines and (thio)-phosphoryl chloride, any phosphoramidates may be produced according to the above mentioned reactions for ester formation as exemplified by crufomate (**18**). However, a P-N bond is usually

introduced at the final step of the reaction sequence, such as in the vinyl phosphoramidothionate insecticide propetamphos (**19**).[24]



crufomate (**18**)



propetamphos (**19**)

When the enolic metal salt of acetoacetate ester is used in reaction with $PSCl_3$, the *Z*- isomer is almost exclusively obtained, whereas the tetrabutylamm- onium salt gives exclusively the *E*-isomer, which is preferable as an intermediate because of the lower mammalian toxicity of the final product in comparison with the *Z*-isomer.

The addition reactions of phosphoryl chloride to cyanamides and isothiocyanates were applied to prepare herbicidal methylene phosphoramidates.[25]

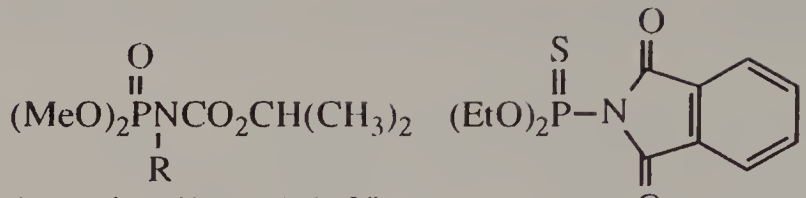
2. Reaction of trivalent phosphorus compounds with amines: Dialkyl phosphites react smoothly with primary or secondary amines or ammonia in carbon tetrachloride to give dialkyl phosphoramidates in good yields.[26] This reaction proceeds through the formation of a dialkyl phosphorochloridate intermediate.

Trialkyl phosphites react with chlorourea giving dialkylphosphinylureas with some pesticidal activity. Trialkyl phosphites also react with azides to form a P-N bond. By this reaction an insecticidal urethanephosphonate demuphos (**20**) is prepared.[27]

3. Modification of phosphoramidates: The amide nitrogen of phosphoramidates is acylated by acid chlroides or anhydrides in the presence of a strong base. For example, the fungicide ditalimfos (**21**) can be synthesized from diethyl phosphoramidothionate and phthalic anhydride by the action of sodium hydride. The lithium salts of phosphoramidates react with chloroformates to give urethane phosphates, selective insecticide candidates.[28]

The addition of alcohols to isocyanatophosphate esters is applied for the synthesis of the insecticide avenin (**22**).[29] By converting a phosphoramidate into the *N*-sulfenylchloride, a carbamate can be linked to the phosphoramidate through the sulfur bridge. The carbamate insecticide methomyl can be made less toxic

by such modification.[30a]



demuphos [R = Me] (20)
avenin [R = H] (22)

ditalimphos (21)

F. Phosphonic and Phosphinic Acid Derivatives

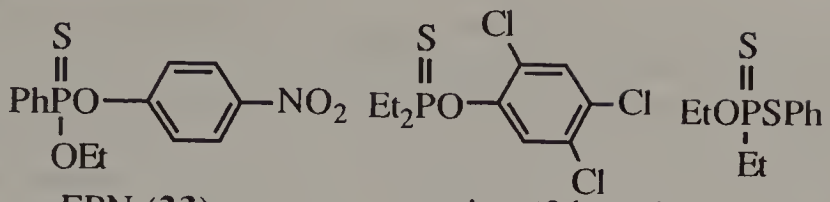
Typical reactions for P-C bond formation are: 1) the arylation or alkylation of PCl_3 by the catalytic action of Lewis acids; 2) the reaction of PCl_3 with organometallic compounds; 3) the reaction of phosphites with haloalkanes, and the addition of phosphites to unsaturated compounds.

1. Reactions of PCl_3 with Lewis acid catalysts: In the presence of aluminum chloride the Friedel-Crafts reaction between PCl_3 and an aromatic hydrocarbon gives an arylphosphonous dichloride-aluminum chloride complex, whose decomposition with phosphoryl chloride followed by sulfuration with thiophosphoryl chloride or sulfur affords an arylphosphonothionic dichloride. The dichloride may be employed for further synthesis of ester derivatives such as EPN (23).[1]

Upon catalysis with aluminum chloride, PCl_3 also reacts with haloalkanes to form complexes having a P-C bond. These give alkylphosphonic dichlorides by hydrolysis, or alkylphosphonothioic dichlorides by reaction with sulfur in the presence of freshly roasted KCl.

Alkylphosphonous dichlorides react similarly with haloalkanes in the presence of aluminum chloride to give complexes having two P-C bonds, which are converted to dialkylphosphinothioic chlorides by heating with sulfur in the presence of potassium chloride, or to dialkylphosphinous chlorides by heating with aluminum powder.[31,32] Agvitor (24) is thus synthesized from diethylphosphinothioic chloride and sodium 2,4,5-trichlorophenoxide.

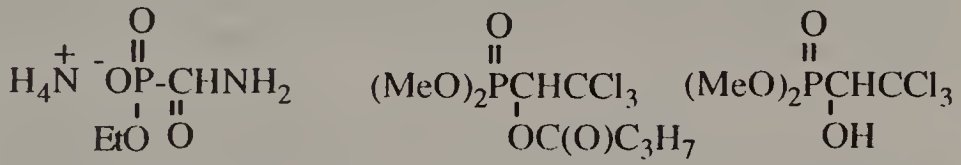
Methylphosphonous dichloride, manufactured industrially by the reaction of PCl_3 with methane at 600°, is converted into several important intermediates.[33]



EPN (23) agvitor (24) fonofos (25)

2. Reaction of PCl_3 with organometallic compounds: Trialkylaluminum reagents react with 3 moles of PCl_3 and sulfur to form alkylphosphonothioic dichloride-aluminum chloride complexes, which are converted into alkylphosphonate type insecticides after decomposition with ice water, as with fonofos (25).[34]

3. Reaction of phosphites with haloalkanes: Trialkyl phosphites react as nucleophiles with haloalkanes to produce alkylphosphonate esters (Michaelis-Arbuzov reaction). An example is the formation of the herbicide fosamine-ammonium (26).



fosamine-ammonium (26) butonate (27) trichlorfon (28)

The Michaelis-Arbuzov reaction is also used to prepare phosphinates. For example, *O*-methyl *S*-propyl methylthiophosphonite reacts with benzyl chloride to afford an insecticidal *S*-propyl benzylmethylphosphinothiolate.

The Michaelis-Arbuzov reaction generally occurs on trivalent phosphorus compounds having the P-OR linkage. The reactivity order is $R_2POR > RP(OR)_2 > P(OR)_3$. Although a dialkyl phosphite is less nucleophilic than trialkyl phosphites, its anion is active enough to react with haloalkanes to give phosphonate esters (Michaelis-Becker reaction). For example, the Michaelis-Becker reaction of dimethyl phosphite with α-chloro-β-trichloroethyl butyrate produces the insecticide butonate (27).[35,36]

4. Addition of dialkyl phosphites to the carbonyl group: Dialkyl phosphites having a P-H bond add to a carbonyl group to form α-hydroxyalkylphosphonates. The insecticide trichlorfon (28) is synthesized by this reaction from dimethyl phosphite and chloral.[37] Since monoalkyl phosphonites add similarly to the

carbonyl group, the phosphinate analogs of trichlorfon can also be produced by the reaction of chloral.[38]

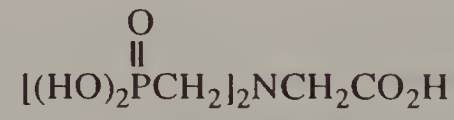
A direct method to prepare trichlorfon from phosphorus trichloride, chloral, and methanol is also available. In this procedure dichlorvos (dimethyl dichlorovinyl phosphate) is not produced, indicating that trimethyl phosphite does not form as an intermediate and consequently the Perkow reaction does not occur.[39] When a mercaptan is used in place of methanol the corresponding *S,S*-dialkyl 1-(alkylthio)alkylphosphonodithiolate is obtained.[40] Thus, an oxaphosphorane is probably formed as a common intermediate for both reactions.

The Mannich reaction of dialkyl phosphites with an amine is used as a method for synthesizing the herbicide glyphosate (29). The phosphonomethylation product of *N*-*t*-butylglycine ester is cleaved with hot hydrobromic acid to give (29) in high yield.[41]

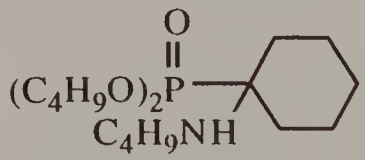
Similar reactions occur also with phosphorous acid in acid media. The plant growth regulator glyphosine (30) is synthesized by this reaction from glycine. The phosphonomethylation product from iminoacetic acid is converted into glyphosate in good yield by oxidative degradation.

Dialkyl phosphites add also to Schiff bases forming α-aminophosphonates. The herbicide buminafos (31) is prepared by this reaction.[42]

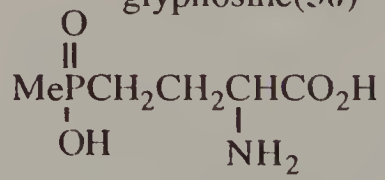
glyphosate (29)



glyphosine(30)



buminafos (31)



phosphinothricin (32)

Furthermore, monoalkyl methylphosphonites obtained by the reaction of methylphosphonous dichloride with alcohols add to alkenes to give phosphinate derivatives. This reaction is applied to synthesize the herbicide phosphinothricin (32).[33]

G. Pyrophosphoric Acid Derivatives

Symmetric pyrophosphate esters are easily synthesized by

the reaction of a dialkyl phosphorochloridate with water in the presence of a base. Hydrolyzed product reacts with unhydrolyzed phosphorochloridate.[43] This reaction can also be applied to the synthesis of dithionopyrophosphates such as sulfotep and pyrophosphoramides such as schradan.[1]

When an ambident nucleophilic dialkyl phosphorothioate ion reacts with a dialkyl phosphorochloridate the oxygen atom of the ion is always phosphorylated to give a monothionopyrophosphate ester,[44] in contrast with the alkylation of the sulfur atom with an alkyl halide. This selectivity in reactions agrees with the hard and soft acids and bases principle; the phosphoryl P, a hard acid, forms a stable bond with the hard base O^-, and the α-carbon of haloalkanes, a soft acid, gives a stable bond with the soft base S^-. Therefore, phosphites are used for *S*-phosphorylation. Thus, pyrophosphate esters having a P-S-P linkage are produced by the reactions of dialkyl phosphites and trialkyl phosphites with, for example, *O,O*-dialkyl *S*-morpholinophosphorodithioates and bis(dialkoxyphosphinothioyl) disulfides respectively.[45,46]

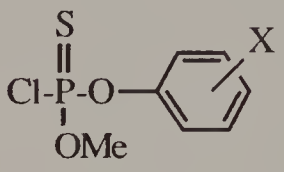
II. Chiral Phosphorus Acid Derivatives

Since the first resolution of enantiomeric *O*-ethyl ethylphosphonothioic acid by Aaron from the epimeric quinine salt in 1958,[47] *O*-alkyl alkylphosphonothioic acids have been resolved by similar methods and led into various phosphonate- and phosphonothionate-type compounds.[48,49] The absolute configuration of some phosphonothioic acids have been assigned based on X-ray analyses.[50-52] The phosphonothioic acids give phosphonothiolate esters with retention of configuration by reaction with haloalkanes, and give phosphonochloridothionates with inversion of configuration by reaction with PCl_5. The chloridothionates are converted into esters and amides, again with inversion.

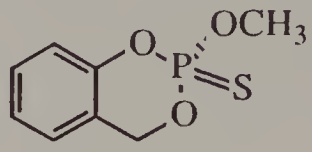
Achiral dimethyl aryl phosphorothionates can be utilized for the preparation of chiral phosphorus agents. For example, methyl parathion or the fungicide tolclofos is demethylated with a chiral base followed by resolution of the produced epimeric salts. The resolved demethylation products are converted to the optically active aryl methyl phosphorochloridothionates (AMPC) (33) which are useful as chiral two-step phosphorylating agents having two kinds of leaving groups with different reactivity.[53,54]

The absolute configuration of AMPC was tentatively assigned by chemical correlation and ^1H NMR measurement of the

diastereoisomer derived from reaction with optically active 1-phenylethylamine. All the optical isomers of 4- or 5-substituted-2-methoxy-1,3,2-oxazaphospholidine 2-sulfides were synthesized utilizing AMPC.[55,56] In this reaction sequence, the amino group displaces chloride first, followed by the displacement of the aryloxy group, all with inversion of configuration.



AMPC (33)



salathion-b (34)

Although the chiral oxazaphospholidines are prepared in high optical purity (> 95% e.e.), the optical purity of salithion enantiomers (34) obtained by the AMPC method is lower (80% e.e.).[55] Purer enantiomers of (34) were synthesized by applying Koizumi's L-proline ester method.[57] The absolute configuration was assigned by the X-ray analysis of the intermediate proline ester phosphoramidate and the established stereochemistry of methanolysis.

This method consists of L-proline ester derivatization from a racemic organophosphate, separation of epimeric pairs, and acid catalyzed alcoholysis, which occurs with inversion of phosphorus configuartion.[58] Aside from salathion, the enantiomers of profenofos, sulprofos, debromoleptophos oxon, and methamidophos have similarly been prepared with high optical purity by applying the proline ester method.[59-62]

Beside L-proline esters, aminosugars and ephedrine are utilized as chiral reagents to derivatize an organophosphate into separable phosphoramidate epimers.[63,64] The acid catalyzed hydrolysis and alcoholysis of the phosphoramide linkage occur with inversion of the phosphorus configuration as noted above.[65]

In order to convert stereospecifically the amide into the thiolate ester, the Wadsworth-Emmons reaction is suitable.[66] This reaction may proceed through a pentacoordinated intermediate with retention of configuration at phosphorus.

The optical purity has been determined after derivatization to a diastereoisomer. NMR spectrometry in the presence of chiral lanthanide shift reagents of optically active phosphinothioic acids is utilized for the determination of optical purity of organophosphates containing a phosphoryl group.[67,68] The NMR method, however,

is not useful for thiophosphoryl compounds which are insufficiently basic to form complexes.[52,64] Recent progress in HPLC using a chiral column has made possible not only the direct determination of optical purity, but allows the isolation of each enantiomer from racemic mixtures of chiral phosphorus compounds.[62,69-73]

III. Reactions of Phosphoryl Esters with Nucleophiles

A. Nucleophilic Substitutions

Almost all natural phosphorus compounds, except those in meteorites, are tetracoordinated phosphoryl derivatives. This emphasizes the stability of the phosphoryl group, usually shown as P=O. It consists of a σ bond and $d\pi$-$p\pi$ bonding involving the overlap of the phosphorus $3d_{xz}$ orbital and the *p* orbital of the neighboring oxygen atom. Since electrons donated from the phosphorus to the oxygen are part of the π bond, we may write the phosphoryl linkage as P=O, quite different from the N-O bonding of amine *N*-oxides. The phosphoryl bond enthalpy (120-150 kcal/mole) is much greater than that of an *N*-oxide (50-70 kcal/mole).[74]

The $d\pi$-$p\pi$ bonding contributes partially to any bonds commonly expressed as single bonds between a phosphorus atom and a heteroatom. Unshared electron pairs on the heteroatom can be supplied to the phosphorus through the $d\pi$-$p\pi$ interaction.

The reactivity of P(V) oxyacid esters is basically due to the positive charge on the phosphorus atom of the polarized phosphoryl group, the bond strength between the leaving group and the phosphorus, and the stability of the products. Nucleophilic substitution occurs not only on phosphorus sites with low electron density [S_N(P); phosphorylation], but also on the α-tetrahedral carbon atom of the ester group [S_N(C); alkylation] since the phosphate anion is a good leaving group.

The nature of the nucleophile greatly affects which reaction occurs. For example, alkoxide ion is preferentially phosphorylated, whereas mercaptide ion favors alkylation. The behavior of nucleopihles agrees with Pearson's HSAB concept.[75] The reactivity of nucleopihles is in the order: $F^- > HO^- > PhO^- > PhS^-$

> Cl^- , Br^-, I^-, $S_2O_3^{2-}$. This is almost the reverse that toward tetrahedral carbon where: $S_2O_3^{2-} > HS^- > I^- > (RO)_2POS^- > HO^- > Br^- > PhO^- > Cl^- > F^-$.[76] The "hard" bases react selectively with the phosphoryl phosphorus, while the "soft" bases prefer the tetrahedral carbon.

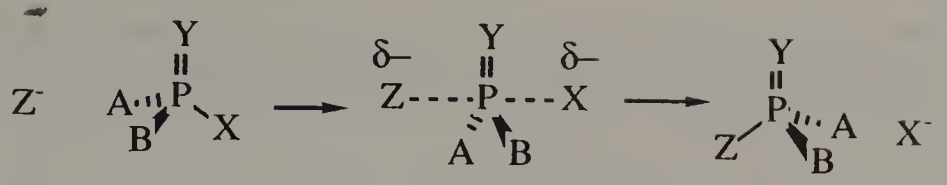
Acetylcholinesterase (AChE), the primary site of insecticidal action of OP insecticides, is inactivated by phosphorylation of the serine hydroxyl group at the catalytic site of the enzyme. Therefore, phosphorylating activity is the most essential function of OP insecticides. On the other hand, their detoxification by glutathione *S*-alkyltransferase occurs by the nucleophilic substitution on the α-carbon of ester alkyl groups by the glutathione SH group. Thus, the alkylation reaction can not be ignored for the biological activity of OP agrochemicals.[77]

B. Reaction Mechanisms of Phosphorylation

There are three mechanisms for nucleophilic substitution on the phosphoryl P atom: $S_N1(P)$, $S_N2(P)$, and the addition-elimination mechanism.

