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Phosphorylated Aldehydes : Preparations and Synthetic Uses*

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***Dedicated to the memory of Professor Henri Normant (1907-1997), one of the founders of French modern organic chemistry**

1. INTRODUCTION

Aldehydes are among the most fundamental chemical functionalities in organic chemistry. In turn, phosphorylated aldehydes are popular reagents which occupy a unique position in organic chemistry and the specific properties of these compounds have given rise to a large number of developmental and synthetic applications.¹ Since the review on the subject written by Razumov *et al.*¹ in 1973, these compounds have received considerably more attention than during the 21 years following their first preparation by Dawson and Burger² in 1952. The number and diversity of papers in the literature attest to the wide acceptance and general utility of these reagents. The intervening 25 years have seen decisive progress in the development of the chemistry of these compounds: the blossoming of research on phosphonate carbanions, including their use in intermolecular and intramolecular Horner–Wadsworth–Emmons reactions; the discovery of phosphonoacetaldehyde in nature; and the application of phosphorylated aldehydes to the preparation of aminophosphonic acids. So much knowledge has been accumulated that the time seemed appropriate to gather the results of phosphorylated aldehyde research in a review. In this review, the various methods for the preparation of phosphonates containing a formyl group in the alkyl substituent linked to phosphorus, the types of reaction they undergo, their use as synthetic intermediates and their conversion into biologically active compounds are summarised.

2. SYNTHESIS OF PHOSPHORYLATED ALDEHYDES

One of the advantages of phosphorylated aldehydes is their synthetic accessibility. In principle, the formyl group can be introduced at any position relative to the phosphorus, and compounds with formyl group in positions 1 to 16 are known (Fig. 1). The methods for the preparation of phosphorylated aldehydes are generally a combination of phosphorus and carbon chemistry. To this end either a trivalent phosphorus compound reacts with an alkyl halide attached at a masked formyl group, or the formyl group is introduced into the alkyl substituent linked to the phosphoryl group using organometallic coupling methods (C-C bond formation) or functional group transformations. The choice of method, P-C versus C-C bond formation, depends on the relative position of the formyl group to phosphorus. The selected preparations here described include compounds containing alkoxy groups on the phosphorus atom.

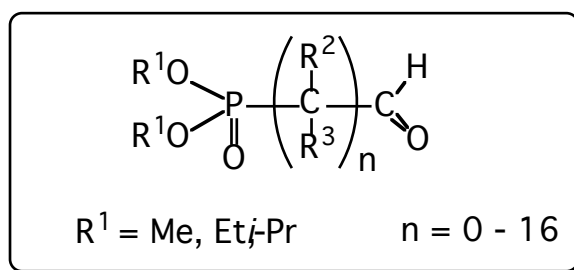


Fig. 1. Dialkyl ω -formylalkylphosphonates.

development of the method remains limited by the availability of diisopropyl ethynylphosphonate **7** on large scale.²⁴

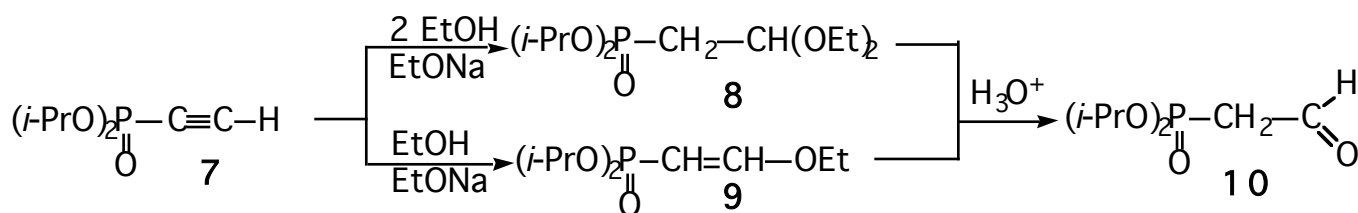


Fig. 4. Synthesis of diisopropyl 1-formylmethylphosphonate from ethynylphosphonate²⁴.

A variation of the MA reaction utilized the chloromethyloxazine as masked formyl group instead of diethyl acetal (Fig. 5). Chloromethyloxazine underwent a smooth reaction with trialkyl phosphites at reflux for 24h to furnish the oxazine phosphonates **11** (R=Me, 40% and R=Et, 80%).²⁵

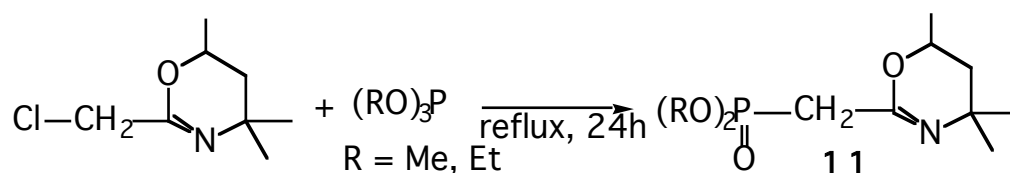


Fig. 5. Synthesis of oxazine phosphonates²⁵

Employing the oxazine phosphonates **11** provided a route to α -substituted phosphonoacetaldehydes. For instance the 1,1-dimethyl oxazine phosphonate **12** was obtained in high yield (93%) by treating the sodium derivative of **11** (R=Et) in DME with methyl iodide in excess. The conversion of **12** into the diethyl 1,1-dimethyl-1-formylmethylphosphonate **13** was accomplished in 62% overall yield by the standard reduction-hydrolysis technique using sodium borohydride at -45°C followed by heating in oxalic acid (Fig. 6). Thus the use of oxazine phosphonates **11** constitutes an entry into α -substituted phosphonoacetaldehydes.²⁵

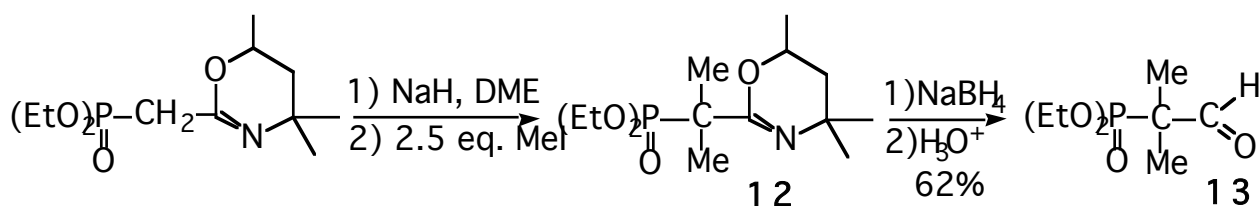


Fig. 6. Synthesis of diethyl 1,1-dimethyl-1-formylmethylphosphonate using the oxazine phosphonate²⁵.

Another variation of the protecting reagent for the formyl group utilizes vinyl acetates. Thus diethyl 1-formylmethylphosphonate **4** was obtained in 66% yield through the hydrolysis of diethyl 2-acetoxy-2-chloroethylphosphonate **14**. Preparation of **14** was achieved by successive reaction of vinyl acetate with phosphorus pentachloride at $7-8^\circ\text{C}$ in CCl_4 , treatment of the unisolated adduct at the same temperature with SO_2 and alcoholysis of the (2-acetoxy-2-chloroethyl)phosphonic dichloride with ethanol at 0°C in Et_2O in the presence of pyridine (Fig. 7). Deprotection of the formyl group, in acetone or dioxane, was a slow operation.²⁶

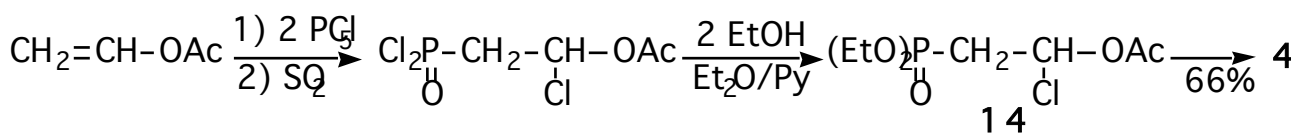


Fig. 7. Synthesis of diethyl 1-formylmethylphosphonate from vinyl acetates²⁶

A recently introduced method is the palladium-catalysed MA reaction of allyl acetates with $(\text{EtO})_3\text{P}$, which provided diethyl allylphosphonates in reasonable yield (65%). This reaction was been applied to the synthesis of diethyl 1-formylmethylphosphonate **4** on a preparative scale (crude 78%, pure 52%) by reductive ozonolysis of diethyl allylphosphonate in CH_2Cl_2 at -70°C over 4h (Fig. 8).²⁷

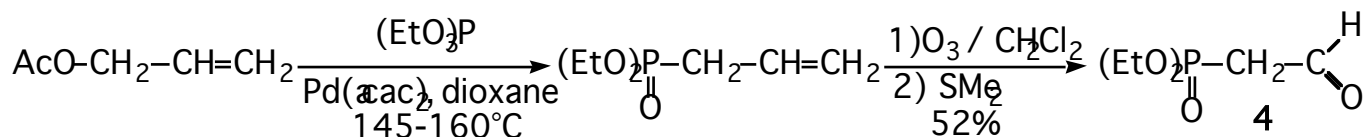


Fig. 8. Synthesis of diethyl 1-formylmethylphosphonate by reductive ozonolysis²⁷

The preparation on a large scale of dialkyl 1-formylethylphosphonates was achieved in good yield (66%) by hydroformylation of several dialkyl vinylphosphonates in the presence of catalytic amounts of $\text{Rh}(\text{COD})\text{Cl}$ dimer in toluene with 1:1 $\text{CO}-\text{H}_2$ ratio.¹⁸⁸

Decisive progress was made with the formylation of organophosphorus compounds containing an active methylene group. This methodology is the procedure of choice for preparing both unsubstituted and α -substituted phosphonoacetaldehydes with or without a functional group next to the formyl group. The aldehydes synthesised include, together with the phosphorus-containing groups, alkyl, aryl and electron withdrawing groups in the α -position.

Two complementary procedures have been successfully developed. One employs a carbanionic route with HCO_2Et ,^{28,29,30,33b} DMF,^{31,149} *N*-formylmorpholine³² or orthoformic esters^{33a,42,43} as formylating agents, the other employs a thermal route with dimethylformamide dialkyl acetal or amins.^{34,35}

In the carbanionic procedure, *n*-BuLi deprotonated the methylene group of **15** to give α -lithioalkylphosphonates **16**, which reacted with DMF or *N*-formylmorpholine to give a transient lithium β -aminoalkoxide **17**. After treatment of the reaction mixture by aqueous acid (3M HCl) the dialkyl 1-formylalkylphosphonates **18** were isolated in near quantitative yield (Fig. 9).^{31,32} By a similar procedure **16** reacted with HCO_2Et to give **18** in comparable yield. This formylation reaction using lithio anions and HCO_2Et has been applied to the synthesis of several phosphonates containing an active methylene group including allyl-,³⁶ benzyl-,³⁰ chloromethyl-,³⁷ bromomethyl-,²⁹ 3,3-diethoxybutyl-³⁸ and thioethylmethylphosphonate.³⁰ Yields of functional dialkyl 1-formyl-alkylphosphonates **18** were high and the only byproduct was the unreacted starting phosphonate.