The $S_N1(P)$ mechanism involves a proposed intermediate monomeric metaphosphate which is too unstable to be isolated. The $S_N1(P)$ mechanism *via* metaphosphate is, however, stereochemically confirmed in the alkaline hydrolysis of optically active methyl *N*-cyclohexylphosphoramidochloridothionate.[78] It is hydrolyzed under alkaline conditions 45,000 times as fast as under neutral conditions to give a racemate product, indicating a process proceeding through a planar metaphosphate intermediate. β-Haloalkylphosphonic acids such as the plant growth regulator ethephon are readily decomposed by the action of hydroxide ion giving alkenes and phosphorylating alcohols, probably *via* a metaphosphate intermediate.[79]

The $S_N2(P)$ mechanism proceeds in a manner similar to an S_N2 reaction on carbon through a transition state as shown below, accompanied by inversion of phosphorus configuration.[80] Upon alkaline hydrolysis of a trialkyl phosphate in ^{18}O-labeled water, the hydrolysis product contained one atom of ^{18}O.[74] Under acidic conditions, however, cleavage of the C-O bond occurs without incorporation of ^{18}O into the product dialkyl phosphate.[81]



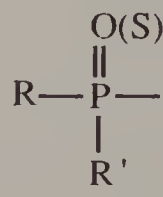
In contrast to alkaline hydrolysis according to an $S_N1(P)$ mechanism, alcoholysis of phosphoramidates under acid conditions proceeds according to an $S_N2(P)$ mechanism with P-N bond cleavage by protonation, resulting in inversion of configuration at phosphorus.[65]

Addition-elimination mechanism: Since phosphorus can form pentacoordinated compounds, it is possible that addition of a nucleophile to the phosphoryl P occurs to form a trigonal bipyramidal type unstable intermediate rather than a transition state in the $S_N2(P)$ mechanism, followed by elimination of a leaving group.[82] This mechanism is not accepted for acyclic phosphate esters.[74] The addition-elimination mechanism is, however, important for cyclic phosphate esters. Five-membered cyclic phosphates are a million times as reactive as acyclic phosphates owing to the ring strain (the bond angle O-P-O of 98-99°). The great enhancement of the reactivity is observed not only in the ring opening, but also in the hydrolysis of the exocyclic ester linkage. Hydrolysis of hydrogen cyclic ethylene phosphate in water-^{18}O caused the incorporation of ^{18}O into "unreacted" cyclic phosphate as well as the ring opened product. These observations were clearly explained by energetically preferable addition and elimination along the axial direction and pseudo-rotation of trigonal bipyramidal intermediates.[83]

C. Criteria of Phosphorylating Activity: Acyl Rule and PXYZ System

Aldridge found in 1952 that the alkaline hydrolysis rate of phosphate esters correlates well with their inhibitory activity against AChE.[84] Although it relates only to the phosphorylating activity, this relationship holds in many cases because the phosphorylation step is very important in the enzyme inhibition process by OP compounds. Schrader pointed out that insecticidal OP compounds are acid anhydrides which have the general structure (35) where "Acyl" indicates an acid residue and R may be an alkoxy, alkyl, or amino group.[85] The stronger is the acid parent of the "anhydride",

the more positive is the charge on phosphorus and the more suitable the "acyl" group serves to leave in nucleophilic displacement.



(35)

However, many OP compounds have much higher activity than expected from the acidity of the leaving group. Expanding the "acyl rule", Clark classified phosphorylating agents into PXYZ systems, where X, Y, and Z are atoms or groups consisting usually of H, C, N, O, S, and halogens.[86] A good phosphorylating agent must have a weak P-X bond. When X is a heteroatom having an unshared electron pair, however, the P-X bond is fortified by a $d\pi$-$p\pi$ overlapping. The reactivity of the P-X bond is increased by reducing the $d\pi$-$p\pi$ contribution. This is attained by introduction of an ordinary $p\pi$ bonding with an sp^2-hybridized Y atom. Atom Z must be capable of accommodating the electrons of the P-X bond. Atom Z withdraws electrons in the ground state as did Schrader's acyl group, as exemplified by a nitro or cyano group at the *p*-position of phenyl phosphate esters. In some cases Z is activated to be electron withdrawing by protonation, oxidation, or other reactions.

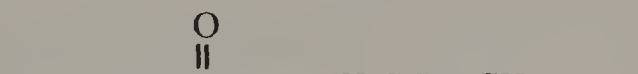
D. Alkylation

Allyl and benzyl esters give relatively stable carbocations, so that alkylation of nucleophiles by an S_N1 mechanism occurs readily. Saligenin cyclic phosphates such as MTBO (9) have high alkylating activity as well as phosphorylating activity. They are transformed into highly active *o*-hydroxybenzyl derivatives by ring opening at the P-O-C(aryl) bond after initial nucleophilic attack on the phosphorus or partial hydrolysis. They react with thiols such as cysteine and glutathione to give corresponding *o*-hydroxybenzyl thioethers.[87,88] The reaction proceeds probably *via* quinoid type cations. Thus, they inhibit not only AChE, but also some SH enzymes.

The glutathione conjugate acts as a competitive inhibitor against glutathione *S*-alkyltransferase. This contributes at least in part to the synergistic activity of saligenin cyclic phosphates with the insecticide fenitrothion, suppressing its degradation by the

enzyme.[88] *S*-Benzyl diisopropyl phosphorothiolate (iprobenfos; IBP) is a useful fungicide and also is synergistic with OP insecticides, particularly malathion. The synergistic effect is due to inhibition of carboxyesterase and dealkylation.[89] The *o*- and *p*-hydroxy derivatives, the possible metabolites of IBP, are potent alkylating agents and inhibit SH enzymes as well as the partial hydrolysis products of saligenin cyclic phosphates.[90] The *p*-hydroxy derivative of another OP fungicide, edifenphos, similarly shows high fungicidal activity.[91] Such a *p*-thioquinol phosphate inhibits SH enzymes.[92] It may possibly be an alkylating agent forming a quinoid product by oxidation.

In regard to ordinary OP insecticides, the alkylation reaction is more significant in the methyl ester group than in the ethyl and higher *n*-alkyl groups. In the course of the manufacturing of OP insecticides having the methyl ester group present, some care is necessary to avoid unwanted reactions owing to methyl group transfer. The methyl group transfers readily to sulfur or nitrogen atoms. Pyridine and tertiary amine bases should be avoided for preparation of the methyl phosphorus esters. On storage, demeton-*S*-methyl (36) generates a methyl sulfonium species which is 1000 times as toxic as the original compound.[93]



demeton-*S*-methyl (36)

The phosphorothioate anion formed by the dealkylation of a phosphorthionate ester is a strong nucleophile and preferentially reacts with an alkylating agent at the sulfur atom giving a phosphorothiolate ester. Thus, phosphorothionate esters are often isomerized to phosphorothiolates in the course of dealkylation.[76] Dealkylation of phosphorothiolate esters prefers C-O bond scission rather than C-S bond scission. There is difficulty in C-S bond heterolysis owing to the similar electronegativities of carbon and sulfur.

Since thiophosphoryl-*S* can serve as a soft nucleophile, the thiono-thiolo rearrangement occurs even in the absence of any special reagents at high temperature (120-180°). It appears to proceed intermolecularly.[76] The *O*-methyl ester group is transferred faster than ethyl and higher alkyl groups; 90% isomerization of parathion and its methyl homolog into the corresponding *S*-alkyl

phosphorothiolates occurred by heating to 150° for 24 hr and 6.5 hr respectively.[94] The isomerization may occur in the course of the preparation of phosphorothionates by heat and during long storage in polar solvents.

The thiono-thiolo conversion is accelerated by alkyl iodides (Pistschimuka reaction). Electron donative substituents on the phosphorus, such as amino and alkyl groups, favor the reaction by increasing the nucleophilicity of the sulfur atom.[95] The Pistschimuka reaction can be used for isomerization of salithion to prepare MTBO.[96] Another type of isomerization occurs as we desulfurize salithion by oxidation with *m*-chloroperbenzoic acid.[97] The isomerized product is not MTBO but 2-methoxy-4*H*-1,3,2-benzoxathiaphosphorin 2-oxide which is also produced by both photo and thermal decomposition of salithion.[98,99] The isomerization is affected by reaction solvents, occurring readily in chloroform but restrained in benzene.[97]

The isomerization occurs much more readily with some phosphorothionates such as demeton-O or the thiono isomer of amiton which have a β-alkylthio- or dialkylaminoethyl esyer group. The β-substituted ethyl group migrates onto the sulfur atom *via* a cyclic onium intermediate.[100]

The sulfur atom of the phosphorothiolate ester group can also accept an alkyl group in transalkylation as exemplified by the formation of a sulfide and dialkyl phosphate from 2-methoxy-4*H*-1,3,2-benzodioxaphosphorin 2-sulfide (MTBO) and an alcohol in the presence of a tertiary amine.[101] Another type of intramolecular transalkylation reaction occurred in the formation of SH-compounds in the hydrolysis of aziridinylphosphinothionates.[102] From studies using optically active compounds, a mechanism for the hydrolytic sulfur rearrangement has been proposed.

IV. Acetylcholinesterase Inhibition by Organophosphates

A. Function of Acetylcholinesterase

Organophosphorus insecticides are neurotoxins and classified as anti-acetylcholinesterases. Excitation of a nerve cell membrane is conducted as an electric nerve impulse along the axon to the nerve terminus where the release of a neurotransmitter is induced by the impulse *via* influx of calcium ion. The transmitter migrates across the syaptic cleft and interacts with a receptor on the

postsynaptic membrane of another neuron or muscle cell, causing action of the membrane. The transmitter which has operated must be removed rapidly, otherwise normal neurotransmission would be disturbed to cause abnormal excitation and eventual death. Acetylcholine is one of the neurotransmitters, operating in the central nervous systems of both vertebrates and insects. At neuromuscular junctions acetylcholine functions in vertebrates but not in insects. Acetylcholine is best hydrolyzed by acetylcholinesterase (AChE).

Esterases are conveniently classified into three groups by their behavior against OP reagents like diisopropyl phosphorofluoridate.[103] A group including arylesterase (EC 3.1.1.2) is not inhibited by OP reagents, but is able to hydrolyze them so that it participates in the detoxification of OP agrochemicals. B-Esterases, such as carboxyesterase (EC 3.1.1.1) and cholinesterases are inhibited by OP reagents and carbamate inhibitors and are called "serine enzymes" because they have a serine residue at their catalytic site. Serine enzymes involve also some proteases such as chymotrypsin. C-Esterases apparently do not interact with OP reagents either to be inhibited by them or to hydrolyze them.

Cholinesterases are distinguishable from other B-esterases by their selectivity toward choline esters as the substrate and their susceptibility to the carbamate inhibitor physostigmine. In a narrow sense, they are divided into acetylcholinesterase (AChE; EC 3.1.1.7) and cholinesterase (EC 3.1.1.8). In order to avoid confusion the latter is often called pseudocholinesterase or butyrylcholinesterase (BChE) based on its substrate specificity. AChE plays the important role in nervous systems as mentioned above, and is found in erythrocytes and electric organs in addition to nerve and muscle tissues in vertebrates. BChE hydrolyzes butyrylcholine and propionylcholine faster than acetylcholine, and occurs widely in plasma, organs such as lung and heart, and the pancreas in vertebrates. It is also present in nerve tissues, but not related to the above-mentioned nerve function.

The hydrolysis of acetylcholine (AX) by AChE proceeds as shown below, where A and HX are the acetyl group and choline respectively.

$$EH + AX \overset{K_d}{\rightleftharpoons} EH\text{-}AX \xrightarrow[-HX]{k_2} EA \xrightarrow[+H_2O]{k_3} EH + AOH$$

EH = AChE

AChE binds acetylcholine to form an enzyme-substrate complex, followed by the acetylation of the esteratic site, a serine OH group. Deacetylation of the acetylated enzyme occurs so rapidly (k_3 ~3.5×10^5 min^{-1}; $t_{1/2}$ of EA ~ 0.1 msec) that the active AChE is immediately recovered to hydrolyze further substrate molecules.

B. Inhibition of Acetylcholinesterase

The reaction between the OP anti-AChE and AChE is basically the same as that between the substrate acetylcholine and the enzyme. However, the OP inhibitors behave as unfavorable substrates. Binding to the enzyme they phosphorylate the esteratic site, but the dephosphorylation occurs so slowly that AChE is essentially inactivated. Approximate values of reaction parameters K_d, k_2, and k_3 for the activated form of ordinary OP insecticides are 10^{-3}-$10^{-4}M$, ~50 min^{-1}, and 10^{-3}-10^{-4} min^{-1} respectively.[3] The half-life of the phosphorylated enzyme is between a few hours and one month.[103] The spontaneous reactivation rate k_3 decreases in the following order: $(MeO)_2P(=O)E > (EtO)_2P(=O)E > (i\text{-}PrO)_2P(O)E$.

Appropriate nucleophiles are able to dephosphorylate and reactivate the phosphorylated enzyme. Fluoride ion, a hard base, reacts well with the phosphoryl P, a hard acid, but its reactivation ability at physiological pH range is lower than oxime reactivators.[104] Some bases having an unshared electron pair on the adjacent atom exert higher nucleophilicity than expected from their basicity (α-effect) and accelerate the degradation of phosphate esters including phosphorylated AChE. Some oximes having appropriate pK_a values such as pyridine 2-aldoxime methiodide (2-PAM) are effective at accelerating the dephosphorylation, and reactivate the inactivated AChE. The optimum pK_a value of pyridine aldoximes is 7.8.[105] In addition to the nucleophilicity toward phosphorus, the affinity of a reactivator to the phosphorylated enzyme is important for reactivation ability. A positive charge and its place relative to the oxime group affects the activity of oxime reactivators.[106] Since the reaction rate of oximes with phosphorylated enzymes is reversible, the produced phosphorylated oximes may be phosphorylating agents.[107] In order to avoid this unfavorable reverse reaction the product phosphorylated oximes should rapidly decompose. The

decomposition rate relates to the acidity of the methine proton of the oxime.[105]

The inactivated AChE changes gradually into a form which is non-reactivatable even by the oximes. This phenomenon, called "aging", is caused by dealkylation of the dialkyloxyphosphinyl AChE. The resulting phosphoric anion can not be attacked by the nucleophiles. The rate of aging depends on the alkyl group, increasing in the order: Et < Me < *i*-Pr.[103] The half-life of diethoxyphosphinyl AChE is about 40 hr at 37° and pH = 7.4, whereas that of the diisopropyl ester is about 2.5 hr. Studies using benzyl esters suggest that unimolecular C-O bond fission occurs in the aging process.[108] Since the chirality of the phosphorus site, however, greatly affects the aging rate, as exemplified by $(R)_P$-cyclopentyloxymethylphosphinyl ChE, which aged 1000 times as fast as its enantiomer, certain functional groups or structures of the enzyme molecule may contribute to the dealkylation process.[109]

C. Reactivity Parameters and Anticholinesterase Activity of Organophosphates

In the series of compounds whose general structure is $(EtO)_2P(O)X$ there is a good correlation between the alkaline hydrolysis rate and the acidity of HX (K_a). When HX is a *p*-substituted phenol, the Hammett σ constant of the substituent correlates well with the inhibitory activity of the phosphate ester against housefly head AChE as well as the alkaline hydrolysis rate.[110,111] The dependence on σ indicates that the enzyme inhibition reaction is a nucleophilic reaction on phosphorus. Huckel molecular orbital calculations indicate that both the phosphorus and the bonded atom on a labile bond in highly reactive OP compounds are positively charged.[112] Superdelocalizability ($S_P^{(N)}$) for a nucleophilic reaction on phosphorus of substituted phenyl phosphates correlates well with alkali hydrolysis rate and anticholinesterase activity.[113]

In the *meta* substituted derivatives, however, the anticholinesterase activity is not correlated well by σ, the hydrophobicity parameter π, or their combination. This is probably due to steric effects. A good correlating equation for diethyl phenyl phosphates including both the *para* and *meta* substituted derivatives is obtained by introducing the steric parameter E_S^m.[114] The equation indicates that the stereoelectronic character of *para* derivatives is superior to

the *meta* isomers for inhibition, although the latter may readily bind to the enzyme.

Kamosita found that the equilibrium constant K_d of the reversible enzyme-inhibitor complex was more affected by substituents on the benzene ring of dimethyl phenyl phosphates than phosphorylation rate k_2 and proposed an equation relating K_d to empirical substituent constants.[115] This work suggests that the electron-withdrawing effect of substituents is very important for the enzyme-inhibitor complex formation.

Although the physicochemical parameters correlate well with biological (insecticidal) activity in certain cases, there are some exceptions as a result of biokinetic factors. For example, the 2,4-dinitro, *p*-formyl and *m*-trimethylamino derivatives of diethyl phenyl phosphate are much less insecticidal than expected from the parameters. In the first case this is due to extremely high reactivity which results in decomposition of the compound before interacting with AChE in the insect. The absence of insecticidal activity in the second and third examples may be due to rapid metabolic detoxification and poor penetration through the outer layer of the insect respectively. Since the insecticidal action appears after many biological steps in the insect including membrane penetration, transportation, metabolism, and interaction with the target site, the compound suffers complicated influences from many factors. Consequently, the simple chemical reactivity and even the anti-AChE activity are often inconsistent with the insecticidal activity.

The reactivity of phosphate esters is also affected by the alkyl ester groups, though not so distinctively as by the acyl group. Owing to the inductive effect of alkyl groups, the methyl esters are generally more reactive than the corresponding ethyl and higher *n*-alkyl esters, as exemplified by methyl parathion which decomposes 5 times faster than the ethyl homolog.[116]

Regarding enzyme inhibition, the effect of the alkyl ester group is not as simple as expected from the inductive effect. In the homologs of paraoxon and malaoxon, unbranched chains through C_4 are roughly equipotent with regards to phosphorylation rate toward AChE, whereas the isopropyl group shows a 20-fold drop in rate.[117] In a series of dimethoxon homologs, deviation in k_2 values by the change of the *O*-alkyl group reaches 100-fold.[118] It depends on the enzyme source, k_2 increasing toward bovine

erythrocyte and housefly head AChEs in the following orders: *i*-Pr < Me < Et < *n*-Pr < *n*-Bu,[118] and *i*-Pr < *n*-Bu < *n*-Pr < Me < Et,[121] respectively.