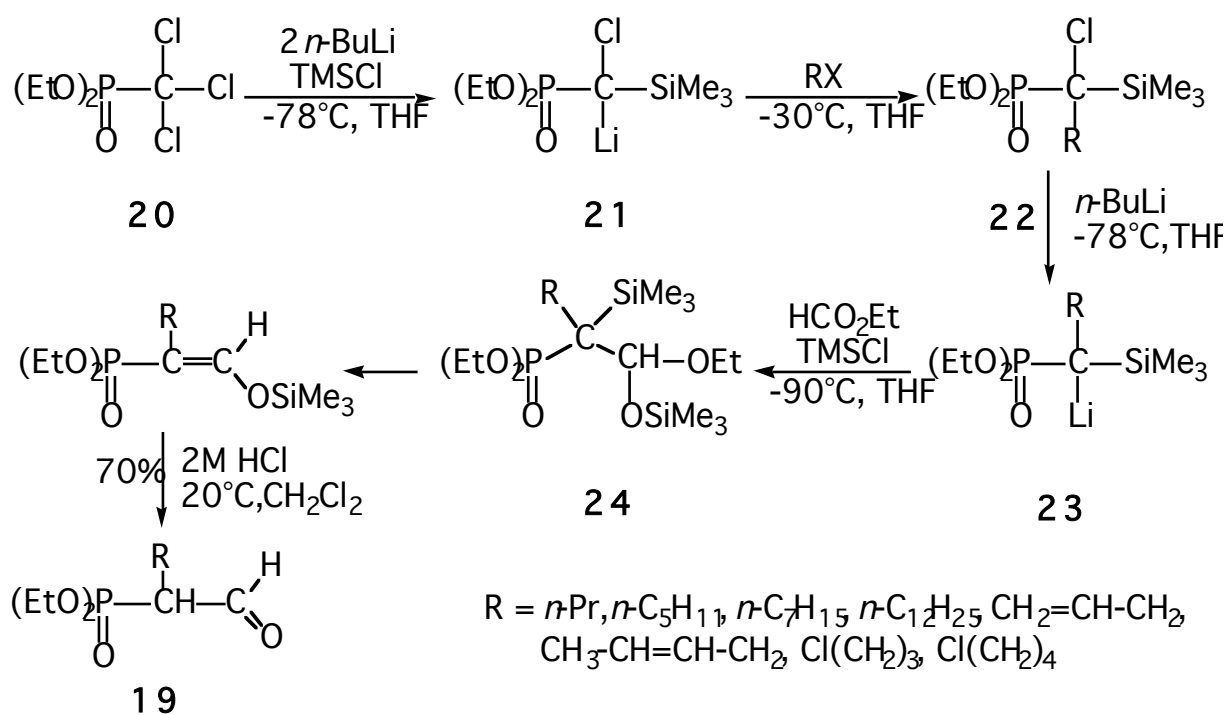


Fig. 11. Synthesis of diethyl 1-formylalkylphosphonates from diethyl trichloromethylphosphonate⁴¹

Formylation of methylene group with orthoformic esters is a more limited reaction. In the presence of sodium in Et₂O at room temperature, orthoformic esters effect a formylation reaction with a number of relatively acidic (Z=Cl,^{33a} Br,^{33a} Ph^{33a,42}) or very acidic phosphonates **25** (Z=CN,^{33b} CO₂R,^{33b} COR^{29,33a,43}). Yields of functionalized diethyl 1-formylmethylphosphonates **27**, after aqueous acid treatment of the diethyl acetals or enol ethers, are relatively modest (32 to 50%), which renders this methodology not competitive with methods that use formylating agent at low temperature.

When phosphonates **25** containing powerful electron withdrawing groups Z are subjected to formylation by HCO₂Et, the corresponding phosphorylated aldehydes **27** are obtained in low yields (25 to 30%).^{28,29,30} Full utilization of this carbanionic route is handicapped by the Z groups, which promote a stabilisation of the anionic form unfavourable to the reaction. This may be overcome by use of a thermal route (Fig. 12). In the thermal procedure, an aminomethylene fragment is introduced on the methylene group by the reaction of the phosphonates **25** with a N,N-dimethylformamide dialkyl acetal to produce phosphorylated enamines **26** in pure form. The phosphorylated enamines **26** are then converted to the 1-formyl-methylphosphonates **27** by further acid or basic hydrolysis.^{34,35} By contrast to the carbanionic route, the electron withdrawing effect of the Z group appears as a favourable factor in the thermal route.

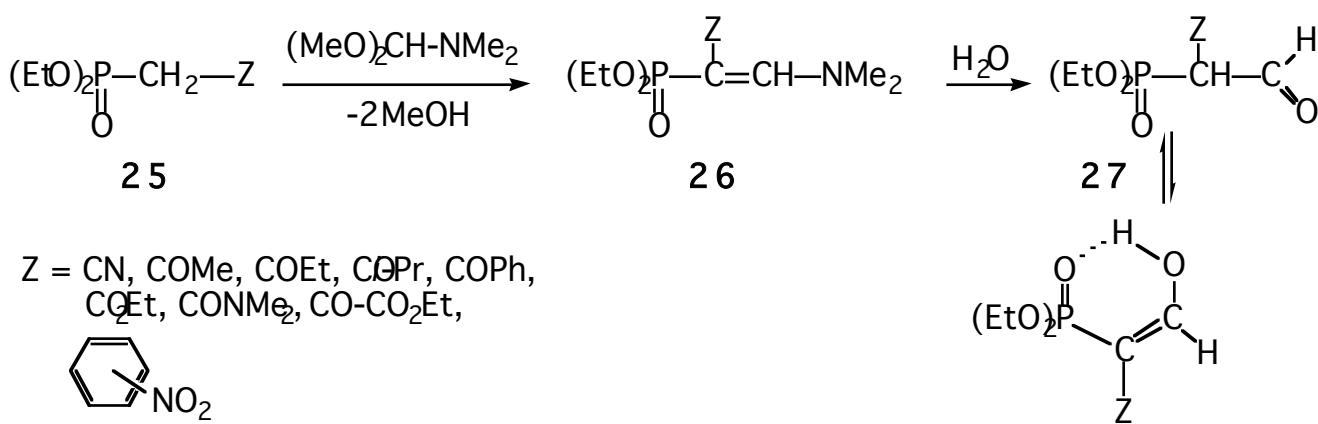


Fig. 12. Synthesis of diethyl 1-formylalkylphosphonates by thermal route³⁵

A large variety of *N,N*-dimethylformamide dialkyl acetals are commercially available. They have a greater reactivity than the orthoformate esters and they offer the advantages of neutral conditions and greater yields than those obtained by other methods. The *N,N*-dimethylformamide dimethyl acetal and *tert*-butoxybis(dimethylamino)methane have been shown to be useful in reaction with phosphonates bearing a good electron withdrawing group Z. On reaction with functionalized phosphonates **25**, *N,N*-dimethylformamide dimethyl acetal undergoes spontaneous elimination of methanol at room temperature when Z=CN and CO-CO₂R; with Z=CONR₂, CO₂R and COR the reaction requires 2h at reflux and when Z=C₆H₄NO₂ 8h at reflux is necessary. The enamine phosphonates **26** are always obtained in nearly quantitative yield. However, the number of compatible functional groups is limited since phosphonates with Z=CH(OEt)₂, Cl, CH=CH₂, CH=CHCl, C₆H₅, *o*-ClC₆H₄, *p*-ClC₆H₄ and S₂Et are inert. Formyl deprotection can be realized at room temperature either by treatment with 3M HCl in biphasic medium (Z=*o*- or *p*-NO₂C₆H₄, CO₂R, CONR₂) or with 2M NaOH. The yields are generally excellent (83-90%) and the phosphonates containing a formyl group next to the Z group are isolated mainly in the enol form.³⁵

Another attractive preparation of 1-formylphosphonates includes the rearrangement of epoxides to carbonyl compounds, which is a well established reaction offering a true synthetic utility. An advantageous synthesis of diethyl 1,1-disubstituted 1-formylmethylphosphonates **29** has been developed using readily available diethyl 1,2-epoxyphosphonates **28** and catalytic isomerisation induced by Lewis acids (Fig. 13). The boron trifluoride etherate is an effective catalyst in the rearrangement of **28**. The [1,2] migration of the phosphoryl group is conducted with high selectivity and in good yield. Both symmetrical and unsymmetrical aliphatic and cyclic phosphorylated aldehydes **29** can be obtained by this way.⁴⁴⁻⁴⁸

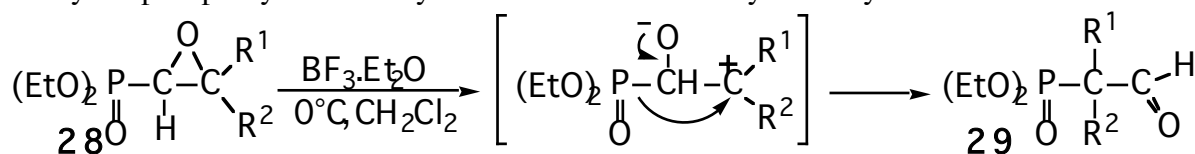



Fig. 13. Synthesis of diethyl 1,1-dialkyl-1-formylmethylphosphonates from 1,2-epoxyphosphonates⁴⁸.

Table 1. Synthesis of diethyl 1,1-dialkyl-1-formylmethylphosphonates⁴⁸.

29	a	b	c	d	e	f	g	h	i	j	k	l
R ¹	Me	Me	Me	Me	Me	Me	Me	Me	Et	<i>n</i> -Pr	<i>i</i> -Pr	<i>i</i> -Bu
R ²	Me	Et	<i>i</i> -Pr	<i>n</i> -Pr		<i>t</i> -Bu	<i>n</i> -Pent	Ph	Et	<i>n</i> -Pr	<i>i</i> -Pr	<i>i</i> -Bu

of α -substituted 3,3-diethoxy-propylphosphonates **35** by treatment of **34** with *n*-BuLi in THF at -50°C and subsequent alkylation of the stable α -lithiophosphonate carbanion. The yields of **35** are moderate to good (62-70%). The acetals are hydrolyzed in the same conditions as above (1M HCl) to give diethyl 2-alkyl-2-formylethylphosphonates **36** ($\text{R}^1 \neq \text{H}$) and 2-formylethylphosphonate **36** ($\text{R}^1 = \text{H}$) in yields ranging from 50 to 85%. Distillation of these compounds is frequently accompanied by extensive polymerisation.^{17b}

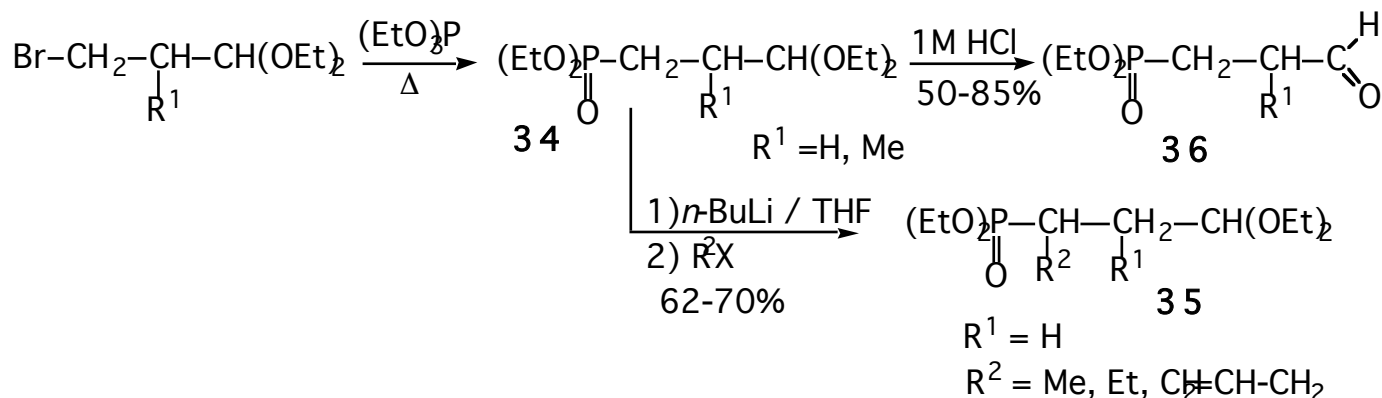


Fig. 16. Synthesis of diethyl 2-formylethylphosphonate via the MA reaction^{17b}.