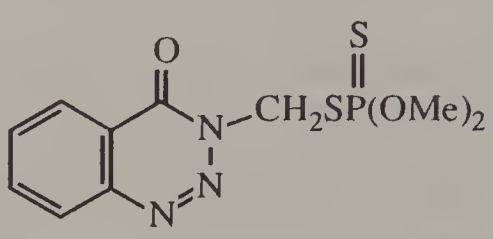
D. Steric Effects on Anticholinesterase Activity

Since the inhibition of serine enzymes by OP proceeds *via* formation of an enzyme-inhibitor complex, the affinity of the inhibitor with the enzyme ($1/K_d$) is important as well as the phosphorylating ability (k_2). The complex formation is greatly affected by steric factors of the inhibitor. Honey-bee AChE is much less sensitive than housefly AChE to the diisopropyl homolog of paraoxon. This is due, at least in part, to the affinity for bee AChE being 0.1 that for fly AChE.[119]

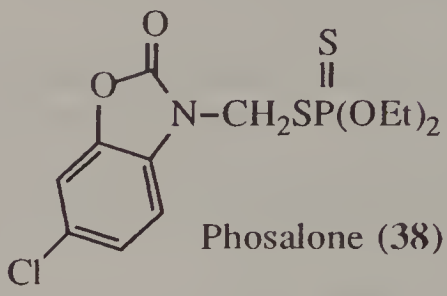
Organophosphates whose structure resembles acetylcholine are generally potent AChE inhibitors more than is expected from their reactivity. The protonated amiton and the active metabolite of demeton which have a positively charged center as an ammonium N and a sulfon S, respectively, at three atoms distance from the phosphoryl site are typical examples. The distance between the esteratic site and the binding site in AChE is estimated at about 5 angstroms, corresponding to that (4.7 angstroms) between the carbonyl C and the tertiary ammonium N in the acetylcholine molecule. When the cationic or most positive center of an OP molecule binds to the binding site of AChE, the phosphoryl group may approach to the esteratic site. Jacobson[120] measured the distance between the phosphorus and the most positive center in various OP insecticide molecules using X-ray crystallography and found in azinphos-methyl (37), for example, the carbonyl C at the 4-position (which has the lowest electron density in the molecule) to be 4.83 angstroms from the phosphorus. In this context it is interesting to note that many OP insecticides containing a heterocycle in the molecule, exemplified by methidathion (12), phosalone (38), and phosmet (39), have similar P-S-C-N-C=O functions.

Since the binding site is located on the hydrophobic region, hydrophobic interaction with a non-charged bulky alkyl group at an appropriate position is also effective for binding with AChE. Structure-activity studies on dimethoate related compounds indicated that substituents on the amido N three atoms from the phosphorus affect the formation of the AChE-OP complex.[121] The affinity increases in the order NHMe < NMe_2 < $N(n\text{-}Pr)_2$. The

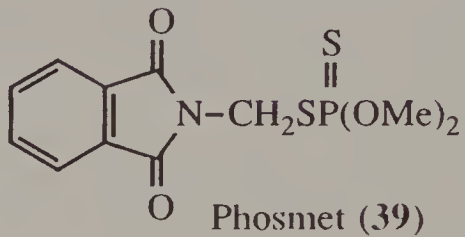
alkyl substituent on the ester O affects the phosphorylation rate as well as complex formation.



Azinphos-methyl (37)



Phosalone (38)



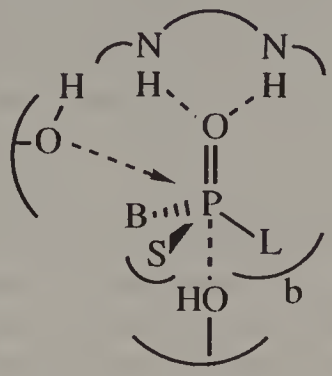
Phosmet (39)

The features of AChE differ among animal species. Dimethyl phenyl phosphates having a methyl (fenitrothion), trifluoromethyl (fluorothion) or chloro (chlorthion) substituent at the *meta* position have a very low mammalian toxicity in comparison with the corresponding nonsubstituted esters. Fenitroxon shows lower affinity toward mammalian AChE but higher affinity toward insect AChE than does methyl paraoxon.[122] This was presumed to be due to possible differences between the AChEs in the distance between the binding and esteratic sites.[122]

Although the substrate acetylcholine itself is an achiral molecule, AChE is able to recognize the chirality of OP inhibitors. When the structure of the enantiomer of a pair *more* potent toward housefly AChE is viewed with the leaving group toward the observer, and the P=O group vertical (P down), most reported compounds, including profenofos and its activated sulfoxide, have a smaller substituent at the left side and a larger substituent toward the right side.[123,124] Exceptions are methamidophos and acephate.[62]

This is also the case for the steric structure-insecticidal activity relationships of phosphorothionates, being consistent with the observation that the oxidative desulfuration proceeds with retention of the configuration. Steric size relationships for inhibitors binding at the target site of AChE is shown below for an "oxyanion hole"[125] where hydrogen bonding from backbone NH exist to the

phosphoryl oxygen, and the serine OH attacks the P site.

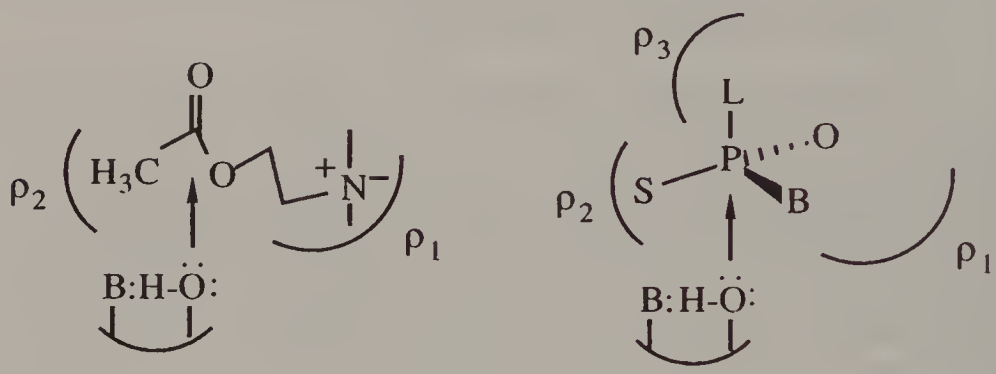


L = leaving group; S = smaller non-leaving group; B = larger non-leaving group; b = binding site

Organophosphorus compounds may inhibit not only AChE but also other serine enzymes. Their selectivity in enzyme inhibition is greatly due to the structure of non-leaving groups and the steric configuration about phosphorus. The above-mentioned limited size on the left side in the oxyanion hole of insect AChE appears important for the selectivity of OP inhibitors. For example, the anti-AChE activity of ethyl *p*-nitrophenyl alkylphosphonates decreases by 90% upon changing the alkyl group from C_3 to C_5, while the inhibitory activity against chymotrypsin reaches a maximum at C_7 and C_8.[126] (+)-*p*-Nitrophenyl ethyl(phenyl)phosphinate is 84 times as active as the (-)-enantiomer for the inhibition of bovine AChE, whereas the latter is 12 times as active as the former against α-chymotrypsin.[73] The selectivity of saligenin cyclic phosphates in inhibition of housefly AChE and aliesterase varies remarkably with the size of the exocyclic ester group on phosphorus. Thus, the phenyl ester inhibits aliesterase more than 100 times as greatly as it inhibits AChE, whereas the methyl ester inhibits aliesterase and AChE 0.6 and 20 times as much respectively as does the phenyl ester.[127]

The transition state of AChE in reaction with the planar carbonyl of substrate acetylcholine may be different from that in reaction with the tetrahedral OP-inhibitors; the serine OH group at the esteratic site may attack the carbonyl from the side opposite to the leaving group. Based on a physicochemical approach, Jarv, *et al.* concluded that the leaving groups of substrates and OP

inhibitors bind to different loci at the enzyme active site, and a bigger non-leaving alkoxy group of the OP-inihbitor binds to the locus where the substrate leaving group binds.[128] Thus, they presented a model for the active site of AChE in which there are three binding loci in addition to a site which forms a hydrogen bond with the carbonyl oxygen atom, as shown below. The loci ρ_1, ρ_2 and ρ_3 bind the leaving group, the acyl part of the substrate, and the leaving group of OP-inhibitors, respectively. This model provides a stereochemical mechanism for the inactivation of AChE by OP-inhibitors and for the reactivation of the phosphorylated enzyme.



In this study, however, allyl acetates were used as substrates rather than choline-like compounds, and *O*-alkyl *S*-butyl methylphosphonothiolates and *O*-ethyl *S*-alkyl methylphosphonothiolates were used as inhibitors. If pseudorotation occurs once in a putative trigonal bipyramidal intermediate in enzyme phosphorylation, the leaving group of an OP-inhibitor can bind at the locus where the choline function normally binds. This process results in the retention of configuration at phosphorus, whereas Jarv's model shows inversion. Such stereochemical investigations have not as yet been performed.

V. Structure and Activity of Organophosphorus Agrochemicals

A. Phosphate Esters

A relatively small number of phosphate type insecticides are currently utilized, including dichlorvos, mevinphos, dicrotophos, naled, chlorfenvinphos, propaphos, bomyl, coroxon, and

haloxon. Vinyl phosphates are the most improtant in this class, some of which exhibit systemic activity. Vinyl phosphate insecticides have structures obeying the "acyl" rule or the PXYZ system by carrying halogen atoms on the double bond or a conjugated carbonyl group. They have potent anti-AChE activity, but the activity does not always correlate with alkaline hydrolyzability. For example, although the ethyl homolog of *E*-bomyl is hydrolyzed 570 times as rapidly as the ethyl homolog of *E*-mevinphos, the anti-AChE activity of the former is rather weaker than the latter.[129] Since the phosphorylating activity of vinyl phosphates may be increased by protonation, interaction with an acidic group near the esteratic site of AChE may activate the vinyl phosphate. Such interaction may be affected by steric factors. Actually, *E*-mevinphos is 10-20 times as active as the *Z*-isomer as an anti-AChE agent, showing a higher phosphorylating rate.[130]

The insecticide naled is converted to dichlorvos, the active form, by debromination. Beside the active form of the phosphorothionate type insecticides, only a few examples of aromatic phosphate esters are used as insecticides. Propaphos exhibits a systemic activity effective to OP resistant planthoppers. Coroxon and haloxon are antihelmintics. Bisdichlorophenyl ethyl phosphate, phosdiphen, is a fungicide. The 2-propynyl ester (fospargyl) is synergistic with some insecticides by the inhibition of cytochrome P450.

B. Phosphorothionate Esters

Except for a small number of the above-mentioned enol phosphates, almost all OP insecticides are of the thiono (P=S) type, which are generally more stable, lipophilic, and penetrable through insect integument than the corresponding oxons (P=O). In the phosphorothionate class, particularly dialkyl aryl phosphorothionates and derivatives of nitrogen containing heterocycles, many important insecticides have been used. The thinon-thiolo isomerization occurs readily upon heating and by other routes. Thus, crude preparations of phosphorothionate insecticides often contain phosphorothiolate isomers which are generally more toxic to mammals than are the corresponding phosphorothionates. The term "phosphorothioate" does not distinguish the isomers.

In contrast with phosphate type insecticides, vinyl esters are not utilized yet as insecticides in the phosphorothionate class, except for methacrifos which has recently been developed as a grain

protectant.[131] Almost all phosphorothionate insecticides are aromatic or heteroaromatic esters. According to the acyl rule, insecticidal dialkyl phenyl phosphorothionates have an electron-withdrawing group, such as a nitro group, at the *p*-position. Acyl, alkoxycarbonyl, carbamoyl, cyano, sulfenyl, and sulfonyl groups are also effective as the substituent.[132,133] The methylthio group of fenthion is transformed into the electron-withdrawing sulfenyl and then sulfonyl group by biooxidation. Plural halogen atoms are required for halophenyl esters. Dimethyl phenyl phosphorothionates having an alkyl group or a halogen atom at the *m*-position, such as fenitrothion and chlorthion, show much lower mammalian toxicity than the corresponding *m*-unsubstituted compounds. This is partially due to the lower affinity of *m*-substituted phenyl phosphates with mammalian AChE in comparison with the unsubstituted esters.[122] The effect of a *m*-substituent for lowering mammalian toxicity, however, is observed only in dimethyl phenyl phosphorthionates, but not in the diethyl homologs. Toclophos-methyl is a fungicide and has no insecticidal activity.[134]

Nitrogen-containing heteroaromatic phosphorothionate insecticides, such as diazinon and isoxathion have no particular electron-withdrawing group, but a P-O-C=N linkage, except for the new soil insecticide butathiophos,[135] in the molecule and are expected to be activated by protonation at nitrogen. In such an oxime phosphorothionate as phoxim, a cyano group on an α-carbon is essential for insecticidal activity, consistent with a PXYZ system. The sulfide linkage of demeton-type insecticides is oxidatively metabolized into sulfoxide and then sulfone linkages in plants and other organisms. The products are polarized and relatively stable, providing systemic properties in plants.

Since phosphorothionates are almost inactive as *in vitro* inhibitors of AChE, they must be transformed into oxons in order to exert insecticidal activity. The thiophosphoryl group is less strongly polarized than the phosphoryl group owing to the similar electronegativities of sulfur and phosphorus. The superdelocalizability of the phosphorus atom in parathion is only 1.056 compared to 1.119 with paraoxon.[113] Although chemical reactivity (alkali hydrolysis rate) differs only about 10-fold between them, the anticholinesterase activity differs by more than 10,000-fold. Thus, the thiono effect is probably due not only to the low electrophilicity of the phosphorus atom, but also to some other factors, including

the lack of hydrogen bonding on the sulfur atom in the "oxyanion hole".

C. Phosphorothiolate Esters

Phosphorothiolate esters include the active metabolites of phosphorothiolothionate insecticides and the demeton-S type insecticides. Beside them, several asymmetric *S*-propyl phosphorothiolate insecticides have been developed, including profenofos, trifenofos, difenprofos, pyraclorfos, and zolaprophos. The insecticidal activity of *O*-alkyl *O*-aryl *S*-alkyl phosphorothiolates is strongly affected by the hydrophobicity of the *S*-alkyl group. An alkyl group whose π value is 2, corresponding to an *n*-propyl group, has been concluded to be most effective for a variety of insects.[136] They are also effective against OP-resistant insects.[137]

Phosphorothiolate esters (O=P-SR) show much higher reactivity than the corresponding phosphate esters (O=P-OR). For example, the *S*-aryl isomer of parathion is hydrolyzed 22 times as fast as paraoxon in alkaline solution.[138] This is larger than expected from the difference in K_a values of thiophenol and phenol. The fission of the P-S bond occurs easily. However, if a more acidic group is involved in the ester linkage, it acts as a leaving group. Even in such a case the reactivity of the phosphorothiolate is very high. For example, *O,S*-diethyl *O*-*p*-nitrophenyl phosphorothiolate is hydrolyzed at the *p*-nitrophenyl ester linkage 470 times as fast as the corresponding phosphate ester.[139]

Such high activity of phosphorothiolate esters despite the low electronegativity of sulfur may be attributed to: 1) little $d\pi$-$p\pi$ contribution to the P-S linkage because of poor overlap between the *3d* orbital of P and the *3p* orbital of S in a long bond and of antibonding overlap between the *d* orbital and the *2p* orbital of S; 2) the low bond strength of the P-S bond; 3) the polarizability of the sulfur atom.[3]

Phosphorothiolate esters are, in general, more potent than the corresponding phosphate esters in anti-AChE activity as well (thiolo effect). The enhancement of anti-AChE activity by replacing an oxygen atom of a phosphate ester with a sulfur atom is particularly remarkable in the case that the activity of the original phosphate ester is poor. For example, diethyl *S*-*p*-tolyl phosphorothiolate is 50,000 times as active as the corresponding phosphate,[138] whereas the thiolate analogue of *p*-nitrophenyl phosphate is only 6 times as active as the phosphate. The thiolo

effect is not always high in some *S*-alkyl esters. The oxidative activation of the thiolate ester linkage has been observed in profenofos[140] and pyraclofos,[141] suggesting their transformation into the sulfoxides. Similar activation was also proposed for the thiolothionate insecticide prothiofos.[142] Although the substituted aryloxy groups of these OP insecticides are Schrader's acyl, the *S*-propyl group is converted into a better leaving group by oxidative activation. The two different leaving groups may contribute to the efficiency against OP-resistant insects.[143] (*R*)(-)-Profenofos is less potent *in vitro* as an AChE inhibitor, but is converted into a more potent inhibitor by oxidation than is the (*S*)-isomer. AChE reacts well with the oxidized product of (*R*)(-)-profenofos, but less with that of the (*S*)-isomer.[140]

Some phosphorothiolate type fungicides are also known. *O,O*-diisopropyl *S*-benzyl phosphorothiolate (iprobenfos, IBP) as well as *O*-ethyl *S,S*-diphenyl phosphorodithiolate (edifenphos) inhibit transmethylation from adenosylmethionine to phosphatidylethanolamine in the Greenberg pathway for phosphatidylcholine biosynthesis.[144] Although iprobenfos metabolites hydroxylated at *o*- or *p*-positions have not yet been found, they are potent alkylating agents and inhibit SH enzymes.[90] Edifenphos gives the fungicidal *p*- hydroxy metabolite.[91] Thioquinol phosphate esters are also SH inhibitors with fungitoxicity.[92]

S,S,S-Tributylphosphorotrithiolate (DEF) is a plant growth regulator effective as defoliant for cotton.

D. Phosphorothiolothionates

Many important insecticides have been developed in the class of compounds which have P=S and P-S-C linkages. They are often called simply "phosphorodithioates", which does not always mean there is a P=S linkage present. Many insecticides of this class have a heteroatom on the α- or β-carbon of an *S*-aliphatic group which is involved in a carboxy ester, amide, amine, heterocycle, sulfide, or sulfoxide. Some phosphorothiolothionates having a sulfide group in the molecule have been known as systemic insecticides, as exemplified by thiometon, phosrate, and terbufos. The sulfide is oxidized to the sulfoxide and transported in plants. Replacing the *S*-ethyl group in phorate by a substituted thiophenol group increases acaricidal activity (phenkapton).

Since the discovery of malathion and dimethoate as insecticides with low mammalian toxicity, many related insecticides

degradable by carboxyesterase or amidase have been developed. Phosphorothiolothionates bearing a carboxamide group, as dimethoate, mecarbam, *etc.*, exhibit plant systemic activity. Modifications in the carboxamide function resulted in herbicidal activity with aromatic and heterocyclic amine derivatives; the herbicides anilofos and piperophos have been developed.

Many phosphorothiolothionate insecticides derived from nitrogen-containing heterocycles have a P-S-C-N-C=O linkage in the molecule, as exemplified by phosmet, phosalone, and azinphos. This is also the case for the non-heterocyclic insecticide fosmethilan. The distance between P and the carbonyl C is about 4.8 angstrom, probably playing an important role for binding to the target site of AChE.[120]

In contrast with phosphorothionate insecticides, only a few aryl phosphorothiolothionate esters have been utilized so far as insecticides. However, some asymmetric *O*-alkyl *O*-aryl *S*-propyl phosphorothiolothionate insecticides such as sulprophos and prothiofos have recently been developed and are interestingly effective against certain OP-resistant insects.[137]

Phosphorothiolothionates are converted into phosphorothiolates by oxidative desulfuration.