Reaction of $(\text{EtO})_3\text{P}$ with dihalogenoalkenes at $120-140^\circ\text{C}$ provides the diethyl 3-halogeno-propen-2-ylphosphonates **37** (56 to 90% yield) which upon treatment with alcoholates or thiolates in ethanol at room temperature results in the only formation of the substitution products in the γ -position (Fig. 17). The enol- **38** and thioenolether **39** were converted by hydrolysis with 5M HCl at reflux to the corresponding diethyl 2-alkyl-2-formylethylphosphonate **36** ($\text{R}^1 \neq \text{H}$) or 2-formylethylphosphonate **36** ($\text{R}^1 = \text{H}$) thus giving an entry into β -substituted phosphonopropionaldehydes.⁵²

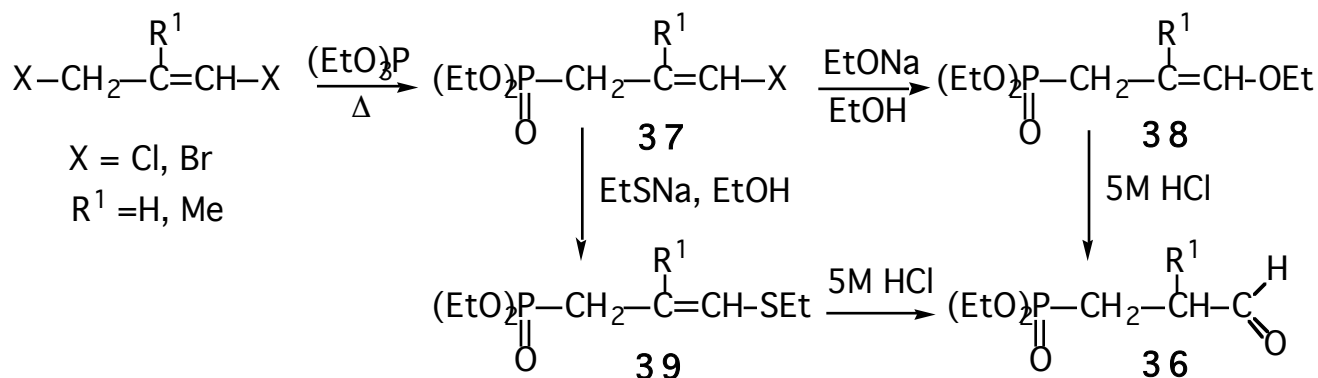


Fig. 17. Synthesis of diethyl 2-alkyl-2-formylethylphosphonates via the MA reaction⁵².

Unsaturated dialkyl 2-formylphosphonates have been obtained via alkoxyacetals **41**. These were prepared from the reaction of PCl_5 with alkyl allyl ethers at 7°C in C_6H_6 . On treatment with RONa in Et_2O , the (3-alkoxy-3-chloropropenyl)phosphonic dichlorides **40** resulting from decomposition of the adduct with SO_2 (41% yield for $\text{R}^1 = \text{Et}$ and 24% for $\text{R}^1 = n\text{-Pr}$) produced a number of dialkyl 3,3-dialkoxy-propenylphosphonates **41** in yields ranging from 56 to 82% (Fig. 18). However, in experiments aimed at the isolation of the corresponding dialkyl 2-formylvinylphosphonates by hydrolysis of **41**, only clear viscous, undistillable resins were obtained. In view of their instability, phosphonoacroleins were not isolated in a free state but were identified as their 2,4-dinitrophenylhydrazones derivatives.⁵⁴

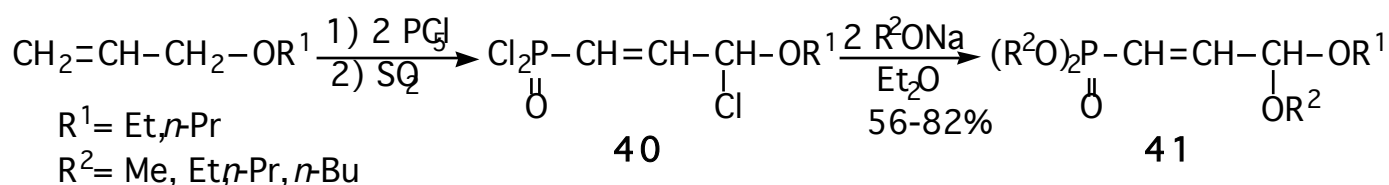


Fig. 18. Synthesis of dialkyl 3,3-dialkoxypropenylphosphonates from alkyl allyl ethers⁵⁴.

In contrast, the diethyl 2-formylethynylphosphonate **43** is a distillable colorless liquid, which proved to be stable when stored for several months at 0°C. It is obtained on preparative scale in high yield by hydrolysis with 97% HCO₂H of the diethyl 3,3-diethoxypropynylphosphonate **42**. Catalytic hydrogenation of **42** (5% Pd/CaCO₃) gave a mixture *Z*- and *E*- of acetals, from which the *Z*- isomer **44** was isolated in 60% yield. Formolysis of pure **44** using 97% HCO₂H gave a mixture of *Z*- and *E*- aldehydes from which the *Z*- diethyl 2-formylvinylphosphonate **45** *Z*- was isolated in 60% yield by distillation (Fig. 19).⁵⁵

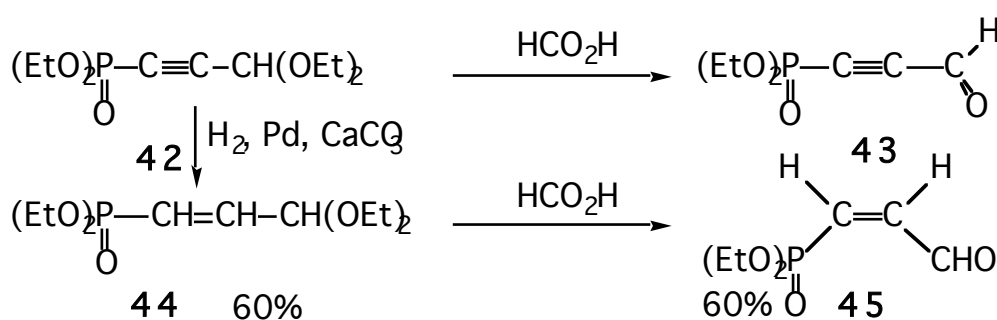


Fig. 19. Synthesis of diethyl 2-formylethynyl- and *Z*-2-formylvinylphosphonates⁵⁵.

Preparation of pure *E*- diethyl 2-formylvinylphosphonate **45** in 52% yield involved the oxidation with pyridinium chlorochromate (PCC) in CH₂Cl₂ at room temperature of diethoxyphosphinylallyl alcohol **47**, which was prepared from the diethyl 2,3-epoxyprop-1-ylphosphonate **46**. Compound **46** underwent ring opening at 0°C with sodium methoxide in methanol followed by treatment with Dowex (H⁺) resin to give the crude allylic alcohol in quantitative yield (Fig. 20).⁵⁶

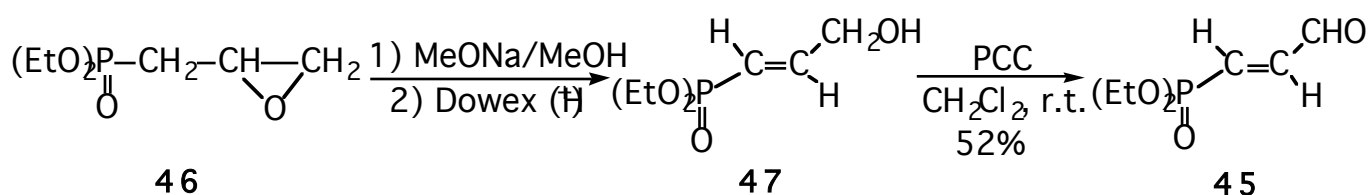


Fig. 20. Synthesis of *E*-diethyl 2-formylvinylphosphonate⁵⁶.

Very recently the preparation of diethyl 3,3-diethoxy-2-hydroxypropylphosphonate **48** was reported with 38% yield through the condensation of lithium diethylphosphite with D-glyceraldehyde diethyl acetal at -80°C in THF in the presence of BF₃·Et₂O (Fig. 21). Deprotection of the aldehyde was accomplished with 0.1M HCl at 40°C to give **49**.^{57,58}

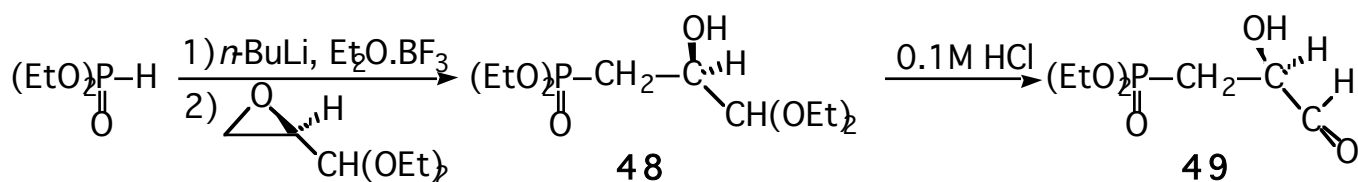


Fig. 21. Synthesis of diethyl 2-formylphosphonate by epoxide ring opening⁵⁷.

The method of converting vinyl to carbonyl groups by reductive ozonolysis has received much attention and has been applied with success to a variety of phosphonates containing homoallyl groups, including α -functionalized phosphonates.⁵⁹⁻⁶¹ The homoallyl group is often introduced by condensation of allylbromide with diethyl 1-lithioalkylphosphonates.^{60,61} For instance, a convenient preparation of **52** (Fig. 22) was achieved by ozonolysis of diethyl 1-allyl-1,1-difluoromethylphosphonate **51**, which itself was prepared in 64% yield from **50** after treatment of diethyl difluoromethylphosphorylcadmium bromide intermediate with allyl bromide.⁶²

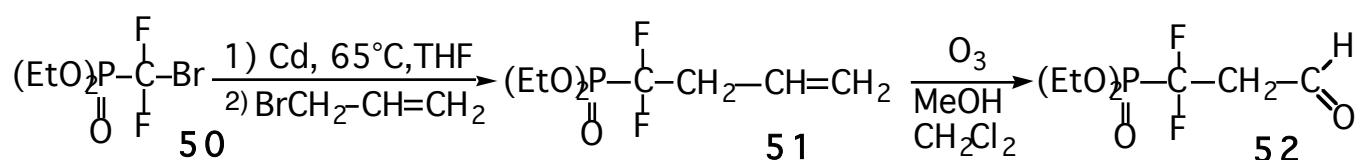


Fig. 22. Synthesis of diethyl 1,1-difluoro-2-formylethylphosphonate by reductive ozonolysis⁶².

Lactols have appeared as effective precursors in the synthesis of phosphorylated aldehydes. They have been utilized as starting materials for the conversion of phosphorylated 1,2-glycols to corresponding aldehydes via an oxidation with NaIO_4 in basic medium (Malaprade reaction). The lactol oxidative opening provided the diethyl 2-formyl-2-(hydroxymethyl)ethylphosphonate, which eliminated water during purification by chromatography on silica to produce diethyl 2-methylene-2-formylethylphosphonate.⁶³

A reaction of significant synthetic importance for the generation of dialkyl 2-formylethylphosphonates **36** ($\text{R}^1=\text{H}$) is the addition of trivalent phosphorus reagents to α,β -unsaturated aldehydes.⁶⁴ This Michael / Michaelis–Arbuzov strategy (Fig. 23) is the method of choice for incorporating substituents at any position between the phosphoryl and formyl groups. Addition was observed to occur under quite mild conditions in a conjugate manner with a wide range of Michael type substrates.^{53,65} The reaction of $(\text{EtO})_3\text{P}$ with α,β -unsaturated aldehydes in the presence of a proton source was first investigated.

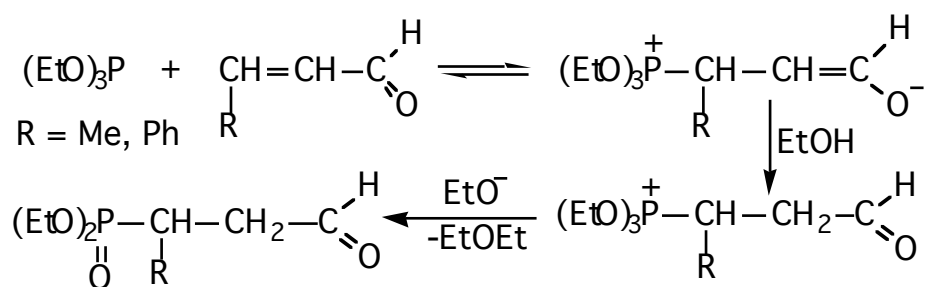


Fig. 23. Addition of $(\text{EtO})_3\text{P}$ to α,β -unsaturated aldehydes in the presence of ethanol^{66a}.