E. Phosphoramide Derivatives

This section deals with the derivatives of phosphoramidic acid and phosphoramidothioic acids, which have a P-N bond in the molecule. The amide group contributes to absorbability into plants, so that many useful systemic insecticides have been developed.

Phosphoramides of secondary amines are stable to alkaline hydrolysis and have little anti-AChE activity because of the high electron-donating ability of the amido nitrogen giving $d\pi$-$p\pi$ bonding between P and N. This reduces the positive charge at phosphorus. They are, however, unstable to acid hydrolysis because protonation of the nitrogen generates a positive charge.

The secondary phosphorodiamides schradan and dimefox exert potent inhibitory activity against AChE only when they are oxidatively activated, probably into the *N*-oxide or methylol.[3,145,146] They are very toxic to mammals and are not currently used as insecticides.

The electron donating ability decreases in the order R_2N > RNH >> RO, suggesting that the primary phosphoramides should be somewhat more susceptible than *N,N*-dialkylphosphoramides, but much more stable than phosphates. However, *N*-monoalkyl-

phosphoramides are more susceptible to alkaline hydrolysis than expected. For example, *N,N*-dipropylphosphorodiamidic chloride is hydrolyzed over 4 million times as fast as *N,N,N',N'*-tetramethyl phosphorodiamidic chloride in alkaline solution.[147] Since *N*-alkylphosphoramides behave as weak acids, the alkaline hydrolysis proceeds probably through removal of the amide proton followed by halide elimination forming a very reactive monomeric metaphosphate type intermediate.

O,S-Dimethyl *N*-methylphosphoramidothiolate and the *N*-unsubstituted homolog (the insecticide methamidophos) are rapidly hydrolyzed at a rate comparable to methyl paraoxon; their pseudo hydrolysis constants (min^{-1}) at pH 11.5 and 30° were 0.018, 0.032, and 0.016 respectively.[119] Since substitution reaction with other nucleophiles, such as fluoride ion, is not as fast as alkaline hydrolysis, the reaction with hydroxide ion is presumed to proceed through a metaphosphate type intermediate.[16]

The thiolo effect discussed previously is not obvious in *S*-alkyl phosphoroamidothiolates, probably because of a potent electron donating ability of the amido nitrogen to the phosphorus center. Methamidophos shows only a poor anti-AChE activity in comparison with methyl paraoxon; their bimolecular inhibition constants k_i ($M^{-1}min^{-1}$) against housefly head AChE are 9.2×10^2 and 2.9×10^5 respectively.[119] Methamidophos shows, however, much more insecticidal potency than expected from its *in vitro* anti-AChE activity. Chemical or biochemical oxidation increases the AChE inhibitory activity of methamidophos.[148] The unstable oxidation product exerted phosphorylating activity and was partially reduced to methamidophos by treating with trimethyl phosphite, suggesting that the oxidation converted the phosphoramidothiolate into the sulfoxide. Although this is not always supported by others,[149] formation of the *S*-oxide by oxidation of methamidophos with *m*-chloroperbenzoic acid has been confirmed by means of ^{13}C NMR studies.[150]

Acephate is the *N*-acetyl derivative of methamidophos and has very low mammalian toxicity. It is transformed, at least in part, to methamidophos in a bioactivation step.[149]

O-Alkyl *S*-substitutedphenyl phosphoramidothiolates show higher AChE inhibitory activity but less insecticidal activity than do *S*-alkyl analogs.[151] In such highly active *S*-aryl phosphoramidothiolates, the thiolate-S oxidation may accelerate only the degradation.

Several phosphoramidates based on substituted phenols have been developed into commercial insecticides. Isofenphos is a soil insecticide with systemic activity. It is a poor anti-AChE agent and is activated by chemical or biochemical oxidation.[152,153] Isophenfos oxon is also a poor inhibitor and is bioactivated.[70,153,154] The enhancement of inhibitory activity on housefly head AChE by bioactivation depends on stereochemistry. (+)-Isofenphos oxon showed 420-fold greater activity than the (-)-isomer after activation with the rat liver microsomal system.[70] Thus, two steps of the bioactivation process, *i.e.* oxidative desulfuration and *N*-dealkylation, have been proposed to give ultimately *O*-ethyl *O*-[2-(isopropoxycarbonyl)phenyl] phosphoramidate, which has 2300-fold greater inhibitory potency than isofenphos oxon.[153] However, an unknown more active metabolite is supposed for several reasons: 1) the *in vivo* AChE inhibitory activity of *N*-deisopropylisophenfos oxon is lower in the American cockroach with SKF treatment;[155] 2) its anti-AChE activity is increased by mfo treatment;[152] and 3) (-)-isofenphos is transformed to the oxon more rapidly than the (+)-isomer by the action of mfo, whereas (+)-isofenphos and its oxon are more potent than their enantiomers in insecticidal activity.[156]

The anti-AChE activity of alkyl substituted phenyl *N*-alkylphosphoramidates correlates with the hydrolysis rate and the hydrophobic property (π) of the ring-substituent.[157] Moreover, the steric factor of an *N*-alkyl group affects markedly the anti-AChE activity. Small and electron releasing groups are preferable as substituents on the amide nitrogen for AChE inhibition.[119]

Systemic insecticides phosfolan and mephosfolan are unique dithiolane iminophosphates, and fosthietan is a related dithietane derivative. The dithiolane iminophosphates are poor AChE inhibitors *in vitro* and are activated by mfo and chemical oxidations into irreversible inhibitors which are 160- 47,000-fold more potent than the parent compounds.[158] The oxidation products (sulfoxides and sulfones) react with nucleophiles at the imino carbon rather than at the phosphorus suggesting an unusual mode for inhibition of AChE.[159]

The systemic insecticide avenin, with a low mammalian toxicity, consists of phosphoramide and carbamate functions which share a nitrogen atom. The high mammalian toxicity of some carbamate insecticides is decreased by derivatizing them to phosphoramidates. PSC and U-56,295 are such examples of

proinsecticides.[28,30b]

Several *O*-alkyl *O*-aryl *N*-branchedalkylphosphoramidothionates such as amiprofos-methyl and butamifos have been developed as herbicides. Quantitative structure-activity studies on *O*-substitutedaryl *O*-ethyl *N*-isopropylphosphoramidothionates indicated that the herbicidal activity is mainly affected by the hydrophobicity and position of the ring substituents.[160] Amiprofos suppresses mitosis by inhibiting the biosynthesis of microtubule.[161] The (-)-enantiomer of herbicidal *O*-ethyl *O*-2-nitro-5-methylphenyl *N*-isopropylphosphoramidothionate was much more potent than the (+)-enantiomer.[162]

When the 5-methyl group of the herbicide butamifos was replaced by a methoxy group, a highly fungicidal compound against *Pseudopernospora cubensis* was obtained.[163] Introduction of another methoxy group at the 4-position increased the fungicidal activity.[164] The fungicide ditalimfos is the *N*-dimethylphosphinothioyl derivative of phthalimide. Another fungicide, phosbutyl, is a phosphoramidothionothiolate. The dibutyl (BPA) and dihexyl (HPA) esters of *N*-methyl-*N*-phenylphosphoramidic acid show negative cross resistant activity against *Pyricularia oryzae* strains resistant to phosphorothiolate type fungicides.[165] BPA inhibits the phospholipid *N*-methylation by the resistant strains more specifically than that in the normal strains.[166]

Many aziridine derivatives of phosphoric acid have been investigated for insect chemosterilants.[167] They are biological alkylating agents. Tepa, thiotepa, metepa, and apholate are typical examples. The non-aziridine containing phosphoramide hempa (hexamethylphosphoric triamide) also shows insect sterilizing activity.[168] Hempa is biooxidatively demethylated *via* a highly reactive methylol intermediate which appears to be the active principle for sterilization.[169]

F. Cyclic Phosphates and Phosphoramidates

The extremely high reactivity of five-membered cyclic phosphates has been well demonstrated through studies relating to the hydrolysis intermediates of RNA. The hydrolysis rate of ethylene phosphate is 10^7 to 10^8 times that of dimethyl phosphate, in contrast to six-membered cyclic phosphates which hydrolyze some 10-fold faster than the open-chain esters.[170,171] The five-membered cyclic phosphate structure is fitted to neither the acyl rule nor PXYZ systems, but its high ring strain makes the $d\pi$-$p\pi$

contribution in the P-O bond low, and consequently decreases the electron density at phosphorus;[172,173] O-P-O bond angles of five-membered phosphates and acyclic phosphates are 98-99° and 102-108° respectively.[174]

Although some five-membered cyclic phosphates as di(1,2-dimethylethylene) pyrophosphate can be utilized as phosphorylating agents,[175] they are so labile that they decompose in the insect body before exerting any anti-AChE or insecticidal effect.[176,177] Introduction of an amide nitrogen into the ring system causes appropriate stabilization and a phosphorylating agent, 2-phenoxybenzoxazaphosphole 2-oxide, has been developed.[178] However, these benzene ring-fused five-membered cyclic phosphoramidates have no insecticidal activity.

The chemical reactivity of OP is important, but only a factor for their biological activity. The high insecticidal activities were attained by introducing a branched alkyl group, such as isobutyl or isopropyl, to the 4-position of 2-methoxy-1,3,2-oxazaphospholidine 2-sulfides (MOS).[179-181] This idea came from the finding of L-leucine as an insect neuroactive substance.[182] The cyclic phosphoramidates have two chiral centers at the phosphorus and the carbon atom at the 4-position. The insecticidal activity is affected by the stereochemistry[53,183] and the most active stereoisomer is $(R)_P(S)_C$ without exception.[71] Similar derivatization from octopamine, an insect neurotransmitter, afforded the highly insecticidal 5-phenyl analog.[56] It is interesting to note that either the 4-phenyl or 5-alkyl regioisomer is poor in insecticidal activity and that the most potent stereoisomers are $(R)_C$ for 5-phenyl and $(S)_C$ for 4-alkyl derivatives, coinciding with the structures of natural D-octopamine and L-leucine, respectively. Thus, the most potent insecticides in these series are $(S)_C(R)_P$ 4-isobutyl-MOS and $(R)_C(R)_P$ 5-phenyl-MOS.

Six-membered cyclic phosphates derived from alkanediols are poor in anti-AChE activity.[176] The *p*-nitrophenyl derivative (2-*p*-nitrophenoxy-1,3,2-dioxaphosphorinane 2-oxide) is chemically reactive as well as is paraoxon, but shows little anti-AChE and insecticidal activities.[176] Some six-membered cyclic phosphorus ester halogenides have anti-AChE activity[184] and an experimental insecticide UC 8305 has been patented.[185] These activities are, however, based on the "acyl" rule and the ring structure may relate only to certain steric effects.

On the other hand, six-membered cyclic phosphates derived from *o*-hydroxybenzyl alcohol (saligenin) exert high reactivity and biological activities.[3,11a,186] Of them the first compound, 2-*o*-tolyoxy-4*H*-1,3,2-benzodioxaphosphorin 2-oxide, was found as the neurotoxic metabolite of tri-*o*-tolyl phosphate[187] and its structural modifications afforded the insecticide salithion.[188] Although the acidity of saligenin is almost the same as that of phenol, and far less than that of *p*-nitrophenol, the alkaline hydrolysis rate is greater than that of paraoxon.[181] Compared with diethyl phenyl phosphate, whose hydrolysis rate is only 1/300 that of paraoxon, saligenin cyclic phosphates are much more reactive than expected. The endocyclic O-P-O angle (104°) of salithion is in the range of angles in normal acyclic phosphate esters.[189] The two endocyclic C-O-P angles (~120°) indicate sp^2-hybridization and possible $d\pi$-$p\pi$ bonding with phosphorus. Thus, strain in the ring of saligenin cyclic phosphates appears rather small. Fusion of a benzene ring, however, appears to activate the six-membered cyclic phosphate ester group. In this context, it is noteworthy that cAMP is remarkably active in contrast with six-membered monocyclic phosphates; the δH_{hydro} values of cAMP and trimethylene phosphoric acid are -59.2 and -12.6 kJ/mole.[190] Saligenin cyclic phosphates react stoichiometrically with serine enzymes to phosphorylate them and inactivate them by opening the ring at the P-O (aryl) bond.[187]

An outstanding contrast was observed in the effect of *p*-substitution between the salithion series and parathion series. The insecticidal activity of the latter is progressively increased by *p*-substitution with increasing electron-withdrawing ability of the substituent, whereas introduction of any electron-withdrawing or releasing group in the ring decreases the activity of salithion.[191] Introduction of a methyl group at the 4-position also reduces the biological activity.[192] 4-Alkylidene analogs also show similar biological activities as saligenin cyclic phosphates.[193]

The biological activities of saligenin cyclic phosphates are greatly influenced by the exocyclic substituent on the phosphorus atom. All of the aryl esters manifest a high delayed neuropathy, but no insecticidal activity.[194] On the contrary, the corresponding cyclic esters having a small alkyl group on phosphorus did not cause ataxia in hens with sublethal doses, but exhibited a high insecticidal activity.[194-197] This specificity relates to their selectivity in enzyme inhibition. When the size of the exocyclic

substituent increases, the ester becomes a more selective inhibitor of aliesterase.[127] In contrast, the ester carrying a small substituent is more selective to AChE. Therefore, the exocyclic substituent is regarded as the selectophore in the biological actions.

The *S*-methyl isomer (MTBO) of salithion has a higher phosphorylating activity by the thiolo effect than the corresponding *O*-ester salioxon. Since the *o*-hydroxybenzyl group formed by the ring opening in the course of phosphorylation can readily be removed by an appropriate nucleophile and the *S*-methyl group can be activated by oxidation, MTBO has been utilized as a two-step phosphorylating agent to synthesize biologically important phosphate esters, including cAMP.[198]

Although bicyclic phosphates (2,6,7-trioxa-1-phosphabicyclo[2.2.2]octanes; BP) show high chemical reactivity comparable to fenitroxon in alkaline hydrolysis, they have no anti-AChE activity.[199,200] BPs bearing a hydrophobic bulky group, such as isopropyl and *t*-butyl, at the 4-position have high mammalian toxicity.[201-203] It has been demonstrated that they are anti-GABA agents and interfere with the GABA-gated chloride channel site as picrotoxinin.[204-206] BPs have only weak insecticidal activity.[207] The insect target site appears distinct from the vertebrate's at the point of their molecular recognition. The *n*-propyl BP is more toxic to insects in comparison with *t*-butyl BP and binds much more tightly to the housefly synaptic membrane.[208] The phosphorus ester function can be replaced by orthobenzoate, maintaining anti-GABA activity,[209] and 4-*n*-butyl-1-[(*p*-trimethylsilyl)ethynylphenyl]-2,6,7-trioxabicyclo[2.2.2]octane is a remarkably selective insecticide.[210]

G. Derivatives of Phosphonic and Phosphinic Acids

Phosphonate insecticides having one P-C bond in the molecule are divided into three main types. These are: α-hydroxyalkylphosphonates, such as trichlorfon, phenylphosphonothionates, such as EPN, and alkylphosphonothionates, such as fonofos. Only two derivatives of phosphinic acids, which have two C-P bonds, are known as insecticides, agvitor and nibufin. Two phosphinate herbicides, glyfosinate (ammonium salt of phosphinothricin) and bialaphos, have recently been noted. These herbicides are discussed in another Chapter of this work.

Because there is no $d\pi$-$p\pi$ contribution to the P-C bond, the electrophilicity of the phosphorus atom in phosphonate esters is

rather high in spite of the low electronegativity of the carbon atom. Consequently, phosphonate esters are generally more reactive than the corresponding phosphate esters. This does not mean that the cleavage of the P-C bond occurs in the nucleophilic displacement reaction on phosphorus, but that the "acyl" group leaves.

Methylphosphonates bearing a proper leaving group exert high anti-AChE activity.[211] The alkyl group of ethyl *p*-nitrophenyl alkylphosphonates affects the anti-AChE activity more than alkaline hydolyzability. Only the steric substituent constant E_S^c correlates well with the AChE inhibition rate k_i, indicating that the steric effect of the alkyl group is most important for the AChE inhibition. The large alkyl groups prevent the proper contact of the phosphoryl function with the esteratic site of AChE.[119] However, the variation of non-leaving groups has less effect on biological activities in phosphonate esters than in phosphate esters, as exemplified by the fact that *n*-butyl *p*-nitrophenyl ethylphosphonate is as active as the methyl ester homolog in insecticidal activity. Moreover, phenylphosphonates such as EPN are also active. Thus, the phosphonate class is expected to have a greater variety of structures for possible insecticides than the phosphate class.

The effects on biological activities of the ring substituents on the phenolic group differ markedly between phosphonate and phosphate classes. The introduction of a methyl group onto the *m*-position of methyl parathion causes a great decrease in mammalian toxicity, but only a small effect is observed with methylphosphonothionate and EPN.[212] On the other hand, the introduction of a methyl group onto the *p*-position of the fonofos-type *S*-phenyl alkylphosphonodithioates decreases the mammalian toxicity, whereas it decreases only the insecticidal activity in the corresponding phosphorodithioate.[34]

The cleavage of the P-C bond occurs only in special cases. The anti-AChE inhibition by phosphorocyanidates such as the nerve gas tabun is undoubtedly attributable to the reactivity of the P-CN bond. No compound of this type is usable as an agrochemical. The insecticide trichlorfon exerts anti-AChE activity after being converted into the vinyl phosphate dichlorvos under physiological conditions of pH. This activation process may be an "opportunity factor" for occurrence of detoxication contributing to low mammalian toxicity. The acylation of the α-hydroxyl group further decreases the toxicity.[214] The butyryl derivative is the insecticide butonate.

There is some analogy in structure-biological relationships between phosphonate and phosphate esters. For example, the insecticide mecarphon is the analog of mecarbam. Compare the structure of a herbicidal *O*-aryl *N*-alkylchloromethylphosphonamidothionate, isophos, with those of phosphoramidothionate herbicides DMPA and others. *S*-Benzyl phenylphosphonothiolate (ESBP) has fungicidal activity as well as the corresponding *S*-benzyl phosphorothiolate. *O,O*-Diphenyl dichloromethylphosphonate was reported to show anti rice-blast activity as well as the thiolate type fungicide edifenphos, *O*-ethyl *S,S*-diphenyl phosphorodithiolate.[215]

Many EPN-type and fonofos-type insecticides have been resolved and steric structure-biological activity relationships have been investigated.[216,217] In these chiral OP insecticides the (*R*) isomers are generally more potent than the (*S*) isomers in insecticidal activity. On the other hand, the delayed neurotoxicity on hens is observed only in the (*S*) isomers and racemates of EPN-type phenylphosphonothionates.[216]

Phosphinate esters are in general more chemically reactive, but rather poor in insecticidal activity compared to the corresponding phosphonate esters. Since no aging occurs, however, in the inactivated AChE, phosphinate-type insecticides with low mammalian toxicity may be discovered. On the other hand, a pyridinylmethylphenylphosphinate ester is a systemic fungicide inhibiting fungal ergosterol biosynthesis.[218a] Similar activity is found in a triazolylmethyldiphenylphosphine sulfide,[218b] whose thiophosphoryl group is replaced by a methylsilane giving the fungicide fusilazole.