The use of a protic solvent such as an alcohol or a phenol provides not only a source of a proton for the anionic site of the zwitterionic adduct, but also a nucleophile for the required dealkylation step. Further efforts demonstrated that better yields were obtained using phenol (82% with crotonaldehyde) rather than simple alcohols.⁶⁶

Besides alcohol or phenol, a variety of associated reagents including dialkyl chlorophosphates⁶⁷ and silyl halides⁶⁸ have also been added as a trap in the reaction medium. Frequently, the use of these different reagent systems gave conjugate addition products.⁶⁴ In recent years, some striking developments with conjugate addition reactions have been accomplished using either phosphorus reagents bearing silyl ester

linkages such as $X_2\text{POSiR}_3$ or $X_2\text{POR}$ and R_3SiCl . Reactions with α,β -unsaturated aldehydes were carried out with 1 equivalent of each reagent either neat or in a solvent at ambient temperature (Fig. 24). A comparison of different reagents reveals that the reaction of acrolein, methacrolein and cinnamaldehyde proceeds quite readily, but with some complications. Although in certain instances low yield of conjugate addition products can be isolated, the major product formed is the product of addition at the carbonyl carbon (Abramov product).⁶⁸

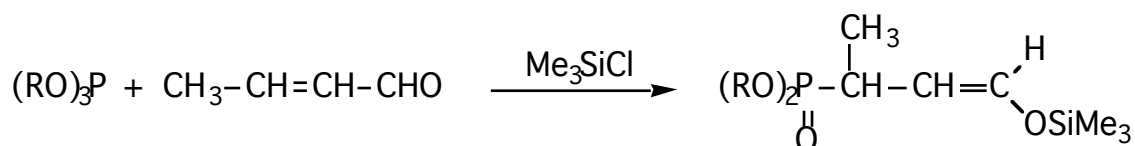


Fig. 24. Addition of trialkylphosphite to crotonaldehyde in the presence of Me_3SiCl .⁶⁸

The conjugate addition has been observed in the reaction of arylmethylenemalonalddehydes with trimethylphosphite. The reaction proceeds via an unstable intermediate, whose existence has been proven on the basis of spectral and chemical evidence, and which is easily hydrolysed to give a phosphonomethylene-malonaldehyde.⁶⁹

Full utilization of α,β -unsaturated aldehydes is often handicapped by the complications reported above. These disadvantages are overcome when the unprotected α,β -unsaturated aldehyde is replaced with an aldimine **53**, which is activated as an iminium salt (Fig. 25).

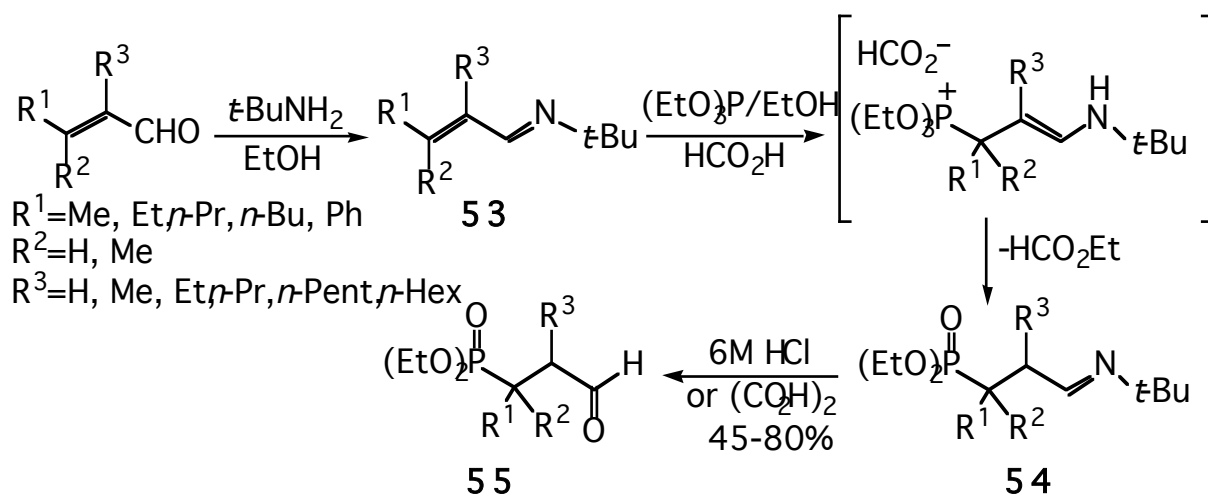


Fig. 25. Synthesis of diethyl 2-formylalkylphosphonates from aldimines⁷⁰.

$(\text{EtO})_3\text{P}$ does not react with aldimines in ethanol. By contrast, the addition of 1 equivalent of HCO_2H to the mixture $(\text{EtO})_3\text{P}/\text{EtOH}/\text{aldimine}$ induces an exothermic reaction resulting in the exclusive formation of **54**. Undoubtedly, the 1,4-addition of $(\text{EtO})_3\text{P}$ is promoted by initial protonation at nitrogen thus activating the double bond (Michael addition) and generating the formate for the dealkylating step (MA reaction). The dialkyl-substituted formylphosphonates **55** are obtained by hydrolysis of the imine function with 6M HCl or 1M oxalic acid. The method provides a ready and convenient access to a broad range of substituted diethyl 2-formylalkylphosphonates **55** in satisfactory yields (45-80%).⁷⁰

2.4. n=3.

The MA reaction for the synthesis of diethyl 3-formylpropylphosphonate has been realized from 4-bromobutylaldehyde diethyl acetal and 2-(3-bromopropyl)-1,3-dioxolane (Fig. 26). The latter reacts with $(\text{EtO})_3\text{P}$ at 110°C for 10h to give the cyclic acetal **56** in 83% yield. Hydrolysis of acetal with 0.35M HCl in dioxane at 100°C for 2h produces the diethyl 3-formylpropylphosphonate **57** in nearly quantitative yield.^{18a}

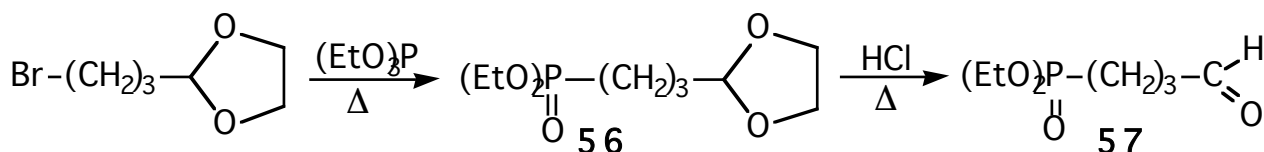


Fig. 26. Synthesis of diethyl 3-formylpropylphosphonate via the MA reaction^{18a}.

Since the double bond is an ideal precursor for the generation of a cyclopropyl ring an attractive procedure involving the addition of the carbenoid followed by transformation of an ester group into an aldehyde has been developed (Fig. 27). For example, the CuSO_4 -induced addition of ethyl diazoacetate to diethyl allylphosphonate in cyclohexane at reflux produced diethyl cyclopropylmethylphosphonate **58** in 30% yield as a 1:3 mixture of *cis*- and *trans*- isomers. The ester was hydrolysed to the acid which was treated with borane to give the alcohol **59**. Subsequent oxidation of the intermediate **59**, using PCC, afforded the aldehyde **60** in 83-86% yields respectively.⁷¹ The method has been extended (vide infra) to the preparation of higher analogs ($n=4$ and 5).⁷¹

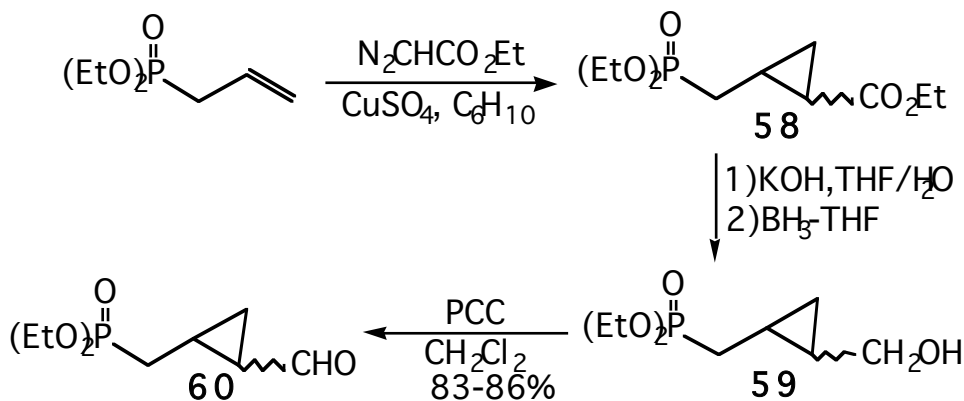


Fig. 27. Synthesis of diethyl 3-formylalkylphosphonate via addition of carbenoid to allylphosphonate⁷¹.

Unsaturated 3-formylphosphonates have been obtained by a MA reaction using 1,1-diethoxy-4-bromo-2-butene^{72a} or 1-acetoxy-4-chloro-2-butene^{72b,c} as masked formyl group (Fig. 28). The former reacts with $(\text{EtO})_3\text{P}$ at 135°C to give the diethyl 4,4-diethoxy-2-butenylphosphonate in 50% yield; deprotection was accomplished in 98% using a cold-saturated aqueous solution of tartaric acid.^{72a} The latter reacts with $(\text{EtO})_3\text{P}$ or $(i\text{-PrO})_3\text{P}$ at $125\text{-}140^\circ\text{C}$ in the presence of catalytic amount of NaI to give the corresponding phosphoryl acetates **61** in 81% ($\text{R}=\text{Et}$) and 54% ($\text{R}=i\text{-Pr}$) with $E:Z=90:10$ in both cases. By refluxing **61** for 20h in ethanol or methanol with a catalytic amount of *p*-toluenesulfonic acid, the alcohols **62** were smoothly obtained in almost quantitative yield (95-97%) $E:Z=90:10$. The Jones reagent proved to be the best reagent (65-68% yield) for the oxidation of the alcohols **62** to the aldehydes **63**. The dialkyl 3-formylallylphosphonates **63** are reasonably stable if stored under argon at -20°C .^{72c} Preparation of diethyl 3-formyl-2-methyl-allylphosphonate **64** is an example of the above process using the 1-bromo-2-methyl-4-acetoxy-2-butene as starting material and was accomplished in 86% yield $E:Z=55:45$.

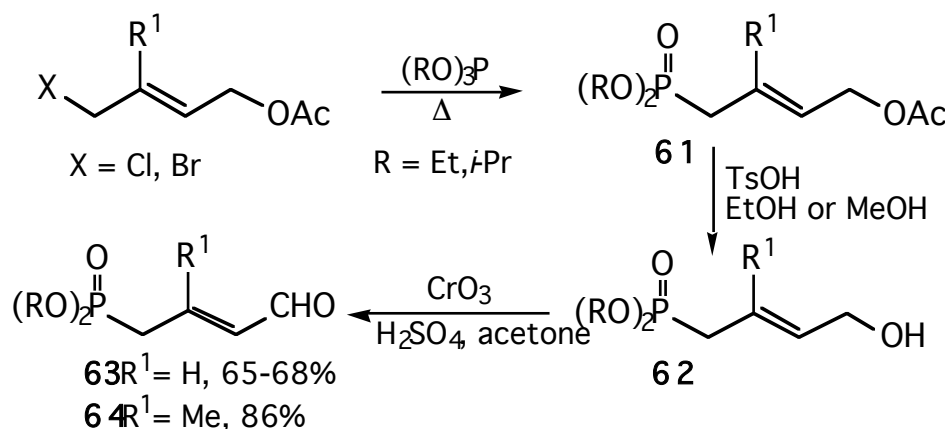


Fig. 28. Synthesis of dialkyl 3-formylallylphosphonates via the MA reaction^{72c}.

By contrast, the 3-formyl-3-methyl-allylphosphonate **67** was prepared from diethyl crotylphosphonate **65**, incorporating the formyl group by a carbanionic route (Fig. 29). Compound **65**, on treatment with 3 equivalents of LDA, underwent successively silylation with TMSCl and formylation with HCO_2Et to give the oxoanion **66**, which after acid hydrolysis lead exclusively to the *E*-diethyl 3-formyl-3-methyl-allylphosphonate **67** in 78% yield.⁷³

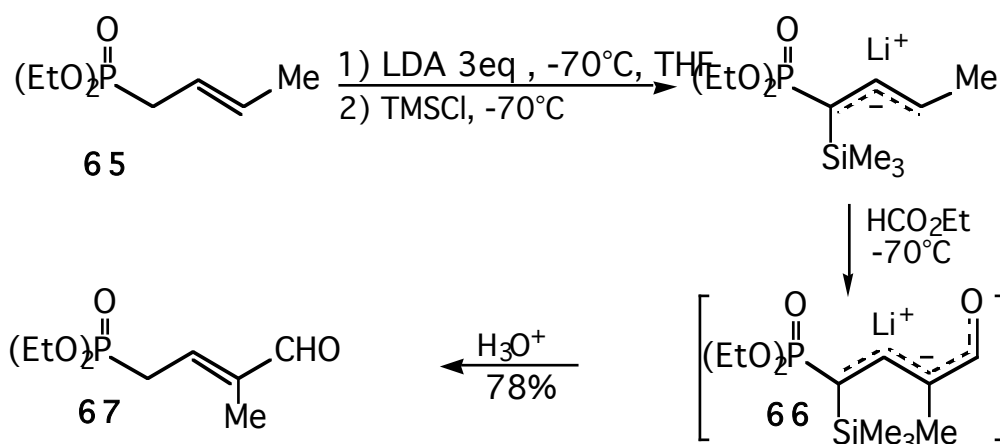


Fig. 29. Synthesis of diethyl 3-formyl-3-methyl-allylphosphonate⁷³.

The synthetically useful diethyl 2-oxopropylphosphonate **68** is known to give a stable dianion **69** at ambient temperature. In the presence of 2 equivalents of LDA this dianion was smoothly reacted at low temperature with HCO_2Et to provide a stabilized bis-enolate **70**, which was soluble in water. Acidification with 4M HCl produced the diethyl 3-formyl-2-oxo-propylphosphonates **71** in high yields (81-89%). This "one-pot" procedure offers a short and efficient means for obtaining a variety of compounds from readily available starting materials **68** (Fig. 30).⁷⁴ Recently, another preparation of **71** ($R^1=R^2=H$) was reported and involves a multi-step route using diethyl 2-oxo-propylphosphonate **68** ($R^1=R^2=H$) as starting material.⁷⁵

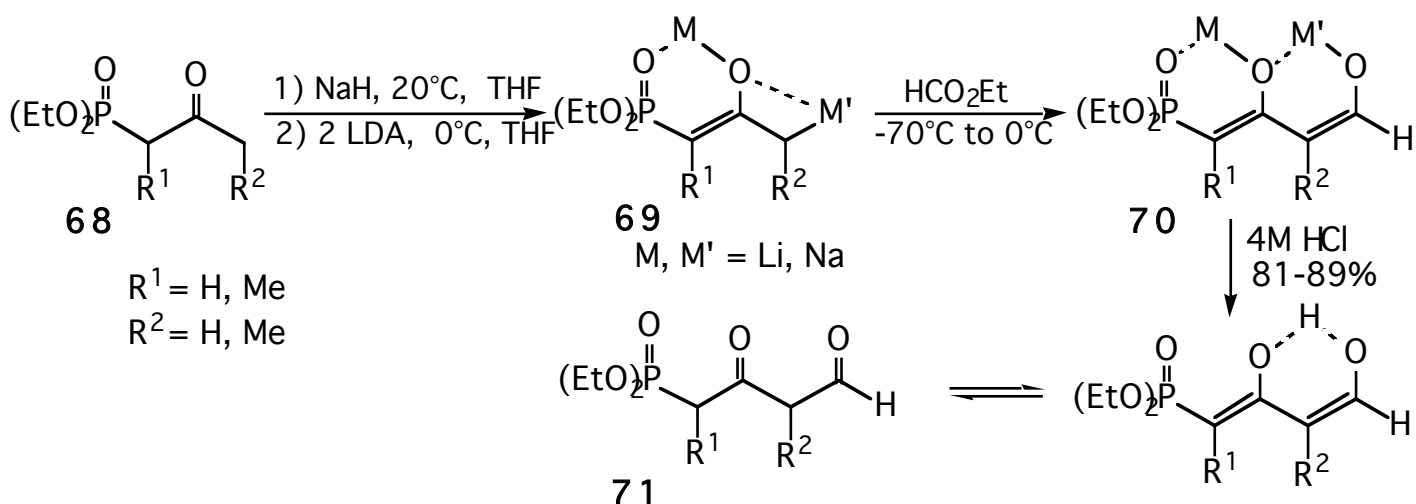


Fig. 30. Synthesis of diethyl 3-formyl-2-oxo-propylphosphonate⁷⁴.

The ring opening reaction of D-glycidaldehyde diethyl acetal at -80°C in THF by the diethyl 1-lithiomethylphosphonate in the presence of boron trifluoride etherate provided a convenient preparation of diethyl 4,4-diethoxy-3-hydroxybutylphosphonate **72** in 78% yield. Unmasking of the aldehyde functionality was accomplished using 0.1M HCl at 40°C to give the diethyl 3-hydroxy-3-formylpropyl-phosphonate **73** (Fig. 31).^{57,76}

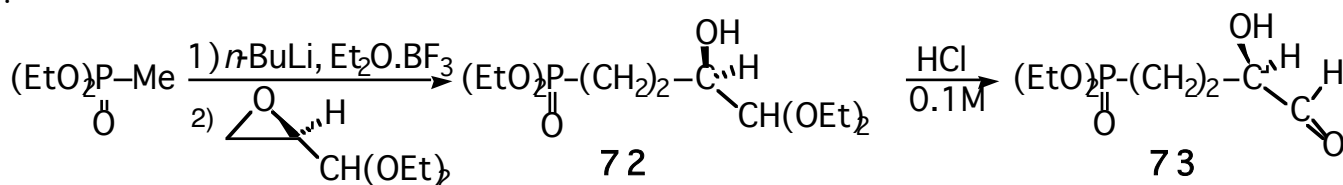


Fig. 31. Synthesis of diethyl 3-hydroxy-3-formylpropylphosphonate by epoxide ring opening⁵⁷.

An attractive application of the oxidative cleavage of phosphorylated 1,2-glycols **75** with sodium metaperiodate (Malaprade reaction) has been demonstrated in the synthesis of diethyl 3-formylalkylphosphonates **76** (Fig. 32). It was accomplished on preparative scale using the 1,2:5,6-di-O-isopropylidene- α -D-glucofuranose **74**. This mild method is advantageous and the resulting aldehyde was obtained in almost quantitative yield.⁷⁷

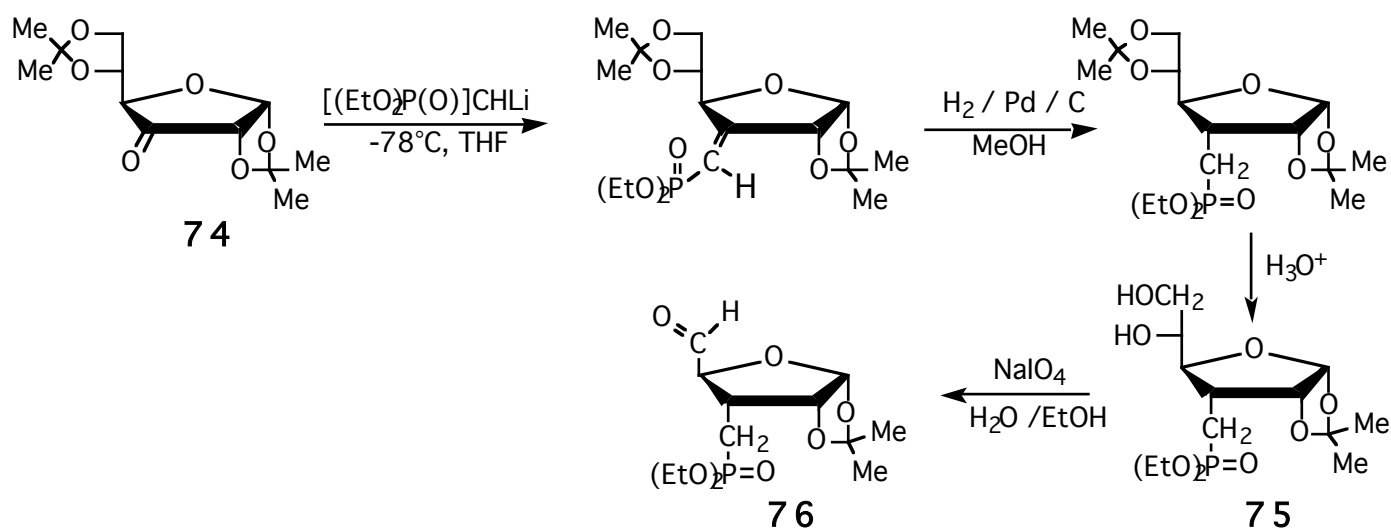


Fig. 32. Synthesis of diethyl 3-formylphosphonate **76** by oxidation of 1,2-glycols⁷⁷.

Several variations on the preparation of phenylphosphonates containing a formyl group in the γ -position have been reported. They are based on the phosphorylation, via Michaelis-Arbuzov or Michaelis-Becker reactions, of aromatic substrates **77** containing a protected primary alcohol (Fig. 33). Further oxidation of the alcohol into aldehyde **78** was accomplished under a wide range of conditions using activated MnO_2 in CHCl_3 at room temperature (53%),⁷⁸ PCC in CH_2Cl_2 (83-86%)⁷¹ or the Swern reaction (>95%).⁷⁹

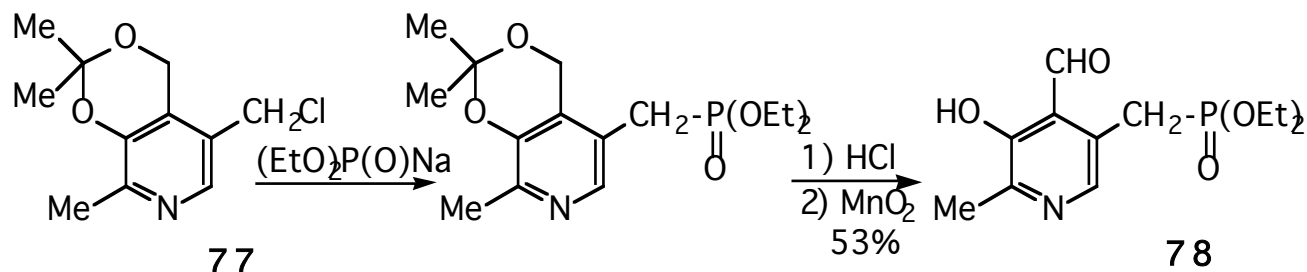


Fig. 33. Synthesis of diethyl 3-formylphosphonate by primary alcohol oxidation⁷⁸.