Some phosphonic and phosphinic acids or their salts show different types of biological activities from the neutral phosphonate esters. β-Chloroethylphosphonic acid (ethephon) is a plant growth regulator, producing the ripening hormone ethylene by decomposition. Of α-amino acid related phosphonic acids, the herbicide glyphosate and the plant growth regulator glyphosine have been developed. The former blocks the shikimate pathway for aromatic amino acid biosynthesis by competing with phosphoenolpyruvate to inhibit 5-enolpyruvylshikimate-3-phosphate synthase.[219a] Phosphonomycin also competes with phosphoenolpyruvate to inhibit pyruvate-UDP-*N*-acetylglucosamine transferase and blocks bacterial cell wall formation.[219b] Alaphosphin exerts anti-bacterial activity, inhibiting the biosynthesis of bacterial

cell-wall peptidoglycan as an alanine-analog.[220] Phosphonoformate is a metabolite of the herbicide fosamine[221] and shows an anti-viral activity by inhibiting DNA polymerase as a pyrophosphate analog.[222] The systemic fungicide fosetyl-aluminum (ethyl aluminum phosphate) releases phosphonate ion, which can be converted to phosphoric acid by tolerant fungi but can not by sensitive fungi, and competes with phosphate ion to lead to a physiological state similar to phosphate starvation.[223,224] Bialaphos and its active metabolite phosphinothricin (glufosinate) are potent herbicides, acting as transition-state analogs to inhibit glutamine synthetase.[225]

H. Derivatives of Pyrophosphoric Acid

Since the development of TEPP as the first commercial organophosphorus insecticide in 1943, the derivatives of pyrophosphoric acid have actively been investigated, but only a small number of the compounds of this class have been utilized.

The pyrophosphate esters are active according to Schrader's "acyl" rule. However, the tetraamide schraden does not inhibit AChE *in vitro*. It is oxidatively activated but it is not known if the activated form is the *N*-oxide or the *N*-methylol. All of the pyrophosphoric acid derivatives except tetrapropyl dithiopyrophosphate (NPD) are highly toxic to mammals.

I. Phosphites

Although important as intermediates for the synthesis of phosphoryl type agrochemicals, only a few phosphites are utilized as agrochemicals. The defoliant merphos, tributyl phosphorotrithioite, is produced by the reaction of phosphorus trichloride with butyl mercaptan.[226] It is converted into the active phosphoryl compound DEF by autooxidation.

DEF is synergistic with the insecticide malathion, inhibiting carboxyesterase *in vivo* by further biooxidation probably into the *S*-oxide.[140] Tris[2-(2,4-dichlorophenoxy)ethyl] phosphite, the major active ingredient of the herbicide 2,4-DEP, may be activated into 2,4-D by hydrolysis followed by oxidation in soil or plants.

J. Phosphonium Salts

Some phosphonium salts are used as plant growth regulators. Chlorphonium produced by the reaction of 2,4-dichlorobenzyl chloride with tributylphosphine retards the growth of plants probably by interfering with gibberellin biosynthesis, as do

other onium compounds.[227] The triphenyltin related phosphonium salt decafentin is a fungicide.

K. Chiral Phosphorus Compounds

A variety of organophosphorus pesticides having a chiral phosphorus atom in the molecule have been developed, including phosphonate derivatives such as EPN and fonofos, phosphoramidates such as acephate, and the herbicide butamiphos, the phosphorothiolate profenofos, the phosphorothionate salathion, and the phosphorothiolothionate prothiofos. Optical resolution of these have actively been performed and clarified the remarkable stereospecificity in their biological activity.[216,217]

The effects of organophosphates on anti-AChE activity are well documented.[217] AChE inhibition by organophosphates is highly stereoselective. Almost all reported results using chiral organophosphates whose absolute configuration was confirmed support the restricted space hypothesis for the left side of the AChE oxyanion hole discussed previously. Of the four stereoisomers of *O-sec*-butyl *S*-2-(dimethylammonium)ethyl ethylphosphonothiolate which contain chiral carbon and phosphorus atoms, the most potent inhibitor against bovine erythrocyte AChE is the $(S)_C(S)_P$ isomer followed in decreasing order by $(R)_C(S)_P >> (S)_C(R)_P > (R)_C(R)_P$.[228] This is also the case against housefly-head AChE. The $(S)_C(S)_P$ isomer is more potent than its enantiomer by 5,300- and 10,300-fold against the bovine enzyme and the housefly enzyme respectively, with regard to the bimolecular inhibition rate constant. The great differences in anti-AChE activity are attributable to differences in the affinity constant (300- and 290-fold) and the phosphorylation constant (17- and 35-fold), both of which are greatly affected by the configuration of phosphorus which interacts directly with the esteratic site of AChE. The effect of OP stereochemistry on horse serum BChE is not so large, being only 560-fold. The effect of asymmetry at carbon is rather small in comparison with that at phosphorus. Similar results have been obtained with some other organophosphates.[217]

The insecticidal activity is, of course, affected by the steric structure of organophosphates. For example, the insecticidal activity (LD_{50}; μg/g) of $(S)_C(S)_P$ and its enantiomer for *O-sec*-butyl *S*-2-(ethylthio)ethyl ethylphosphonothiolate are 6.9 and >500, respectively, and their housefly-head AChE inhibitory

activities ($M^{-1}min^{-1}$) are 1.7 x 10^6 and 1.3 x 10^3, respectively.[229] The enantiomeric difference in insecticidal activity of actual thionate type insecticides is definite, but varies over a large range. For salathion with susceptible housefly, LD_{50} difference is only 2.4-fold,[230] whereas that of cyanofenphos toward rice stem borer is more than 24-fold.[231] The biochemical oxidative desulfuration of the thiophosphoryl group proceeds mainly with retention of the phosphorus configuration,[232-234] so that the more potent thionate enantiomers are generally isosteric with the more potent anti-AChE oxon enantiomers.

The effects of chirality in the leaving group of organophosphates on the anti-AChE activity and insecticidal activity are not so remarkable, but are as distinctive as that at the phosphorus center. (+)-Diethylmalaoxon is several times as active as an anti-AChE agent as its enantiomer, and (+)-diethylmalathion is twice as toxic as its enantiomer.[235] In phenthoate, the (+)-isomer is more toxic than the (-)-isomer toward mosquitos, rice stem borer, and mouse, whereas the reverse situation holds toward the housefly. These results are consistent with the inhibitory activity of the enantiomeric oxons against the corresponding AChEs.[236] In five-membered cyclic phosphoramidates, including various 4-alkyl- and 5-aryl-2-methoxy-1,3,2-oxazaphospholidine 2-sulfides, the configuration of the carbon atom at the 4- or 5-position influences the insecticidal activity more than the phosphorus configuration.[56,71]

The biological effects of phosphorus chirality also vary considerably by species of insect.[216] (*S*)-Salathion and the isosteric (*R*)-salioxon are more potent than their enantiomers in insecticidal activity against housefly and in inhibitory activity toward housefly AChE, respectively,[230] whereas their activities toward *Tribolium castaneum* larvae are completely reversed.[237]

More interestingly, the characteristics in biological activities differ by configuration at phosphorus. (*S*)-(-)-EPN induces delayed neuropathy in hens by administration of 40.6-89.2 mg/Kg, whereas the (*R*)-(+)-isomer does not do so even at 89.2 mg/Kg.[238] The insecticidal activity of EPN enantiomers is in the reverse relationship. Similar relationships are also observed in leptophos, debromoleptophos, and dibromoleptophos oxon.[52,61]

Some asymmetric phosphoramidothionate herbicides were resolved and differences in their herbicidal activities have been reported.[162]

VI. Organophosphorus Agrochemicals

Agvitor - 2,4,5-trichlorophenyl diethylphosphinothionate
Alaphosphin - *N*-alanyl-1-aminoethylphosphonic acid
Amiprofos - ethyl 2-nitro-4-methylphenyl *N*-isopropylphosphoramidothionate
Amiprofos-methyl - methyl 2-nitro-4-methylphenyl *N*-isopropylphenylphosphoramidothionate
Amiton - diethyl *S*-(2-diethylaminoethyl) phosphorothiolate hydrogen oxalate
Anilofos - dimethyl *S*-(*N*-*p*-chlorophenyl-*N*-isopropylcarbamoylmethyl) phosphorothiolothionate
Apholate - 2,2,4,4,6,6-hexakis(1-aziridinyl)-2,2,4,4,6,6-hexahydro-1,3,5,2,4,6-triazatriphosphorine
Avenin - dimethyl *N*-(isopropoxycarbonyl)phosphoramidate
Azinphos-methyl - dimethyl *S*-(4-oxobenzotriazino-3-methyl) phosphorothiolothionate
Bialaphos - L-2-amino-4-[hydroxy(methyl)phosphinyl]butyryl-L-alanyl-L-alanine
Bomyl - 1,3-bis(methoxycarbonyl)-1-propen-2-yl dimethyl phosphate
Buminafos - dibutyl 1-(*N*-butylamino)cyclohexylphosphonate
Butamifos - ethyl 2-nitro-5-methylphenyl *N*-*sec*-butylphosphoramidothionate
Butathiofos - diethyl 2-isobutylpyrimidin-5-yl phosphorothionate
Butonate - dimethyl 1-butyryloxy-2,2,2-trichloroethylphosphonate
Carbophenothion - *S*-(*p*-chlorophenyl)thiomethyl diethyl phosphorothiolothionate
Chlorfenvinphos - 2-chloro-1-(2,4-dichlorophenyl)vinyl diethyl phosphate
Chlorphonium - 2,4-dichlorobenzyltributylphosphonium chloride
Chlorpyrifos - diethyl 3,5,6-trichloro-2-pyridyl phosphorothionate
Chlorthion - 3-chloro-4-nitrophenyl dimethyl phosphorothionate
Coroxon - 3-chloro-4-methylcoumarin-7-yl diethyl phosphate
Crufomate - 2-chloro-4-*tert*-butylphenyl methyl *N*-methylphosphoramidate
Debromoleptophos - 2,5,-dichlorophenyl methyl phenylphosphonothionate
Decafentin - decyltriphenylphosphonium bromochlorotriphenylstannate
DEF - *S,S,S*-tributyl phosphorotrithiolate
Demeton - *O,O*-diethyl 2-ethylthioethyl phosphorothioate
Demeton-O - *O,O*,-diethyl *O*-ethylthioethyl phosphorothionate

Demeton-S - *O,O*-diethyl *S*-2-ethylthioethyl phosphorothiolate
Demeton-S-methyl - *O,O*-dimethyl *S*-2-ethylthioethyl phosphorothiolate
Demuphos - dimethyl *N*-methyl-*N*-(isopropoxycarbonyl)phosphoramidate
2,4-DEP - tris- and bis-β-(2,4-dichlorophenoxy)ethyl phosphites
DFP - diisopropyl phosphorofluoridate
Diazinon - diethyl 2-isopropyl-6-methyl-4-pyrimidinyl phosphorothionate
Dichlorvos - 2,2-dichlorovinyl dimethyl phosphate
Dicrotophos - 3-(dimethoxyphosphinyloxy)-*N,N*-dimethyl-*cis*-crotonamide
Dimefox - *N,N,N'N'*-tetramethylphosphorodiamidic fluoride
Dimethoate - dimethyl *S*-(*N*-methylcarbamoylmethyl) phosphorothiolothionate
Dimethoxon - dimethyl *S*-(*N*-methylcarbamoylmethyl) phosphorothiolate
Dioxathion - 1,4-dioxan-2,3-ylidene bis(*O,O*-diethyl phosphorothiolothionate)
Disulfoton - dimethyl *S*-(2-ethylthioethyl) phosphorothiolothionate
Ditalimfos - *N*-(diethoxyphosphinothioyl)phthalimide
DMPA- 2,4-dichlorophenyl methyl *N*-isopropylphosphoramidothionate
Edifenphos - *S,S*-diphenyl ethyl phosphorodithiolate
EPN - ethyl *p*-nitrophenyl phenylphosphonothionate
Ethephon - 2-chloroethylphosphonic acid
Fenitrothion - dimethyl 3-methyl-4-nitrophenyl phosphorothionate
Fenthion - dimethyl 3-methyl-4-methylthiophenyl phosphorothionate
Fonofos - ethyl *S*-phenyl ethylphosphonothiolothionate
Fosamine-ammonium - ammonium ethyl carbamoylphosphonate
Fosetyl-aluminum - aluminum tris-(ethyl hydrogen phosphite)
Fosmethilan - *S*-[(*N*-2-chlorophenyl)butyrylamidomethyl] dimethyl phosphorothiolothionate
Fospargyl - dipropargyl ethyl phosphate
Fosthietan - 2-(diethoxyphosphinylimino)-1,3-dithietane
Glufosinate - 2-amino-4-[hydroxy(methyl)phosphinyl]butyric acid ammonium salt
Glyphosate - *N*-(phosphonomethyl)glycine
Glyphosine - *N,N*-bis(phosphonomethyl)glycine
Haloxon - bis(2-chloroethyl) 3-chloro-4-methylcoumarin-7-yl phosphate

Hempa - hexamethylphosphoric triamide
IBP (Iprobenfos) - *S*-benzyl diisopropyl phosphorothiolate
Isofenfos, ethyl 2-isopropoxycarbonylphenyl *N*-isopropylphosphoramidothionate
Isomalathion - *S*-[1,2-bis(ethoxycarbonyl)ethyl] *O,S*-dimethyl phosphorodithiolate
Isophos- 2,4-dichlorophenyl *N*-isopropylchloromethylphosphonamidothionate
Isoxathion - diethyl 5-phenyl-3-isoxazolyl phosphorothionate
Leptophos - 4-bromo-2,5-dichlorophenyl methyl phenylphosphonothionate
Malaoxon -*S*-[1,2-bis(ethoxycarbonyl)ethyl] dimethyl phosphorothiolate
Malathion -*S*-[1,2-bis(ethoxycarbonyl)ethyl] dimethyl phosphorothiolothionate
Mecarbam - diethyl *S*-(*N*-ethoxycarbonyl-*N*-methylcarbamoyl-methyl) phosphorothiolothionate
Mephosfolan - 2-(dimethylphosphinylimino)-4-methyl-1,3-dithiolane
Merphos - tributyl phosphorotrithioite
Metepa - tris(2-methyl-1-aziridinyl)phosphine oxide
Methacrifos - (*E*)-dimethyl 2-methoxycarbonyl-1-propenyl phosphorothionate
Methamidophos - *O,S*-dimethyl phosphoramidothiolate
Methidathion - dimethyl *S*-(2-methoxy-1,3,4-thiadiazol-5-(4*H*)-onyl-4-methyl) phosphorothiolothionate
Mevinphos - dimethyl 1-methoxycarbonyl-1-propen-2-yl phosphate
Mipafox - *N,N'*-diisopropylphosphorodiamidic fluoride
MTBO - 2-methylthio-4*H*-1,3,2-benzodioxaphosphorin 2-oxide
Naled - 1,2-dibromo-2,2-dichloroethyl dimethyl phosphate
Nibufin - *p*-nitrophenyl dibutylphosphinate
NPD - *O,O,O,O*-tetrapropyl dithiopyrophosphate
Paraoxon - diethyl *p*-nitrophenyl phosphate
Parathion - diethyl *p*-nitrophenyl phosphorothionate
Phenkapton - *S*-(2,5-dichlorophenylthiomethyl diethyl phosphorothiolothionate
Phenthoate - dimethyl *S*-[(α-ethoxycarbonyl)benzyl] phosphorothiolothionate
Phorate - diethyl *S*-(ethylthiomethyl) phosphorothiolothionate
Phosalone - *S*-(6-chlorobenzoxazolone-3-ylmethyl) diethyl phosphorothiolothionate
Phosdiphen - bis(2,4-dichlorophenyl) ethyl phosphate

Phosfolan - 2-(diethoxyphosphinylimino)-1,3-dithiolane
Phosmet - dimethyl *S*-phthalimidomethyl phosphorothiolothionate
Phosphinothricin - 2-amino-4-[hydroxy(methyl)phosphinyl]butyric acid
Phosphonoformate - phosphonoformic acid sodium salt
Phosphonomycin - (1*R*,2*S*)-1-epoxypropylphosphonic acid
Phoxim - (diethoxyphosphinothioyloxyimino)phenylacetonitrile
Piperophos - dipropyl *S*-(2-methylpiperidinocarbonylmethyl) phosphorothiolothionate
Profenofos - 4-bromo-2-chlorophenyl ethyl *S*-propyl phosphorothiolate
Propaphos- dipropyl *p*-methylthiophenyl phosphate
Propetamphos - 1-isopropoxycarbonyl-1-propen-2-yl methyl *N*-ethylphosphoramidothionate
Prothiofos - 2,4,-dichlorophenyl ethyl *S*-propyl phosphorothiolothionate
PSC - 2,3-dihydro-2,2-dimethyl-7-benzofuranyl *N*-dimethoxyphosphinothioyl-*N*-methylcarbamate
Pyraclofos - 1-(*p*-chlorophenyl)pyrazol-4-yl ethyl *S*-propyl phosphorothiolate
Salioxon - 2-methoxy-4*H*-1,3,2-benzodioxaphosphorin 2-oxide
Salithion - 2-methoxy-4*H*-1,3,2-benzodioxaphosphorin 2-sulfide
Schradan - *N,N,N',N'*-tetramethylphosphorodiamidic anhydride
Sulfotep - *O,O,O,O*-tetramethyl dithiopyrophosphate
Sulprofos - ethyl *p*-methylthiophenyl *S*-propyl phosphorothiolothionate
Tepa - tris(1-aziridinyl)phosphine oxide
TEPP - tetraethyl pyrophosphate
Terbufos - diethyl *S*-*tert*-butylthiomethyl phosphorothiolothionate
Thiodemeton - diethyl *S*-(2-ethylthioethyl) phosphorothiolothionate
Toclofos-methyl - 2,3-dichloro-4-methylphenyl dimethyl phosphorothionate
Trichlorfon - dimethyl 1-hydroxy-2,2,2-trichloroethylphosphonate
Trichloronat - ethyl 2,4,5-trichlorophenyl ethylphosphonothionate

VII. Bibliography

1. Schrader, G. (1963). *Die Entwicklung neuer insektiziden Phosphorsaure-Ester*, Verlag-Chemie, Weinheim.
2. Fest, C., and Schmidt, K.-J. (1973). *The Chemistry of Organophosphorus Pesticides*, Springer-Verlag, Berlin.
3. Eto, M. (1974). *Organophosphorus Pesticides: Organic and Biological Chemistry*, CRC Press, Cleveland.