The preparation of the configurationally unstable diethyl 3-(*S*)-*tert*-butoxycarbonylamino-3-formylpropyl-phosphonate has also been reported, and involves reduction of a methyl ester group with DIBAL-H in toluene at -78°C .⁸⁰

An interesting procedure for the preparation of arylphosphonates bearing a formyl group is the phosphate-phosphonate rearrangement of the protected phosphorylated 4-hydroxybenzyl alcohol **79**. On treatment with LDA in THF at -78°C , compound **79** underwent an *o*-metallation with spontaneous migration of the phosphoryl group to give the phenylphosphonate **80** in 77% yield. Subsequent benzylation of the phenolic OH and desilylation afforded **81**, which was oxidized with activated MnO_2 in THF at room temperature to give the dimethyl *m*-formylphenylphosphonate **82** in 96% yield (Fig. 34).⁸¹

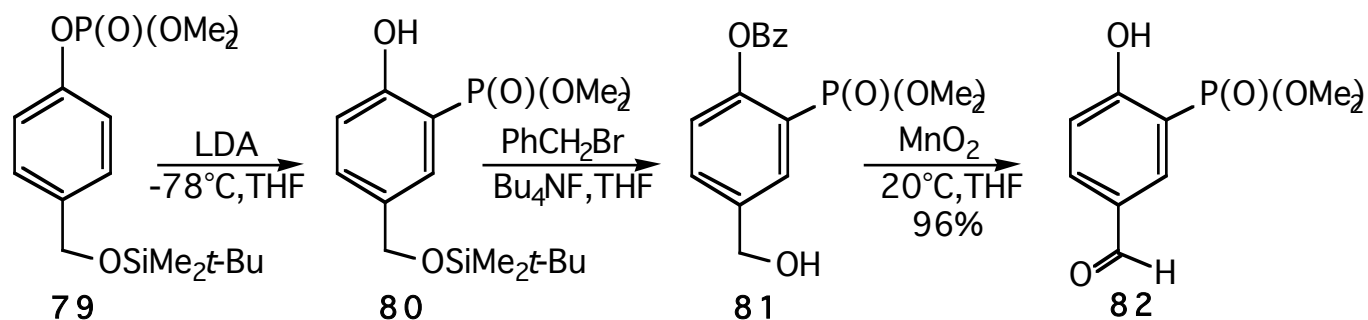


Fig. 34. Synthesis of dimethyl 3-formylphosphonate by phosphate-phosphonate rearrangement⁸¹.

An efficient synthesis of a variety of arylmethylphosphonates bearing electron-withdrawing groups (CO_2Et , CN, SO_2Me) at the α -carbon and a formyl group on the aromatic ring has been reported. They were prepared by treatment of diethylphosphoryl-stabilized carbanions with aryl halides in DMF or HMPA in the presence of CuI at 100°C for 5h. In the case of protected *o*-formyliodobenzene, the coupling reaction with the sodium derivative of triethyl phosphonocarboxylate gave, after acid work-up, the corresponding diethyl *o*-formylbenzylphosphonate in 75% yield.⁸²

2.5. $n=4$.

Two reactions were found to be best suited to the synthesis of diethyl 4-formylalkylphosphonates. The first one is a straightforward method to diethyl 4-formylalkylphosphonates **84** ($m=1$) from unprotected

aldehyde functionality, as demonstrated by experiments involving $(\text{EtO})_3\text{P}$ and bromoaldehydes **83**. At 100-110°C, the MA reaction provided the diethyl 4-formylalkylphosphonate **84** ($m=1$). However, the yields were much lower for the *cis*-cyclopropylaldehydes compared to those of the *trans* isomers (27% versus 62%). Presumably, this can be attributed to unwanted condensation with the *cis*-disposed aldehyde group (Fig. 35).⁷¹ The reaction has been extended to the preparation of **84** ($m=2$) with comparable results (12 and 58%).⁷¹

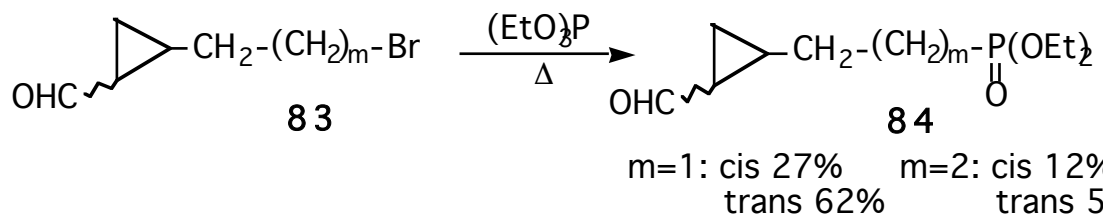


Fig. 35. Synthesis of diethyl 4-formylalkylphosphonate from unmasked aldehydes⁷¹.

In search for a flexible route to a wide range of variously substituted arylidene cyclopropanes, the carbene derived by metallic copper-induced decomposition of diethyl diazomethylphosphonate was added to an unsaturated acetal to give the diethyl 2-(3,3-dialkoxy-2,2-dimethylpropyl)cyclopropylphosphonate in 53-73% yields. It was found that cuprous trifluoromethanesulfonate was a particularly effective catalyst for this reaction.¹⁹¹

The second reaction has been observed with lactones which have been shown to be useful in several synthetic schemes. The reaction is phosphorus reagent dependent. When submitted to diethyl 1-lithiomethylphosphonate, the γ -lactone **85** underwent a ring opening reaction to give an hydroxyphosphonate **86** retaining the carbonyl group in β -position to phosphorus (Fig. 36). Subsequent Swern oxidation of the hydroxyphosphonate **86** provided the diethyl 4-formyl-2-oxobutylphosphonate **87**.⁸⁴

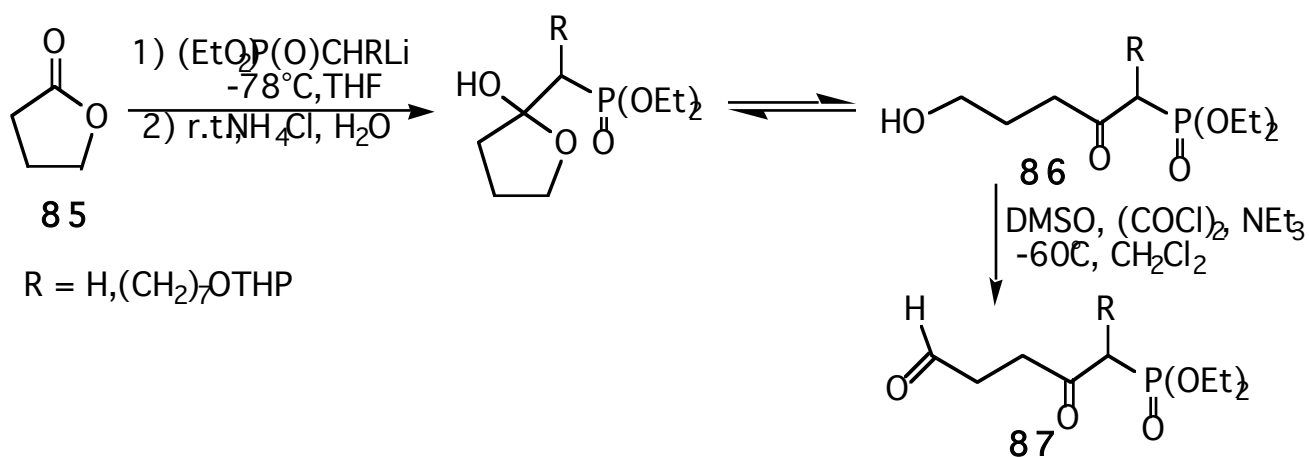


Fig. 36. Synthesis of diethyl 4-formyl-2-oxobutylphosphonates from γ -lactones⁸⁴.

By contrast, reduction of the lactone to the lactol followed by reaction with the sodium derivative of tetraethyl methylenediphosphonate gives an hydroxyphosphonate **88** containing a double bond α,β to phosphorus. Catalytic hydrogenation of the double bond followed by Swern oxidation of the hydroxyphosphonate **89** lead to the aldehyde **90** (Fig. 37). The alcohol **89** was also oxidized using $\text{SO}_3\cdot\text{Py}$ complex in DMSO and NEt_3 . This procedure allows the use of higher temperatures than the Swern protocol and provide

the aldehyde in good yield. Thus lactones appear to be valuable synthetic intermediates well suited to the preparation of a variety of phosphorylated aldehydes.⁸⁵

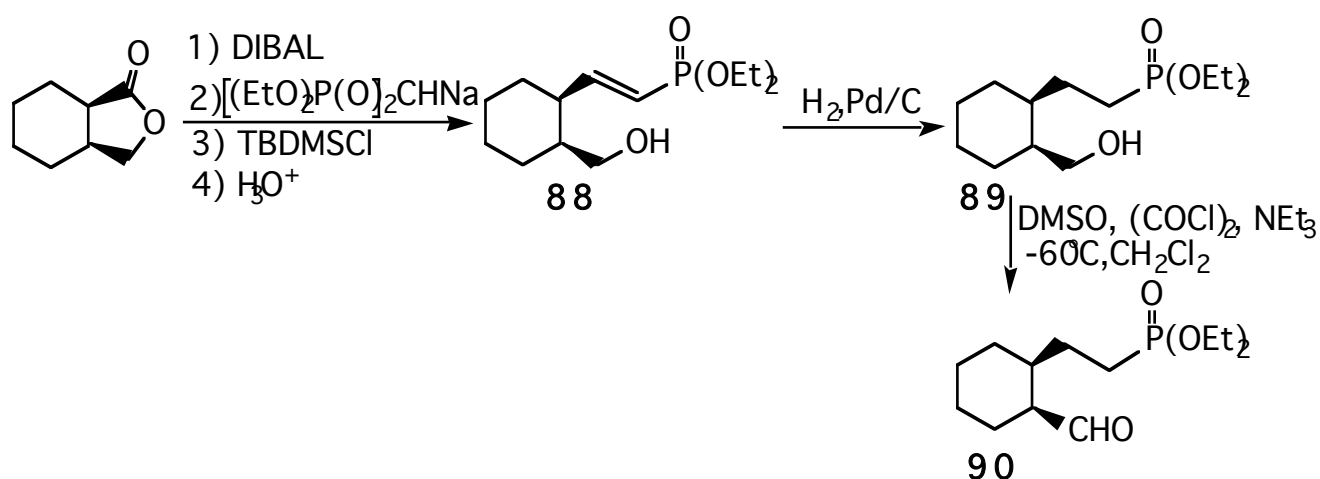


Fig. 37. Synthesis of diethyl 4-formylalkylphosphonate from γ -lactones⁸⁵.

A quite similar process was used in the preparation of phosphonic acid analogs of pyridoxal phosphate (Fig. 38). The sodium derivative of tetraethyl methylenediphosphonate was condensed with $\alpha^4,3$ -*O*-isopropylidene-isopyridoxal **91** to give diethyl $\alpha^4,3$ -*O*-isopropylidene- α^5 -pyridoxylidenemethylphosphonate **92** in yields up to 65%. Selective acid hydrolysis with 10% HCO_2H at reflux gave the key intermediate diethyl 2-(3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)vinylphosphonate in 98% yield. After catalytic hydrogenation of the double bond using 5% Pd/C in EtOH, several oxidation methods were studied, including MnO_2 in water, $\text{CrO}_3\cdot\text{Py}$ and DMSO-DCC. Finally, oxidation with activated MnO_2 in CHCl_3 proceeded smoothly to give the diethyl 2-(4-formyl-3-hydroxy-2-methyl-5-pyridyl)ethylphosphonate **93**.⁸⁶

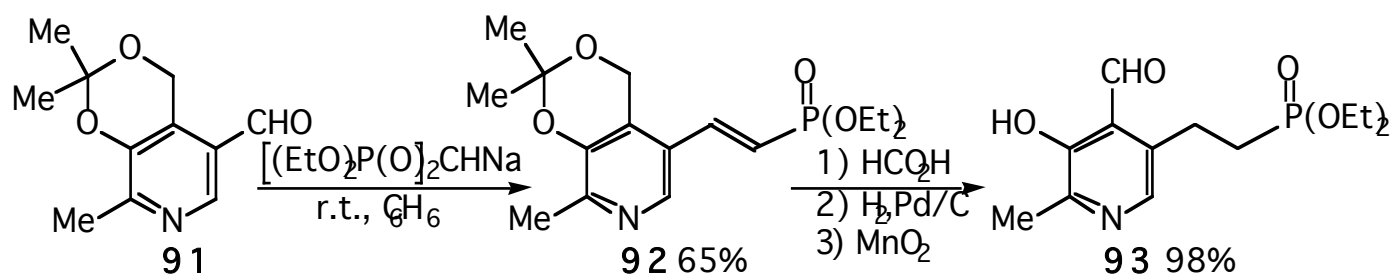


Fig. 38. Synthesis of phosphonic analog of pyridoxal phosphate⁸⁶.