4. Sasse, K. (1964). *Houben-Weyl Methoden der Organischen Chemie*, Vol. 12, Bd. 1 & 2, (Muller, E., ed.) Thieme Verlag, Stuttgart.
5. Kosolapoff, G.M., and Maier, L. (1976). *Organophosphorus Compounds*, Vol. 1-7, Wiley, New York.
6. Edmundson, R.S. (1988). *Dictionary of Organophosphorus Compounds*, Chapman & Hall, London.
7. Stiles, A.R., Reilly, C.A., Pollard, G.R., Tieman, C.H., Ward, L.F., Phillips, D.D., Soloway, S.B., and Whetstone, R.R. (1961). Preparation, physical properties, and configuration of the isomers in PHOSDRIN® insecticide, *J. Org. Chem., 26*: 3961.
8. Casida, J.E. (1955). Isomeric substituted vinyl phosphates as systemic insecticides, *Science, 122*: 597.
9. Lorenz, W., Henglein, A., and Schrader, G. (1955). The new insecticide *O,O*-dimethyl 2,2,2-trichloro-1-hydroxyethylphosphonate, *J. Am. Chem. Soc., 77*: 2554.
10. Fukuto, T.R., and Metcalf, R.L. (1954). Isomerization of β-ethylmercaptoethyl diethyl thionophosphate (Systox), *J. Am. Chem. Soc., 76*: 5103.
11a. Eto, M. (1976). Chemistry and biochemistry of salithion and related compounds, *Rev. Plant Protec. Res., 9*: 1.
11b. Kobayashi, K., Eto, M., Hirai, S., and Oshima, Y. (1966). An improved method for preparation of 2-substituted-4*H*-1,3,2-benzodioxaphosphorin 2-sulfides, *J. Agr. Chem. Soc., Japan, 40*: 315.
12. Sasaki, M., Moriguchi, K., and Yanagi, K. (1988). Synthesis of 2-methoxy-4*H*-1,3,2-benzodioxaphosphorin 2-sulfide and related compounds utilizing intramolecular cyclization reactions, *Agric. Biol. Chem., 52*: 159.
13. Schrader, G., Hannes, K., and Scheinpflug, H. (1968). Preparation of phosphorodithiol diesters, *Japan. Pat. 43-5747.*
14. Kawada, H., Okuda, I., Yoshinaga, E., and Kado, M. (1970). IBP (Kitazin P®), *Noyaku Seisan Gijitsu (Pesticide and Technique), 22*: 70.
15. Okada, Y., and Kono, Y. (1982). Synthesis and insecticidal activity of 4-pyrazolyl phosphates, *5th Internat. Cong. Pestic. Chem. Abstracts*: IIa-12.
16. Quitad, G.B., Fukuto, T.R., and Metcalf, R.L. (1970). Insecticidal anticholinesterase, and hydrolytic properties of phosphoramidothiolates, *J. Agric. Biol. Chem., 18*: 189.

17. Eto, M.-Y., Iio, M., Omura, H., and Eto, M. (1977). Synthesis of a new phosphorylating agent, 2-methylthio-4*H*-1,3,2-benzodioxaphosphorin 2-oxide (MTBO) from its thiono isomer, *J. Fac. Agr., Kyushu Univ., 22*: 25.
18. Rufenacht, K. (1968). Zur Chemie von GS 13005, einem neuen insektiziden Phosphorsaureester, *Helv. Chim. Acta, 51*: 518.
19. Clark, E.L., Johnson, G.A., and Mattson, E.L. (1955). Evaluation of *O,O*-dialkyl *S*-alkylthiomethyl phosphorodithioates, *J. Agric. Food Chem., 3*: 834.
20. Bacon, W.E., and LeSuer, W.M. (1954). Chemistry of the aliphatic esters of phosphorothioic acids. III. Alkoxide cleavage of *O,O,S*-trialkyl phosphorodithioates, *J. Am. Chem. Soc., 76*: 670.
21. Pellergrini, G., and Santi, R. (1972). Potentiation of toxicity of organophosphorus compounds containing carboxylic ester functions toward warm-blooded animals by some organophosphorus impurities, *J. Agric. Food Chem., 20*: 944.
22. Dively, W.R., Haubein, A.H., Lohr, A.D., and Moseley, P.B. (1959). Two organophosphorus derivatives of *p*-dioxane with insecticidal and acaricidal activity, *J. Am. Chem. Soc., 81*: 139.
23. Buchel, K.H. (1977). *Pflanzenschutz und Schadlingsbekampfung*, Georg Thieme Verlag, Stuttgart, p.37.
24. Leber, J.P. (1972). New class of vinyl thionophosphate insecticides, *Pesticide Chemistry Proceedings 2nd International IUPAC Congress*, Vol. 1, (Tahori, A.S., ed.) Gordon & Breach, London, p. 381.
25. Pierce, J.B., and Bell, A.R. (1982). Syntheses and herbicidal activity of [(dialkylamino)alkoxymethylene]phosphoramidic esters, *J. Agric. Food Chem., 30*: 1068.
26. Atherton, F.R., Penshaw, H.T., and Todd, A.R. (1945). The reaction of dialkyl phosphites with polyhalogen compounds in presence of bases. A new method for the phosphorylation of amines, *J. Chem. Soc.*: 660.
27. Stopkan, V.V. (1968). Systemic insecticide demuphos, *Khim. Prom. Ukr.*: 18.
28. Fahmy, M.A.H., Fukuto, T.R., Myers, R.O., and March, R.B. (1970). The selective toxicity of new *N*-phosphorothioylcarbamate esters, *J. Agric. Food Chem., 18*: 793.
29. Derkach, G.I., and Slyusanko, E.I. (1965). Mixed diesters of urethanphosphate, *Zh. Obshch. Khim., 35*: 2220.

30a. Dutton, F.E., Gemrich, E.G., Lee, G.L., Nelson, S.J., Parham, P.H., and Seaman, W.J. (1981). Insecticidal phosphoramidothio derivatives of the carbamate methomyl, *J. Agric. Food Chem., 29*: 1111.

30b. Dutton, F.E., Gemrich, E.G., Lee, B.L., Nelson, S.J., Parham, P.H., and Seaman, W.J. (1981). Insecticidal phosphorinanylaminothio derivatives of the carbamate methomyl, *J. Agric. Food Chem., 29*: 1114.

31. Ivin, S.Z., and Karavanov, K.V. (1958). Reaction of sulfur and inorganic sulfide with complex compounds of dialkyltrichlorophosphines and aluminum chloride, *Zh. Obshch. Khim., 28*: 2958.

32. Komkov, I.P., Karavanov, K.V., and Ivin, S.V. (1958). New methods of preparation of alkyldichlorophosphines and dialkylchlorophosphines, *Zh. Obshch. Khim., 28*: 2963.

33. Weissermel, K., Kleiner, H.-J., Finke, M., and Felcht, U.-H. (1981). Advances in organophosphorus chemistry based on dichloro(methyl)phosphane, *Angew. Chem., Int. Ed. Engl., 20*: 223.

34. Menn, J.J., and Szabo, K. (1965). The synthesis and biological properties of new *O*-alkyl *S*-aryl alkylphosphonodithioates, *J. Econ. Entomol., 58*: 734.

35. Sitting, M. (1977). Butonate, *Pesticides Process Encyclopedia*, Noyes Data Corp., Park Ridge, p. 66.

36. Look, M., and White, L.R. (1981). Synthesis of *O,O,*-dimethyl 2,2-dichloro-1-(acyloxy)ethenephosphonates, major constituents in acylated trichlorfons, *J. Agric. Food Chem., 29*: 673.

37. Barthel, W.F., Giang, P.A., and Hall, S.A. (1954). Dialkyl α-hydroxyphosphonates derived from chloral, *J. Am. Chem. Soc., 76*: 4186.

38. Abramov, V.S., and Barabanov, V.I. (1967). Alkyl esters of α-hydroxy-β,β,β-trichloroethyl(butyl)phosphinic acid, *Khim. Org. Soedin. Fosfora. Akad. Nauk SSSR, Otd. Obshch. Tekh. Khim.*: 135.

39. Fricke, G., and Georgi, W. (1963). Uber die Inhaltstoffe eines Reaktionsproduktes aus Chloral, Phosphortrichlorid und Methanol, *J. Pr. Chem., 20*: 250.

40. Botts, M.F., and Regel, E.K. (1969). Nematocidal alkylthioalkylphosphonodithioic acid esters, *U.S. 3,463,840.*

41. Franz, J.E. (1979). Glyphosate and related chemistry,

Advances in Pesticide Science, Part 2, (Geissbuhler, H., ed.) Pergamon Press, Oxford, p. 139.
42. Guenther, E., and Loettge, W. (1971). Herbicidal dialkyl (1-aminocyclohexyl)phosphonates, *Ger. Pat. 3,413,382.*
43. Toy, A.D.F. (1948). The preparation of tetraethyl pyrophosphate and other tetraalkyl pyrophosphates, *J. Am. Chem. Soc., 70*: 3882.
44. Schrader, G., Lorenz, W., and Muhlmann, R. (1958). Monothio-pyrophosphorsaure-tetraalkylester - ihre Herstellung und ihre Eigenschaften, *Angew. Chem. 70*: 690.
45. Almasi, L., and Paskucz, L. (1967). Synthese der asymmetrischen Dithiopyrophosphorsaure-*O,O,O,O*-tetraalkylester, *Angew. Chem., 79*: 859.
46. Melnikov, N.N. (1971). Chemistry of pesticides, *Residue Rev., 36*: 303.
47. Aaron, H.S., Michel, H.O., Witten, B., and Miller, J.I. (1958). The stereochemistry of asymmetric phosphorus compounds. II. Stereospecificity in the irreversible inactivation of cholinesterase by the enantiomorphs of an organophosphorus inhibitor, *J. Am. Chem. Soc., 80*: 456.
48. Hudson, R.F., and Green, M. (1963). Die Stereochemie von Substitutionsreaktionen am Phosphor, *Angew. Chem., 75*: 47.
49. Mikolajczyk, M., Omelanczuk, J., and Para, M. (1972). Configuration of the optically active phosphorus thioacids. I. Chemical correlation of the configuration of *O*-alkyl alkylphosphonothioic acids, *Tetrahedron, 28*: 3855.
50. Lin, G.H.Y., Wustner, D.A., Fukuto, T.R., and Wing, R.M. (1974). Absolute configuration of chiral *O*-2-butyl ethylphosphonothioic acid, *J. Agric. Food Chem., 22*: 1134.
51. Allahyari, R., Lee, P.W., Lin, G.H.Y., Wing, R.M., and Fukuto, T.R. (1977). Resolution and reactions of the chiral isomer of *O*-ethyl *S*-phenyl ethylphosphonodithioate (fonofos) and its analogues, *J. Agric. Food Chem., 25*: 471.
52. Allahyari, R., Hollinghaus, J.G., Lapp, R.L., Timm, E., Jacobson, R.A., and Fukuto, T.R. (1980). Resolution, absolute configuration, and acute and delayed neurotoxicity of the chiral isomers of *O*-aryl *O*-methyl phenylphosphonothioate analogues related to leptophos, *J. Agric. Food Chem., 28*: 594.
53. Hirashima, A., and Eto, M. (1983). Synthesis of optically active cyclic phosphorothionates and phosphoramidothio-

nates with insecticidal activity by using a chiral phosphorylating agent, *Agric. Biol. Chem., 47*: 2831.
54. Wu, S.-Y., and Eto, M. (1984). Stereochemistry of aryl methyl phosphorochloridothionates as chiral two-step phosphorylating reagents, *Agric. Biol. Chem., 48*: 3071.
55. Wu, S.-Y., Hirashima, A., Kuwano, E., and Eto, M. (1987). Synthesis of optically active 1,3,2-oxazaphospholidine 2-sulfides and 1,3,2-benzodioxaphosphorin 2-sulfides, *Agric. Biol. Chem., 51*: 537.
56. Wu, S.-Y., Hirashima, A., Takeya, R., and Eto, M. (1989). Synthesis and insecticidal activity of optically active 2-methoxy-5-phenyl-1,3,2-oxazaphospholidine 2-sulfide, *Agric. Biol. Chem., 53*: 165.
57. Wu, S.-Y., Hirashima, A., Eto, M., Yanagi, K., Nishioka, E., and Moriguchi, K. (1989). Synthesis of highly pure enantiomers of the insecticide salithion, *Agric. Biol. Chem., 53*: 157.
58. Koizumi, T., Kobayashi, Y., Amitani, H., and Yoshii, E. (1977). A practical method of preparing optically active dialkyl phenyl phosphates, *J. Org. Chem., 42*: 3459.
59. Leader, H., and Casida, J.E. (1982). Resolution and biological activity of the chiral isomers of *O*-(4-bromo-2-chlorophenyl) *O*-ethyl *S*-propyl phosphorothioate, *J. Agric. Food Chem., 30*: 546.
60. Hirashima, A., Leader, H., Holden, I., and Casida, J.E. (1984). Resolution and stereoselective action of sulprofos and related *S*-propyl phosphorothiolates, *J. Agric. Food Chem., 32*: 1302.
61. Eya, B.K., and Fukuto, T.R. (1985). The effect of chiral debromoleptophos oxon isomers on acute and delayed neurotoxicity and their inhibitory activity against acetylcholinesterases and neurotoxic esterase, *J. Agric. Food Chem., 33*: 884.
62. Miyazaki, A., Nakamura, T., Kawaradani, M., and Marumo, S. (1988). Resolution and biological activity of both enantiomers of methamidophos and acephate, *J. Agric. Food Chem., 36*: 835.
63. Cooper, D.B., Hall, C.R., Harrison, J.M., and Inch, T.D. (1977). 1,3,2-Oxazaphospholidines from (-)-ephedrine. Intermediates for the stereospecific synthesis of optically active dialkyl alkylphosphono-thioates and -selenoates, trialkyl phosphoro-thioates and -selenoates, dialkyl

methylphosphonates, and trialkyl phosphates, *J. Chem. Soc., Perkin Trans I*: 1969.
64. Hall, C.R., and Inch, T.D. (1979). Asymmetric tetracoordinate pentacovalent organophosphorus compounds their resolution and determination of enantiomeric purity, *Phosphorus Sulfur, 7*: 171.
65. Koizumi, T., Kobayashi, Y., and Yoshii, E. (1976). Acid-catalyzed methanolysis of optically active *N*-cyclohexyl methylphenylphosphinamide - a stereochemical evidence for A-2 mechanism, *Chem. Pharm. Bull., 24*: 834.
66. Stec, W.J. (1983). Wadsworth-Emmons reaction revisited, *Acc. Chem. Res., 16*: 411.
67. Ward, T.M., Allcox, I.L., and Wahl, G.H. (1983). Lanthanide induced shifts due to coordination at phosphoryl and amide sites, *Tetrahedron Lett.*: 4421.
68. Moriyama, M. (1984). Application of optically active phosphinothioic acid as chiral shift reagent to determination of enantiomeric purity, *J. Syn. Org. Chem., Japan, 42*: 355.
69. Okamoto, Y., Honda, S., Hatada, K., Okamoto, I., Toga, Y., and Kobayashi, S. (1984). Chromatographic resolution of racemic compounds containing phosphorus or sulfur atom as chiral center, *Bull. Chem. Soc. Jpn., 57*: 1681.
70. Ueji, M., and Tomizawa, C. (1986). Insect toxicity and anti-acetylcholinesterase activity of chiral isomers of isofenphos and its oxon, *J. Pestic. Sci., 11*: 447.
71. Wu, S.-Y., Takeya, R., Eto, M., and Tomizawa, C. (1987). Insecticidal activity of optically active 1,3,2-oxazaphospholidine 2-sulfides and 1,3,2-benzodioxaphosphorin 2-sulfides, *J. Pestic. Sci., 12*: 221.
72. Itoh, K. (1991). Stereoselective degradation of organophosphorus insecticide salithion in upland soils, *J. Pestic. Sci., 16*: 35.
73. Grothusen, J.R., and Brown, T.M. (1986). Stereoselectivity of acetylcholinesterase, arylester hydrolase and chymotrypsin toward 4-nitrophenyl alkyl(phenyl)phosphinates, *Pestic. Biochem. Physiol., 26*: 100.
74. Emsley, J., and Hall, D. (1976). *The Chemistry of Phosphorus*, Harper & Row, London.
75. Pearson, P.G. (1963). Hard and soft acids and bases, *J. Am. Chem. Soc., 85*: 3533.
76. Hilgetag, G., and Teichmann, H. (1965). The alkylating properties of alkyl thiophosphates, *Angew. Chem., Int. Ed.*

Engl., 4: 914.
77. Eto, M., and Ohkawa, H. (1970). Alkylation reaction of organophosphorus pesticides: its chemical and biochemical significances, *Biochemical Toxicology of Insecticides*, (O'Brien, R.D., and Yamamoto, I., eds.) Academic Press, New York, p. 93.
78. Gerrard, A.F., and Hamer, N.K. (1968). Evidence for planar intermediate in alkaline solvolysis of methyl *N*-cyclohexylphosphoramidic chloride, *J. Chem. Soc. (B)*: 539.
79. Maynard, J.A., and Swan, J.M. (1963). 2-Halogenoalkylphosphonic acids: a new class of phosphorylating agent, *Proc. Chem. Soc.*: 61.
80. Gallagher, M.J., and Jenkins, I.D. (1968). Stereochemical aspects of phosphorus chemistry, *Topics in Stereochemistry*, Vol. 3, (Eliel, E.L., and Allinger, N.L., eds.) Interscience, New York, p.1.
81. Barnard, P.W.C., Bunton, C.A., Llewellyn, D.R., Vernon, C.A., and Welch, V.A. (1961). The reaction of organic phosphates. V. The hydrolysis of triphenyl and trimethyl phosphates, *J. Chem. Soc.*: 2670.
82. Gillespie, R., Ramirez, F., Ugi, I., and Marquading, D. (1973). Displacement reactions of phosphorus(V) compounds and their pentacoordinate intermediates, *Angew. Chem., Int. Ed. Engl., 12*: 91.
83. Dennis, E.A., and Westheimer, F.H. (1966). The geometry of the transition state in the hydrolysis of phosphate esters, *J. Am. Chem. Soc., 88*: 3432.
84. Aldridge, W.N., and Davison, A.N. (1952). The inhibition of erythrocyte cholinesterase by triesters of phosphoric acid, *Biochem. J., 51*: 62.
85. Schrader, G. (1952). *Die Entwickung neuer Insektizide auf Grundlage organicher Fluor- und Phosphor-Verbindungen*, Monographie Nr. 62 zu Angewandte Chemie und Chemie-Ingenieur-Technik, Verlag Chemie, Weinheim.
86. Clark, V.M., Hutchinson, D.W., Kirby, A.J., and Warren, S.G. (1964). The design of phosphorylating agents, *Angew. Chem., Int. Ed. Engl., 3*: 678.
87. Ohkawa, H., and Eto, M. (1969). Alkylation of mercaptans and inhibition of "SH enzymes" by saligenin cyclic phosphate and phosphorothiolate esters, *Agric. Biol. Chem., 33*: 443.
88. Shiotsuki, T., Koiso, A., and Eto, M. (1989). Glutathione

conjugation as a mechanism for glutathione transferase inhibition by saligenin cyclic phosphates, *J. Pestic. Sci., 14*: 337.

89. Yeoh, C.-L., Kuwano, E., and Eto, M. (1982). Effects of the fungicide IBP as a synergist on the metabolism of malathion in insects, *J. Pestic. Sci., 7*: 31.
90. Manabe, A., and Eto, M. (1983). Syntheses and chemical properties of diisopropyl *S*-(*o*- and *p*-hydroxybenzyl) phosphorothiolates, the possible metabolites of the fungicide IBP, *J. Pestic. Sci., 8*: 363.
91. Kurogochi, S., Katagiri, M., Takase, I., and Uesugi, Y. (1985). Metabolism of edifenphos by strains of *Pyricularia oryzae* with varied sensitivity to phosphorothiolate fungicides, *J. Pestic. Sci., 10*: 41.
92. Eto, M., Hashimoto, Y., Ozaki, K., Kassai, T., and Sasaki, Y. (1975). Fungitoxicity and insecticide synergism of monothioquinol phosphate esters and related compounds, *Botyu-Kagaku, 40*: 110.
93. Heath, D.F., and Vandekar, M. (1957). Some spontaneous reactions of *O,O*-dimethyl *S*-ethylthioethyl phosphorothiolate and related compounds in water and on storage, and their effects on the toxicological properties of the compounds, *Biochem. J., 67*: 187.
94. Metcalf, R.L., and March, L.C. (1953). The isomerization of organic thionophosphate insecticides, *J. Econ. Entomol., 46*: 288.
95. Teichmann, H., and Hilgetag, G. (1967). Nucleophilic reactivity of the thiophosphoryl group, *Angew. Chem., Int. Ed. Engl., 6*: 1013.
96. Sasaki, M., Ohkawa, H., and Eto, M. (1973). The conversion of saligenin cyclic methyl phosphorothionate into the thiolate analogs and a new rearrangement reaction, *J. Fac. Agr., Kyushu Univ., 17*: 173.
97. Wu, S.-Y., and Eto, M. (1987). Isomerization of 2-methoxy-4*H*-1,3,2-benzodioxaphosphorin 2-sulfide (salithion) into benzoxathiophosphorin by *m*-chloroperbenzoic acid, *J. Pestic. Sci., 12*: 95.
98. Mikami, N., Ohkawa, H., and Miyamoto, J. (1977). Photodecomposition of salithion (2-methoxy-4*H*-1,3,2-benzodioxaphosphorin 2-sulfide and phenthoate (*O,O*-dimethyl *S*-α-ethoxycarbonylbenzyl phosphorodithioate), *J. Pestic. Sci., 2*: 279.

99. Maeda, N., Kawashima, M., Horide, F., and Tsuji, K. (1983).Thermal decomposition of 2-methoxy-4*H*-1,3,2-benzodioxaphosphorin 2-sulfide (salithion), *J. Pestic. Sci., 8*: 567.
100. Fukuto, T.R., and Stafford, E.M. (1957). The isomerization of *O,O*-diethyl *O*-2-diethylaminoethyl phosphorothionate, *J. Am. Chem. Soc., 79*: 6083.
101. Eto, M., Sasaki, M., Iio, M., Eto, M.-Y., and Ohkawa, H. (1971). Synthesis of 2-methylthio-4*H*-1,3,2-benzodioxaphosphorin 2-oxide by thiono-thiolo conversion and its use as phosphorylating agent, *Tetrahedron Lett., 45*: 4263.
102. Hirashima, A., and Eto, M. (1983). Stereochemistry and reactions of aziridinylphosphinothionates derived from amino acids, *Agric. Biol. Chem., 47*: 829.
103. Aldridge, W.N., and Reiner, E. (1972). *Enzyme Inhibitors as Substrates*, North-Holland Pub. Co., Amsterdam.
104. Heilbronn, E. (1965). Action of fluoride on cholinesterase. II. *In vitro* reactivation of cholinesterases inhibited by organophosphorus compounds, *Biochem. Pharmacol., 14*: 1363.
105. Hagedorn, I., Stark, I., and Lorenz, H.P. (1972). Reactivation of phosphorylated acetylcholinesterase - Dependence upon activator acidity, *Angew. Chem., Int. Ed. Engl., 11*: 307.
106. Wilson, I.B., Ginsburg, S., and Quan, C. (1958). Molecular complementariness as basis for reactivation of alkyl phosphate-inhibited acetylcholinesterase, *Arch. Biochim. Biophys., 77*: 286.
107. Schoene, K. (1972). Reaktivierung von *O,O*-Diathylphosphoryl-Acetylcholinesterase Reaktiverungs-Rephosphorylierungs-Gleichgewicht, *Biochem. Pharmacol., 21*: 163.
108. Benshop, H.P., and Keijer, J.H. (1966). On the mechanism of aging of phosphonylated cholinesterases, *Biochim. Biophys. Acta, 128*: 586.
109. Keijer, J.H., and Wolring, G.Z. (1969). Stereospecific aging of phosphonylated cholinesterases, *Biochim. Biophys. Acta, 185*: 465.
110. Fukuto, T.R., and Metcalf, R.L. (1956). Structure and insecticidal activity of some diethyl substituted phenyl phosphates, *J. Agric. Food Chem., 4*: 930.
111. Hansch, C., and Deutsch, E.W. (1966). The use of substitutent constants in the study of structure-activity

relationships in cholinesterase inhibitors, *Biochim. Biophys. Acta, 126*: 117.
112. Pullman, B., and Valdemoro, C. (1960). Electronic structure and activity of organophosphorus inhibitors of esterases, *Biochim. Biophys. Acta, 43*: 548.
113. Fukui, K., Morokuma, K., Nagata, C., and Imamura, A. (1961). Electronic structure and biochemical activities in diethyl phenyl phosphates, *Bull. Chem. Soc. Jpn., 34*: 1224.
114. Hansch, C. (1970). The use of physiochemical parameters and regression analysis in pesticide design, *Biochemical Toxicology of Insecticides*, (O'Brien, R.D., and Yamamoto, I., eds.) Academic Press, New York, p. 33.
115. Kamoshita, K., and Kirino, O. (1982). Application of quantitative structure-activity relationships to pesticide research, *Kagaku no Ryoiki Zokan, 136*: 203.
116. Ruzicka, J.H., Thomson, J., and Wheals, B.B. (1967). The gas chromatographic determination of organophosphorus pesticides. II. A comparative study of hydrolysis rates, *J. Chromatogr., 31*: 37.
117. Chiu, Y.C., Main, A.R., and Dauterman, W.C. (1969). Affinity and phosphorylation constants of a series of *O,O*-dialkyl malaoxons and paraoxons with acetylcholinesterase, *Biochem Pharmacol., 18*: 2171.
118. Hastings, F.L., and Dauterman, W.C. (1971). Phosphorylation and affinity constants for the inhibition of acetylcholinesterase by dimethoxon analogs, *Pestic. Biochem. Physiol., 1*: 248.
119. Fukuto, T.R. (1971). Relationships between the structure of organophosphorus compounds and their activity as acetylcholinesterase inhibitors, *Bull. Wld. Hlth. Org., 44*: 31.
120. Rohrbaugh, W.J., Meyers, E.K., and Jacobson, R.A. (1976). Crystal and molecular structure of organophosphorus insecticides. Azinphos-methyl, *J. Agric. Food Chem., 24*: 713.
121. Huang, C.T., Dauterman, W.C., and Hastings, F.L. (1974). Inhibition of flyhead acetylcholinesterase by dimethoxon analog, *Pestic. Biochem. Physiol., 4*: 249.
122. Hollingworth, R.M., Fukuto, T.R., and Metcalf, R.L. (1967). Selectivity of sumithion compared with methyl-parathion, *J. Agric. Food Chem., 15*: 235.
123. Sasaki, M., (1985). Stereochemistry and biological activity,

Bioorganic Chemistry of Pesticides, (Eto, M., ed.), Soft Science, Tokyo, p. 210.
124. Eto, M. (1990). Biochemical mechanisms of insecticidal activities, *Chemistry of Plant Protection, 6*, Springer-Verlag, Berlin, p. 65.
125. Kraut, J. (1977). Serine proteases: structure and mechanism of catalysis, *Ann. Rev. Biochem., 46*: 331.
126. Becker, E.L., Fukuto, T.R., Canham, D.C., and Boger, E. (1963). The realtionship of enzyme inhibitory activity to the structure of *n*-alkylphosphonate and phenylalkylphosphonate esters, *Biochem., 2*: 72.
127. Eto, M., Hanada, K., Namazu, Y., and Oshima, Y. (1963). The correlation between antiesterase activity and chemical structure of saligenin cyclic phosphates, *Agric. Biol. Chem., 37*: 723.
128. Jarv, J., Aaviksaar, A., Godovikov, N., and Lobanov, D. (1977). The arrangement of substrate and organophosphorus-inhibition leaving groups in acetylcholinesterase active site, *Biochem. J., 167*: 823.
129. Gatterdam, P.E., Casida, J.E., and Stoutmaire, D.W. (1959). Relation of structure to stability, antiesterase activity and toxicity with substituted-vinyl phosphate insecticides, *J. Econ. Entomol., 52*: 270.
130. Chiu, Y.C., and Dauterman, W.C. (1969). The affinity and phosphorylation constants of the optical isomers of *O,O*-diethyl malaoxon and the geometric isomers of phosdrin with acetylcholinesterase, *Biochem. Pharmacol., 18*: 359.
131. Price, N.R., Hoppe, T., and Watson, H. (1991). Methacrifos as a grain protectant: a comparison of the vapor effects of some organophosphorus insecticides used in grain protection, *Pestic. Sci., 31*: 1.
132. Eto, M., Sakata, M., and Sasayama, T. (1972). Biological activities of *p*-ethylphenyl and *p*-acetylphenyl phosphates and their thiono analogs, *Agric. Biol. Chem., 36*: 645.
133. Fischer, T.H., McHenry, W.H., Alley, E.G., Lofgren, C.S., and Williams, D.F. (1983). Some phosphorothionate imported fire ant toxicants with delayed kill, *J. Agric. Food Chem., 31*: 730.
134. Sasaki, M., Ooishi, T., Kato, T., Takayama, C., and Mukai, K. (1984). Synthesis and antifungal activity of *O,O*-dialkyl *O*-aryl phosphorothioates and related compounds, *J. Pestic. Sci., 9*; 737.

135. Roth, G.A., and McClymont, E.L. (1991). Synthesis of four candidate metabolites of the phosphorothioate insecticide DOWCO 429, *J. Agric. Food Chem., 39*: 612.
136. Mukai, K. (1980). Studies on asymmetric phosphorothiolate esters, *Dissertation Thesis (Kyushu Univ.)*.
137. Kudamatsu, A., Iyatomi, A., Hayashi, A., and Kano, R. (1978). Toxicity of a new series of *S-n*-propyl *O*-ethyl *O*-phenyl phosphorothioates to susceptible and resistant house flies, *Musca domestica* L., *Jap. J. Sanit. Zool., 24*: 317.
138. Murdock, L.L., and Hopkins, T.L. (1968). Insecticidal, anticholinesterase, and hydrolytic properties of *O,O*-dialkyl *S*-aryl phosphorothiolates in relation to structure, *J. Agric. Food Chem., 16*: 954.
139. Heath, D.F. (1961). *Organophosphorus Poisons Anticholinesterases and Related Compounds*, Pergamon Press, Oxford.
140. Wing, K.D., Glickman, A.H., and Casida, J.E. (1984). Phosphorothiolate pesticides and related compounds: oxidative bioactivation and aging of the inhibited acetylcholinesterase, *Pestic. Biochem. Physiol., 21*: 22.
141. Kono, Y., Sato, Y., and Okuda, Y. (1983). Activation of an *O*-ethyl *S-n*-propyl phosphorothiolate, TIA-230, in the central nerve of *Spodoptera* larvae, *Pestic. Biochem. Physiol., 20*: 225.
142. Kimura, S., Soeda, K., Yamamoto, T., and Yamamoto, I. (1984). Activation and detoxication of *S*-alkyl phosphorothiolate insecticides, *J. Pestic. Sci., 9*: 137.
143. Glickman, A.H., Wing, K.D., and Casida, J.E. (1984). Profenofos insecticide bioactivation in relation to antidote action and the stereospecificity of acetylcholinesterase inhibition, reactivation, and aging, *Toxicol. Appl. Pharmacol., 73*: 16.
144. Akatsuka, T., and Kodama, O. (1984). A mode of action of anti-blast substances, *J. Pestic. Sci., 9*: 375.
145. Casida, J.E., Allen, T.C., and Stahmann, M.A. (1954). Mammalian conversion of octamethylpyrophosphoramide to a toxic phosphoramide *N*-oxide, *J. Biol. Chem., 210*: 607.
146. Arthur, B.W., and Casida, J.E. (1958). Biological and chemical oxidation of tetramethyl phosphorodiamidic fluoride (dimefox), *J. Econ., Entomol., 51*: 49.
147. Traylor, P.S., and Westheimer, F.H. (1965). Mechanisms

in the hydrolysis of phosphorodiamidic chlorides, *J. Am. Chem. Soc., 87*: 553.
148. Eto, M., Okabe, S., Ozoe, Y., and Maekawa, K. (1977). Oxidative activation of *O,S*-dimethyl phosphoramidothiolate, *Pestic. Biochem. Physiol., 7*: 367.
149. Magee, P.P. (1982). Structure-activity relationships in phosphoramidates, *Insecticide Mode of Action*, (Coats, J.R., ed.), Academic Press, New York, p. 101.
150. Thompson, C.M., Castellino, S., and Fukuto, T.R. (1984). A carbon-13 nuclear magnetic resonance study on an organophosphate. Formation and characterization of methamidophos (*O,S*-dimethyl phosphoramidothioate) *S*-oxide, *J. Org. Chem., 49*: 1696.
151. Sanborn, J.R., and Fukuto, T.R. (1972). Insecticidal, anticholinesterase, and hydrolytic properties of *S*-aryl phosphoramidothioates, *J. Agric. Food Chem., 20*: 926.
152. Ueji, M., and Tomizawa, C. (1984). Bioactivation of *N*-alkyl substitued phosphoramidothioate insecticides, *J. Pestic. Sci., 9*: 675.
153. Gorder, G.W., Kirino, O., Hirashima, A., and Casida, J.E. (1986). Bioactivation of isofenphos and analogues by oxidative *N*-dealkylation and desulfuration, *J. Agric. Food Chem., 34*: 941.
154. Tomizawa, C., Ueji, M., and Yoshida, T. (1988). Insecticidal activity of phosphoramidothioates and bioactivation of their oxon homologs, *J. Pestic. Sci., 13*: 449.
155. Happners, T.J., Coats, J.R., and Drewer, C.D. (1987). Neurotoxic action of isofenphos and three isofenphos metabolites in the American cockroach, *Periplaneta americana*, *Pestic. Biochem. Physiol, 27*: 76.
156. Ueji, M., and Tomizawa, C. (1987). Metabolism of chiral isomers of isofenphos in the rat liver microsomal system, *J. Pestic. Sci., 12*: 269.
157. Neely, W.B., and Whitney, W.K. (1968). Statistical analysis of insecticidal activity of phosphoramidates, *J. Agric. Food Chem., 16*: 571.
158. Gorder, G.W., Holden, I., Ruzo, L.O., and Casida, J.E. (1985). Phosphinyliminodithiolane insecticides: Oxidative bioactivation of phosfolan and mephosfolan, *Bioorg. Chem., 13*: 344.
159. Gorder, G.W., Holden, I., Ruzo, L.O., and Casida, J.E. (1985). Phosphinyliminodithiolane insecticides: Novel

addition reactions of phosfolan and mephosfolan sulfoxides and sulfones, *Bioorg. Chem., 13*: 353.
160. Yang, H.-Z., Shang, Y.-J., Wang, L.-X., Tan, H.-F., Cheng, M.-R., Xing, X.-D., Chen, R.-Y., and Fujita, T. (1986). Quantitative structure-activity study of herbicidal *O*-aryl *O*-ethyl *N*-isopropylphosphoramidothioates, *Pestic. Biochem. Physiol., 26*: 275.
161. Collis, P.S., and Weeks, D.P. (1978). Selective inhibition of tubulin synthesis by amiprophos methyl during flagellar regeneration in *Chlamydomonas reinhardi*, *Science, 202*: 440.
162. Ohkawa, H., Mikami, N., Mine, A., and Miyamoto, J. (1975). Synthesis and herbicidal activity of the optical isomers of *O*-ethyl *O*-2-nitro-5-methylphenyl *N*-isopropyl-phosphoramidothioate, *Agric. Biol. Chem., 39*: 2265.
163. Kohsaka, H., Oguri, Y., Sasaki, M., and Mukai, K. (1987). Synthesis and antifungal activity of 5-methoxy-2-nitrophenyl phosphoramidothioates, *J. Pestic. Sci., 12*: 415.
164. Kohsaka, H., Oguri, Y., Sasaki, M., and Mukai, K. (1988). Synthesis and antifungal activity of *O*-aryl *O*-ethyl *N-sec*-butylphosphoramidothioates, *J. Pestic. Sci., 13*: 277.
165. Uesugi, Y., Katagiri, M., and Noda, O. (1974). Negatively correlated cross-resistance and synergism between phosphoramidates and phosphorothiolates in their fungicidal actions on rice blast fungi, *Agric. Biol. Chem., 38*: 907.
166. Yoshida, M., Uesugi, Y., Nozoe, K., and Lalithakumari, D. (1987). Inhibition of phospholipid *N*-methylation by dibutyl *N*-methyl-*N*-phenylphosphoramidate in *Pyricularia oryzae* in relation to negative cross-resistance with phosphorothiolates, *J. Pestic. Sci., 12*: 513.
167. Borkovec, A.B. (1966). Insect chemosterilants, *Adv. Pest Control Res.*, Vol. 7 (Metcalf, R.L., ed.), Interscience, New York.
168. Chang, S.C., Terry, P.H., and Borkovec, A.B. (1964). Insect chemosterilants with low toxicity for mammals, *Science, 144*: 57.
169. Borkovec, A.B. (1972).Chemosterilants for male insects, *Pesticide Chemistry, Proceedings 2nd Internat. IUPAC Congress, Insecticides*, Vol. 1 (Tahori, A.S., ed.), Gordon & Breach, London, p. 469.
170. Kumamoto, J., Cox, J.R., and Westheimer, F.H. (1956). Barium ethylene phosphate, *J. Am. Chem. Soc., 78*: 4858.