The vinylic and acetylenic analogs of **93** are known. The former was prepared as a *cis-trans* mixture by Peterson reaction between **91** and the lithium anion of diethyl trimethylsilylmethylphosphonate. Isolation of the *cis*- derivative and subsequent deprotection of the alcohol followed by oxidation with MnO_2 in CHCl_3 lead to the diethyl 2-(4-formyl-3-hydroxy-2-methyl-5-pyridyl)vinylphosphonate. The latter was prepared by reaction of the lithium ethynyl analogue of pyridoxal with diethyl chlorophosphate in Et_2O at -74°C . The corresponding diethyl 2-(4-formyl-3-hydroxy-2-methyl-5-pyridyl)ethynylphosphonate was obtained in 26% yield after deprotection of the alcohol by brief heating with 10% aqueous trifluoroacetic acid and oxidation with MnO_2 .⁸⁷

The Michael addition, using an activated vinylphosphonate **94** and the magnesium derivative of the 2-(2-bromoethyl)-1,3-dioxolane, has been found to be a good method for chain-lengthening of formylphosphonates (Fig. 39). Unmasking of the aldehyde functionality produced **95**.⁸⁸

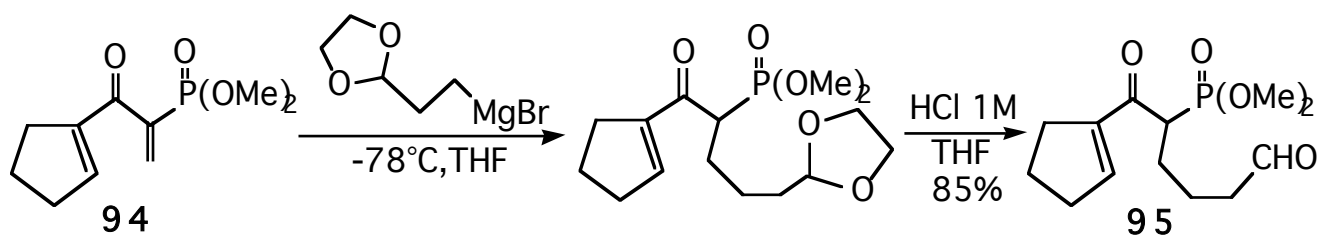


Fig. 39. Synthesis of dimethyl 4-formylalkylphosphonate via Michael addition⁸⁸.

Two routes to diethyl 4-formylalkylphosphonates from 1,2-glycols and lactols demonstrated once more the importance of these substrates. The first route provided diethyl 4-formylalkylphosphonates in almost quantitative yield (98%) from the mild oxidation of phosphorylated 1,2-dideoxy-3,4:5,6-di-*O*-isopropylidene-*D*-arabinose with NaIO_4 at 0°C in H_2O or in a $\text{H}_2\text{O}/\text{EtOH}$ mixture.⁸⁹ In the second route, diethyl 4-formylalkylphosphonates were obtained by opening of the unprotected 5-phosphorylated-*D*-ribofuranose with EtSH in HCl to give a dithioacetal. Subsequent acetylation followed by removal of the thioethyl groups generated the aldehyde.⁹⁰

The aromatic version of the MA reaction between $(i\text{-PrO})_3\text{P}$ and *p*-bromobenzaldehyde at 160°C , catalyzed by NiCl_2 , afforded the diisopropyl *p*-formylphenylphosphonate in 54% yield. The reaction has been extensively studied and it has been shown that electron-donor substituents facilitate reaction, while electron-acceptor substituents make reaction with P(III) compounds more difficult, regardless of their position in the aromatic nucleus.¹⁸⁹

Several other preparative procedures have been reported including the phosphorylation of aromatic substrates containing a free formyl group, a protected formyl group or a potential formyl group. The first procedure was used for the preparation of diethyl 4- or 6-methoxy-3-formylbenzylphosphonates in 83 and 74% yields by a MA reaction between $(\text{EtO})_3\text{P}$ and corresponding methoxyformylbenzyl chlorides at $170\text{--}180^\circ\text{C}$.⁸³ The second procedure used the $\text{Pd}(\text{PPh}_3)_4$ -catalyzed coupling reaction between diethylphosphite and *m*-bromobenzaldehyde protected as 1,3-dioxolane with ethylene glycol.⁹¹ In the third procedure the phosphorylation of substrates was achieved according to a Michaelis-Arbusov or a Michaelis-Becker reaction, followed by generation of the formyl group. The latter operation is usually based on typical formylation reaction using HCO_2Et in basic medium⁹² or by oxidation of benzylic bromide for example.⁹³ A single case of generation of aldehyde group by hydrolysis of a dibromomethylthiophene with diluted H_2SO_4 in dioxane at reflux for 1.5h in 95% yield was recently reported.¹⁸⁶

Under the modified Heck reaction conditions ($\text{Ag}_2\text{CO}_3 / \text{Pd}(\text{OAc})_2 / \text{PPh}_3$), the coupling of diethyl (*Z*)-2-iodovinylphosphonate with acrolein in MeCN at room temperature for 24h afforded the diethyl (1*Z*, 3*E*)-dienylphosphonate with high stereoselectivity in 94% yield.⁹⁴

2.6. **n=5 to 9**

The previously reported preparation of diethyl 4-formylalkylphosphonates **84** ($m=1$) from unprotected aldehyde functionality (Fig. 35) has been extended to provide one of the few known methods for the

transformation of a bromo aldehydes moiety to the corresponding diethyl 5-formylalkylphosphonates **84** ($m=2$).⁷¹ By a similar procedure to that described for $n=3$, the copper-mediated coupling reaction of diethylphosphoryl stabilized carbanions with aryl halides was applied to protected *p*-formyliodobenzene to produce diethyl *p*-formylbenzylphosphonate in 68% yield.⁸²

Most of the diethyl 5- and 6-formylalkylphosphonates containing an *o*-substituted aromatic ring with a masked aldehyde group were obtained by direct displacement of an alkyl halide or mesylate by a Michaelis-Becker reaction. For example, the masked aldehyde group was introduced on 2-methylbenzyl alcohol **96** by treatment with *n*-BuLi and alkylation of the resulting carbanion for 48h by 2-(2-bromoethyl)-1,3-dioxolane (18%) or bromoacetaldehyde dimethylacetal (8.41%). The benzylic alcohols **97** were mesylated and displaced with sodium diethylphosphite to introduce the phosphoryl group (83% and 51%). The aldehydes **98** were unmasked by treatment with a 1:1 THF / 3M HCl at 25°C for 5h (93% and 100%) (Fig. 40).⁹³

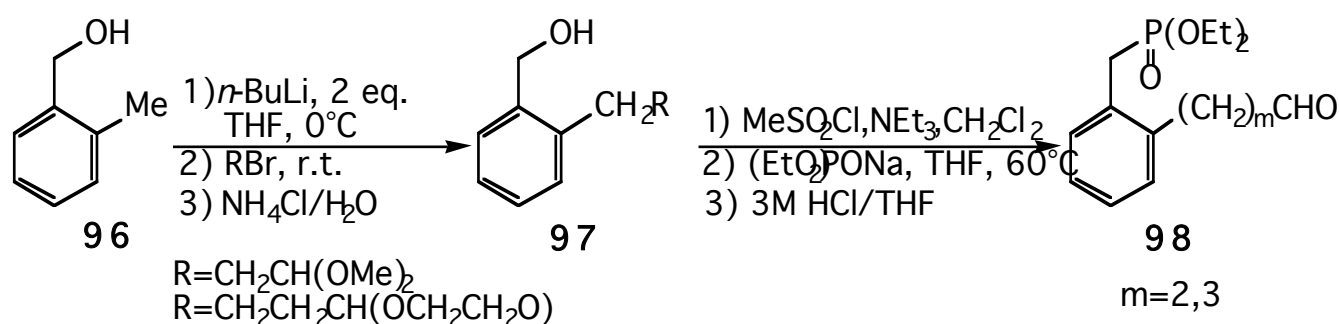


Fig. 40. Synthesis of diethyl 5- and 6-formylalkylphosphonates.

An interesting gap has been realized with the use of α -hydroxyphosphonates, as illustrated by the synthesis of **102** (Fig. 41). Treatment of terephthalaldehyde, containing monoprotected aldehyde function, with the readily acid labile di-*tert*-butylphosphite (Pudovik reaction) in the presence of basic alumina oxide has allowed the facile synthesis of the α -hydroxyphosphonate **99**. Radical deoxygenation of the secondary alcohol **99** was achieved in a two step process through the intermediacy of xanthate **100** with *n*-Bu₃SnH to provide **101**. The diethyl acetal was converted to **102** (29%) by further treatment with CHCl₃ saturated with 1M HCl.⁹⁵

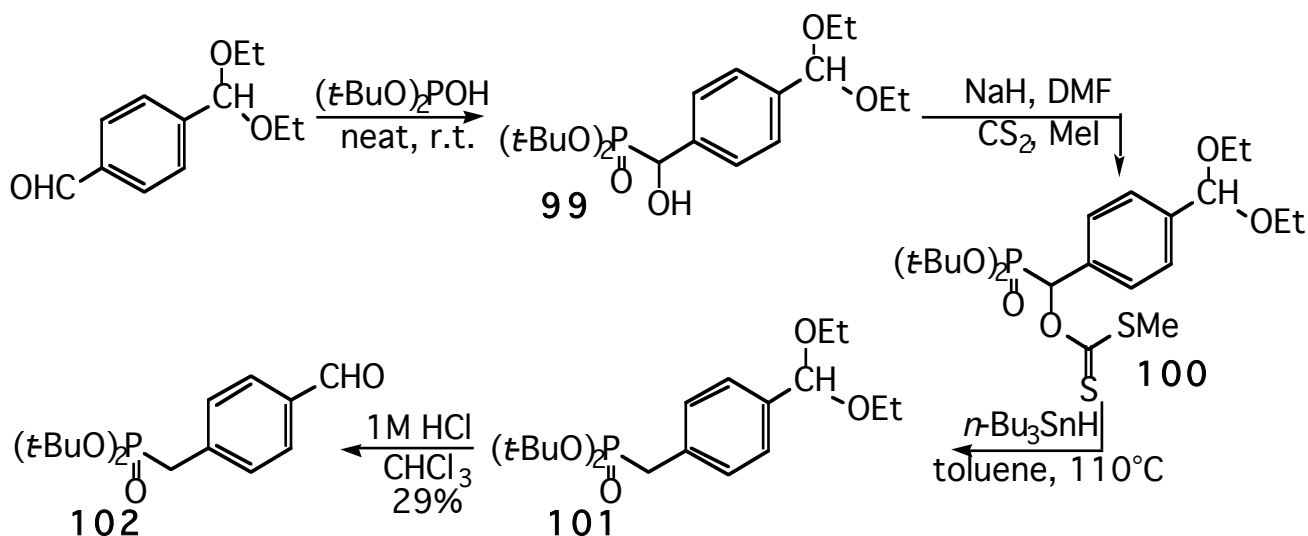


Fig. 41. Synthesis of di-*tert*-butyl 5-formylalkylphosphonate from α -hydroxyphosphonate⁹⁵.

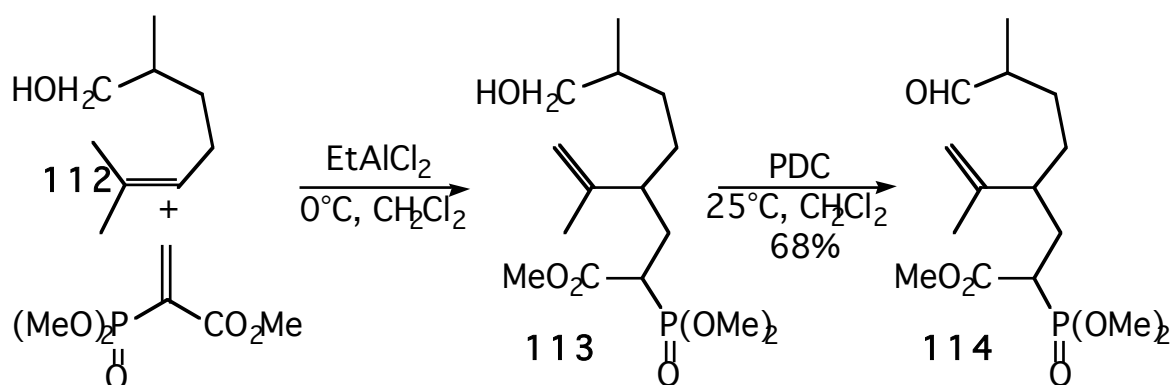


Fig. 44. Synthesis of dimethyl 6-formylalkylphosphonate via ene reaction⁹⁸.