171. Haake, P., and Westheimer, F.H. (1961). Hydrolysis and exchange in esters of phosphoric acid, *J. Am. Chem. Soc., 83*: 1102.
172. Boyd, D.B. (1969). Mechanism of hydrolysis of cyclic phosphate esters, *J. Am. Chem. Soc., 91*: 1200.
173. Blackburn, G.M., Cohen, J.S., and Todd, L. (1964). Cyclic phosphate and phosphite triesters - A ^{31}P NMR study, *Tetrahedron Lett.*: 2873.
174. Kaiser, E.T., Lee, T.W.S., and Boer, F.P. (1971). Structure and enzymatic reactivity of an aromatic five-membered cyclic phosphate diester. Biological implication, *J. Am. Chem. Soc., 93*: 2351.
175. Ramirez, F., Marecek, J.F., and Okazaki, H. (1975). One-flask synthesis of unsymmetrical phosphodiesters. Selective amine catalysis of phosphorylation of primary *vs.* secondary alcohols, *J. Am. Chem. Soc., 97*: 7181.
176. Fukuto, T.R., and Metcalf, R.L. (1965). Reactivity of some 2-*p*-nitrophenoxy-1,3,2-dioxaphospholane 2-oxides and -dioxaphosphorinane 2-oxides, *J. Med. Chem., 8*: 759.
177. Edmundson, R.S., and Lambie, A.J. (1966). Cyclic organophosphorus compounds as possible pesticides. Part I. 1,3,2-dioxaphospholanes, *J. Chem. Soc. (C)*: 2001.
178. Koizumi, T., Yoshida, Y., Watanabe, Y., and Yoshii, E. (1975). 2-Phenoxy-benzoxazaphosphole-2-oxide, a novel phosphorylating agent of alcohols, *Chem. Pharm. Bull., 23*: 1381.
179. Eto, M., Tawata, S., Sakamoto, K., and Oshima, K. (1978). Novel insecticidal five-membered cyclic phosphoramidothionates derived from L-amino acids, *J. Pestic. Sci., 3*: 161.
180. Eto, M., Hirashima, A., Tawata, S., and Oshima, K. (1981). Structure-insecticidal activity relationship of five-membered cyclic phosphoramidates derived from amino acids, *Nippon Kagaku Kaishi*: 712.
181. Eto, M. (1983). Development of insecticidal cyclic phosphoryl compounds through chemical and biochemical approaches, *J. Environ. Sci. Health, B18*: 119.
182. Tashiro, S., Taniguchi, E., and Eto, M. (1972). L-Leucine: a neuroactive substance in insects, *Science, 175*: 448.
183. Tawata, S., Kuwano, E., and Eto, M. (1980). Synthesis and chemical properties of insecticidal 2-alkoxy-4-alkyl-1,3,2-oxazaphospholidine 2-sulfides derived from optically active

amino acids, *Agric. Biol. Chem., 44*: 1489.
184. Hart, G.J., and O'Brien, R.D. (1976). Dissociation and phosphorylation constants for the inhibition of acetylcholinesterase by 2-fluoro, 2-oxo-1,3,2-dioxaphosphorinanes, *Pestic. Biochem. Physiol., 6*: 464.
185. Lanham, W.M. (1960). Bicyclo heterocyclic phosphorus compounds, *U.S. 2,910,499.*
186. Eto, M. (1969). Specificity and mechanism in the action of saligenin cyclic phosphorus esters, *Residue Reviews, 25*: 187.
187. Eto, M., Casida, J.E., and Eto, M. (1962). Hydroxylation and cyclization involved in the metabolism of tri-*o*-cresyl phosphate, *Biochem. Pharmacol., 11*: 337.
188. Eto, M., Kinoshita, T., Kato, T., and Oshima, Y. (1963). Saligenin cyclic methyl phosphate and its thiono analogue: new insecticides related to the active metabolite of tri-*o*-cresyl phosphate, *Nature, 200*: 171.
189. Eto, M., Fukuhara, N., Kuwano, E., and Koyama, H. (1981). Molecular structure and conformation of 4*H*-1,3,2-benzodioxaphosphorins, including the insecticide salathion, *Agric. Biol. Chem., 45*: 915.
190. Gerlt, J.A., Gutterson, N.I., Dalta, P., Belleau, B., and Penney, C.L. (1980). Thermochemical identification of the structural factors responsible for the thermodynamic instability of 3',5'-cyclic nucleotides, *J. Am. Chem. Soc., 102*: 1655.
191. Eto, M., Kobayashi, K., Sasamoto, T., Cheng, H.M., Aikawa, T., Kume, T., and Oshima, Y. (1968). Studies on saligenin cyclic phosphorus esters with insecticidal activity. XII. Insecticidal activity of ring-substituted derivatives, *Botyu-Kagaku, 33*: 73.
192. Wu, S.-Y., Ito, S., and Eto, M. (1987). Metabolic formation of 4-methyl-4*H*-1,3,2-benzodioxaphosphorins from bis(*o*-ethylphenyl) phenylphosphonates in house flies, *Agric. Biol. Chem., 51*: 2935.
193. Tawata, S., Eto, M.-Y., and Casida, J.E. (1982). Insecticidal 4-alkylidene-1,3,2-benzodioxaphosphorinane derivatives, *J. Agric. Food Chem., 30*: 198.
194. Casida, J.E., Baron, R.L., Eto, M., and Engel, J.L. (1963). Potentiation and neurotoxicity induced by certain organophosphates, *Biochem. Pharmacol., 12*: 73.
195. Kadota, T., Okuno, Y., and Miyamoto, J. (1975). Acute

oral toxicity and delayed neurotoxicity of 5 organophosphorus compounds, salithion, cyanox, surecide, sumithion and sumioxon on adult hens, *Botyu-Kagaku, 40*: 49.
196. Eto, M., Kinoshita, Y., Kato, T., and Oshima, Y. (1963). Saligenin cyclic alkyl phosphates and phosphorothionates with insecticidal activity, *Agric. Biol. Chem., 27*: 789.
197. Ohkawa, H., Oshita, H., and Miyamoto, J. (1980). Comparison of inhibitory activity of various organophosphorus compounds against acetylcholinesterase and neurotoxic esterase of hens with respect to delayed neurotoxicity, *Biochem. Pharmacol., 29*: 2721.
198. Eto, M.-Y., Iio, M., Kobayashi, Y., Omura, H., and Eto, M. (1974). Synthesis of ribonucleoside 5'-*S*-methyl phosphorothiolates and ribonucleoside 3':5'-cyclic phosphates from nucleosides applying a new phosphorylating agent, MTBO, *Agric. Biol. Chem., 38*: 2081.
199. Ozoe, Y., Mochida, K., and Eto, M. (1982). Stability of bicyclic phosphates to alkali, *Agric. Biol. Chem., 46*: 555.
200. Ozoe, Y., Mochida, K., and Eto, M. (1982). Reaction of toxic bicyclic phosphates with acetylcholinesterase and α-chymotrypsin, *Agric. Biol. Chem., 46*: 2527.
201. Bellet, E.M., and Casida, J.E. (1973). Bicyclic phosphorus esters: High toxicity without cholinesterase inhibition, *Science, 182*: 1135.
202. Casida, J.E., Eto, M., Moscioni, A.D., Engel, J.L., Milbrath, D.S., and Verkade, J. (1976). Structure-toxicity relationships of 2,6,7-trioxabicyclo[2.2.2]octanes and related compounds, *Toxicol. Appl. Pharmacol., 36*: 261.
203. Eto, M., Ozoe, Y., Fujita, T., and Casida, J.E. (1976). Significance of branched bridge-head substituent in toxicity of bicyclic phosphate esters, *Agric. Biol. Chem., 40*: 2113.
204. Bowery, N.G., Collins, J.F., and Hill, R.G. (1976). Bicyclic phosphorus esters that are potent convulsants and GABA antagonists, *Nature, 261*: 601.
205. Korenaga, S., Ito, Y., Ozoe, Y., and Eto, M. (1977). The effects of bicyclic phosphate esters on the invertebrate and vertebrate neuro-muscular junctions, *Comp. Biochem. Physiol., 57C*: 95.
206. Squires, R.F., Casida, J.E., Richardson, M., and Saederup, E. (1983). [^{35}S]-*t*-Butylbicyclophosphorothionate binds with high affinity to brain-specific sites coupled to γ-amino-

butyric acid-A and ion recognition sites, *Mol. Pharmacol., 23*: 326.
207. Ozoe, Y., Mochida, K., Nakamura, T., Shimizu, A., and Eto, M. (1983). Toxicity of bicyclic phosphate GABA antagonists to the housefly, *Musca domestica* L, *J. Pestic. Sci., 8*: 601.
208. Ozoe, Y., and Eto, M. (1986). Bridged bicyclic organophosphorus compounds as a probe for toxicological study on GABA synapse, *Membrane Receptors and Enzymes as Targets of Insecticidal Action*, (Clark, J.M., and Matsumura, F., eds.), Plenum Press, New York, p. 75.
209. Palmer, C.J., and Casida, J.E. (1987). Bicyclo*ortho*carboxylates: Potent insecticides acting at the GABA-regulated chloride ionophore, *A Site of Action for Neurotoxic Pesticides*, (Hollingworth, R.M., and Green, M.B., eds.), ACS Symposium Series 356, p. 71.
210. Palmer, C.J., Smith, I.H., Moss, M.D.V., and Casida, J.E. (1990). 1-[4-(Trimethylsilyl)ethynyl]phenyl-2,6,7-trioxabicyclo[2.2.2]octanes: a novel type of selective proinsecticide, *J. Agric. Food Chem., 38*: 1091.
211. Yoshikawa, H., Shono, T., and Eto, M. (1986). Synthesis and insecticidal activity of methylphosphonothiolates, *J. Pestic. Sci., 11*: 15.
212. Sakamoto, H., and Nishizawa, Y. (1962). Preparation and biological properties of phenylphosphonothioates, *Agric. Biol. Chem., 26*: 252.
213. Miyamoto, J. (1959). Non-enzymatic conversion of Dipterex into DDVP and their inhibitory action on enzymes, *Botyu-Kagaku, 24*: 130.
214. Arthur, B.W., and Casida, J.E. (1958). Biological activity of several *O,O*-dialkyl alpha-acyloxyethylphosphonates, *J. Agric. Food Chem., 6*: 360.
215. Bendi, S., and Roy, N.K. (1980). Metabolism of *O,O*-diphenyl dichloromethylphosphonate by mycelial cells of *Pyricuaria oryzae*, CAV, *J. Environ. Sci. Health, B15*: 259.
216. Ohkawa, H. (1982). Stereoselectivity of organophosphorus insecticides, *Insecticide Mode of Action*, (Coats, J.R., ed.), Academic Press, New York, p. 163.
217. De Jong, L.P.A., and Benshop, H.P. (1988). Biochemical and toxicological implications of chirality in anticholinesterase organophosphates, *Stereoselectivity of Pesticides Biological and Chemical Problems*, (Ariens, E.J., Van

Rensen, J.J.S., and Welling, W., eds.), Elsevier, Amsterdam, p. 109.

218a. Sasaki, M., Kato, T., Yamamoto, S., and Mukai, K. (1984). Antifungal activity of [hydroxy(pyridin-3-yl)-methyl]phenylphosphinates and related compounds, *J. Pestic. Sci., 9*: 717.

218b. Sasaki, M., Takano, M., and Kato, K. (1987). 1*H*-1,2,4-Triazol-1-ylmethyldiphenylphosphine sulfides, a new class of fungicides, *Agric. Biol. Chem., 51*: 1727.

219a. Cole, D.J. (1985). Mode of action of glyphosate - a literature analysis, *The Herbicide Glyphosate*, (Grossbard, E., and Atkinson, D., eds.), Butterworths, London, p. 48.

219b. Cassidy, P.J., and Kahan, F.M. (1973). A stable enzyme-phosphoenolpyruvate intermediate in the synthesis of uridine-5'-diphospho-*N*-acetyl-2-amino-2-deoxyglucose 3-*O*-enolpyruvyl ether, *Biochem, 12*: 1364.

220. Allen, J.G., Atherton, F.R., Hall, M.J., Hassall, C.H., Holmes, S.W., Lambert, R.W., Nisbet, L.J., and Ringrose, P.S. (1978). Phosphonopeptides, a new class of synthetic antibacterial agents, *Nature, 272*: 56.

221. Chrzanowski, R.L. (1983). Metabolism of [^{14}C]fosamine ammonium in brush and turf, *J. Agric. Food Chem., 31*: 223.

222. Helgstrand, E., Eriksson, B., Johanson, N.G., Lannero, B., Larsson, A., Misiorny, A., Noren, J.O., Szoberg, B., Stenberg, K., Stridh, S., Oberg, B., Alenius, S., and Philipson, L. (1978). Trisodium phosphonoformate, a new antiviral compound, *Science, 201*: 819.

223. Barchietto, T., Saindrenan, P., and Bompeix, G. (1988). Uptake and utilization of phosphonate ions by *Phytophthora citrophthora* and *Nectria haematococca* in realtion to their selective toxicity, *Pestic. Sci., 22*: 159.

224. Barchitto, T., Saindrenan, P., and Bompeix, G. (1990). Effects of phosphonate on phosphate metabolism in *Phytophthora citrophthora*, *Pestic. Sci., 30*: 365.

225. Logusch, E.W., Walker, D.M., McDonald, J.F., and Franz, J.E. (1989). Substrate variability as a factor in enzyme inhibitor design: Inhibition of ovine brain glutamine synthetase by α- and γ-substituted phosphinothricins, *Biochem, 28*: 3043.

226. Sittig, M., (1977). Merphos, *Pesticides Process Encyclopedia*, Noyes Data Corp., Park Ridge, p. 309.

227. Jung, J. (1985). Plant bioregulators: overview, use, and development, *Bioregulators for Pest Control, ACS Symposium Ser., 276*, (Hedin, P.A., ed.), American Chemical Society, Washington, p. 95.
228. Wustner, D.A., and Fukuto, T.R. (1974). Affinity and phosphonylation constants for the inhibition of cholinesterases by the optical isomers of *O*-2-butyl *S*-2-(dimethylammonium)ethyl ethylphosphonothioate hydrogen oxalate, *Pestic. Biochem. Physiol., 4*: 365.
229. Wustner, D.A., and Fukuto, T.R. (1973). Stereoselectivity in cholinesterase inhibition, toxicity, and plant systemic activity by the optical isomers of *O*-2-butyl *S*-2-(ethylthio)ethyl ethylphosphonothioate, *J. Agric. Food Chem., 21*: 756.
230. Hirashima, A., Ishaaya, I., Ueno, R., Ichiyama, Y., Wu, S.-Y., and Eto, M. (1989). Biological activity of optically active salithion and salioxon, *Agric. Biol. Chem., 53*: 175.
231. Ohkawa, H., Mikami, N., and Miyamoto, J. (1978). Metabolism of the optical isomers of cyanofenphos in rice stem borer larvae, *Agric. Biol. Chem., 42*: 445.
232. Lee, P.W., Allahyari, R., and Fukuto, T.R. (1976). Stereospecificity in the metabolism of the chiral isomers of fonofos by mouse liver microsomal mixed function oxidase, *Biochem. Pharmacol., 25*: 2671.
233. Mikami, N., Ohkawa, H., and Miyamoto, J. (1977). Stereospecificity in oxidation of the optical isomers of *O*-ethyl *O*-2-nitro-5-methylphenyl *N*-isopropyl phosphoramidothioate (S-2571) by liver mixed function oxidase and UV light, *J. Pestic. Sci., 2*: 119.
234. Lee, P.W., Allahyari, R., and Fukuto, T.R. (1978). Studies on the chiral isomers of fonofos and fonofos oxon: II. *In vitro* metabolism, *Pestic. Biochem. Physiol., 8*: 158.
235. Hassan, A., and Dauterman, W.C. (1968). Studies on the optically active isomers of *O,O*-diethyl malathion and *O,O*-diethyl malaoxon, *Biochem. Pharmacol., 17*: 1431.
236. Ohkawa, H., Mikami, N., Kasamatsu, K., and Miyamoto, J. (1976). Stereoselectivity in toxicity and acetylcholinesterase inhibition by the optical isomers of papthion and papoxon, *Agric. Biol. Chem., 40*: 1857.
237. Hirashima, A., Ueno, R., Oyama, K., Koga, H., and Eto, M. (1990). Effect of salithion enantiomers on larval growth, carbohydrases, acetylcholinesterase, adenylate cyclase activities and cyclic adenosine 3',5'-monophosphate level of

Musca domestica and *Tribolium castaneum*, *Agric. Biol. Chem.*, *54*: 1013.
238. Ohkawa, H., Mikami, N., Okuno, Y., and Miyamoto, J. (1977). Stereospecificity in toxicity of the optical isomers of EPN, *Bull. Environ. Contam. Toxicol.*, *18*: 534.

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about the book . . .

This **practical** work summarizes the development of organophosphorus chemistry in topical areas *and* details the discipline's **current** state—providing applications and experimental procedures throughout.

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about the editor . . .

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