The palladium-catalyzed arylation of diethyl vinylphosphonate with *p*-bromobenzaldehyde (MeCN, 100°C, 4h) afforded diethyl *p*-formylstyrylphosphonate in 60% yield.⁹⁹

Once more the methodology using lactones has been developed with success. The mixed anhydride **115**, stemming from the opening of a δ -lactone, was treated, after suitable protection, with diethyl α -cupromethylphosphonate to produce the β -ketophosphonate **116** in good yield (69%). Finally, the ozonolysis of **116** gave the diethyl 7-formylalkylphosphonate **117** in high yield (Fig. 45).¹⁰⁰

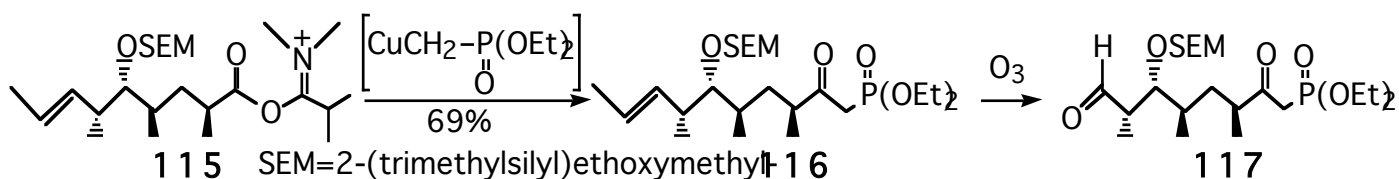


Fig. 45. Synthesis of diethyl 7-formylmethylphosphonate from δ -lactone¹⁰⁰.

Similarly, a lactam was submitted to a ring opening reaction using dimethyl 1-lithiomethylphosphonate in THF at -78°C. On work-up, the *N*-methyl imine generated the dimethyl 6-formylalkylphosphonate, which in turn gave perhydroazulenone on treatment with *tert*-BuOK/*tert*-BuOH.¹⁶²

In an approach to the central eight-membered ring of ceroplastol I, the use of an intramolecular HWE reaction was explored starting from a diethyl 7-formylalkylphosphonate. This C₇ aldehyde, protected as a 1,3-dioxolane, was obtained in 20% yield as a 1:1 mixture of keto acetals by Michael addition in THF at -78°C of an alkenyllithium to the 2-(diethoxyphosphinyl)cyclopentenone. Hydrolysis of the acetal in refluxing acetone/H₂O, TsOH afforded 89% of the desired phosphorylated keto / aldehyde.¹⁰¹

Phosphonates containing an aldehyde group at C₉ are important intermediates have been employed in the incorporation of a C₁-C₉ fragment into macrolide antibiotics (pikronolide,¹⁰² carbonolide B,¹⁰³ erythromycin A¹⁰⁴). They were prepared by treatment of a C₇ dialdehyde, protected at one extremity (double bond or *tert*-butyldimethylsilyl (TBS) ether), with the dimethyl 1-lithiomethylphosphonate at -80°C in THF, which gave the β -hydroxyphosphonates in 74-79% yield. Subsequent oxidation (PDC/DMF¹⁰² or TPAP/NMO/CH₂Cl₂^{103,104}) produced the corresponding β -ketophosphonate in excellent overall yield. Generation of the terminal aldehyde at C₉ was performed by oxidation of the primary alcohol with TPAP/NMO¹⁰³ or of the double bond with OsO₄/NMO/acetone followed by cleavage with NaIO₄.¹⁰²

2.7. n = 11 to 16.

The phosphorylated aldehydes reported in the previous sections can participate, as reagents or substrates, in several useful synthetic schemes including HWE reaction, Strecker and related reactions, reductive amination and formation of heterocycles. By contrast, the phosphorylated aldehydes **118** described in the present section are almost exclusively prepared to achieve formation of macrocycles **119** (11- to 17-membered carbon chain) via an intramolecular HWE reaction (Fig. 46). This widely used cyclisation step represents the best way for preparing macrocyclization products.

The phosphonate group is frequently incorporated at one extremity of the chain using a carbanionic approach. The more widely used method involves the displacement of halogenated derivatives with phosphoryl stabilized carbanions ($Z=CN, CO_2R, COR$).¹⁰⁵⁻¹⁰⁹ The others are accomplished by displacement of chlorine from diethyl chlorophosphate with lithiated functional derivatives,¹¹⁰ or by treatment of a carboxylate with the lithium derivative of a dialkyl methylphosphonate.^{111,112,163} At the other extremity of the chain oxidation of a primary alcohol generates the aldehyde group.

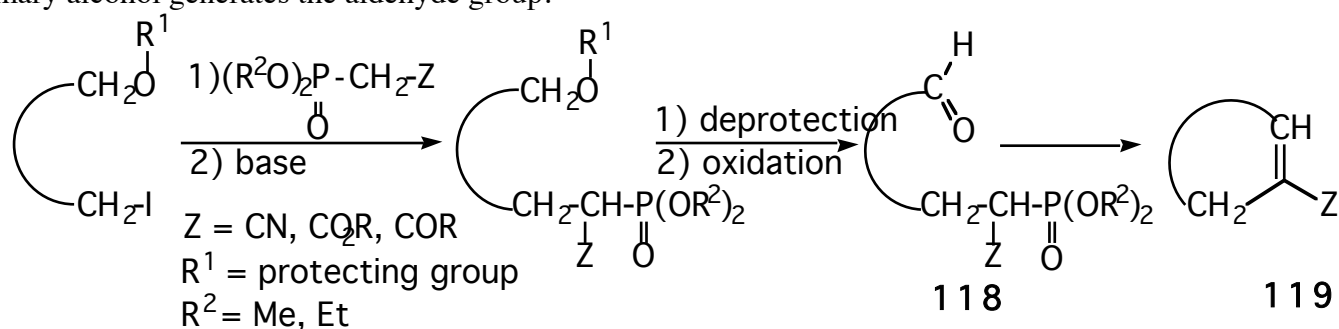


Fig. 46. Formation of macrocycles by intramolecular HWE reaction.

3. REACTIONS OF PHOSPHORYLATED ALDEHYDES

As a consequence of their ready accessibility coupled with their versatile chemical properties, phosphorylated aldehydes represent now an important class of compounds in organic and organophosphorus chemistry. As synthetic intermediates, these compounds owe their interest to the presence in the same molecule of a phosphoryl and a formyl group which govern their chemical reactivity. The purpose of this section is to provide a general overview of the important synthetic reactions which have been designed and developed from phosphorylated aldehydes.

3.1. Reactions of the carbonyl group

Several properties of the formyl group have been demonstrated in the past. For instance, the reaction of phosphorylated acetals with diols yielded phosphorylated 1,3-dioxolanes,¹¹³ 1,3-dioxans,¹¹⁴ and polymethylene acetals.¹¹⁵ The reaction is carried out by heating equimolar amounts of the reactants with simultaneous distillation of the alcohol liberated. The reduction of phosphorylated aldehydes over a platinum catalyst^{42a} or by sodium borohydride¹¹⁶ leads to the corresponding hydroxy derivatives in high yields. Phosphorylated aldehydes are oxidized by peracids¹¹⁷ or by alkaline potassium permanganate¹¹⁸ to the corresponding phosphorylated carboxylic acids. The dimethylhydrazones of **4** are known and prepared at room temperature in 40-98% yields.¹⁹⁵ At 110°C, *p*-toluenesulfonamide adds to **6** to give an adduct which eliminates ethanol when strongly heated to give in 68-80% yields the corresponding phosphorylated vinylsulfonamide, also available from *p*-toluenesulfonamide and **4**.¹¹⁹ The aldolase-catalysed reaction of **4** with dihydroxyacetone phosphate (DHAP) gives a diphosphorylated sugar in 90% yield.¹⁹³ In chloroform solution phosphorylated

acetaldehydes are in equilibrium with the enol form and when treated with HNO_2 they afford the nitrosoenols, which are dimeric in aqueous solution.^{120,121} Although the phosphorylated acetaldehydes condense with sodium derivatives of nitroalkanes to give mainly the phosphonylnitroalcohols, there is also detectable a second sequence, leading to a dienol.¹²² Because of the resultant tautomerism, the course and end-point of the reaction between phosphonylacetaldehydes and active methylene compounds (acetylacetone, cyanoacetic ester, dimedone) can vary. For acidic active-methylene compounds, further reaction with the initial condensation product can occur. The final position of tautomeric equilibrium depends on the nature of the dicarbonyl compound and of the substituents on phosphorus.¹²³ Diethyl 1-formylmethylphosphonate **4** reacts with *n*-BuLi at low temperature in THF to give a lithium enolate. By contrast, the reaction of **4** with *n*-BuLi or $\text{Zn}(\text{OCOMe})_2$ at room temperature for several days preferentially yields the metal complexes of the diphosphorylated butadienolate or the free *E*-enol via aldol condensation (Fig. 47).¹²⁴ The self-condensation of **4** in basic media has been the subject of several reports.¹⁹²

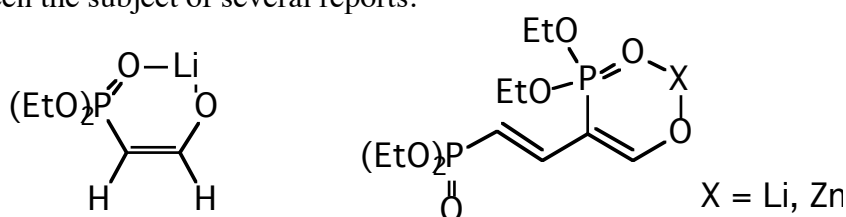


Fig. 47. Reaction of **4** with *n*-BuLi¹²⁴.

The transformation of diethyl 1-formyl- or 1-alkyl-1-formylmethylphosphonates (**4** or **19**) into diethyl 2-oxoalkylphosphonates via diethyl 2-dialkylaminovinylphosphonates has been reported with moderate to good yields (22-85%).¹²⁵

Starting with diethyl 1-formylalkylphosphonates, the synthetically attractive *trans*-2,3-epoxy-4-oxoalkyl-phosphonates are easily available by two methods. The first method employs the Wittig reaction of diethyl 1-formylalkylphosphonates **4**, **19** or **29** with 2-oxoalkylidene-triphenylphosphoranes and subsequent epoxidation of the resulting *E*-4-oxo-2-alkenyl derivatives with $\text{H}_2\text{O}_2 / \text{Na}_2\text{CO}_3$ in MeOH.^{126a} The second procedure involves the $\text{Sn}(\text{OTf})_2$ -mediated aldol reaction of **4**, **19** or **29** with bromomethylketones and subsequent cyclization of the bromohydrins. These epoxides are readily isomerized into 2,4-dioxoalkyl-phosphonates (49 to 81%) on heating in toluene in the presence of catalytic amounts of $\text{Pd}(\text{PPh}_3)_4$ and 1,2-bis(diphenylphosphino)ethane (dppe).^{126b}

3.2. Preparation and reactions of diethyl chloroformyl- and dichloroformylmethyl-phosphonates

Reaction of dialkyl 1-formylmethylphosphonates **120** with Cl_2/CCl_4 results in formation of either chloromethyl **121** or dichloromethyl **122** derivatives (Fig. 48). Several variations on the preparation of these two compounds have been reported. It was shown that chlorination at the α -CH bond of dialkyl 1-formylmethylphosphonates with Cl_2 was selective and temperature dependent, namely: a) in CCl_4 between -10 and -15°C the monochlorinated aldehydes were formed in 70-80% (appearance of a yellow colour indicates the completion of monochlorination), while b) raising the temperature to 0°C resulted in dichlorination (80-90%). Raising the temperature to r.t. can lead to the cleavage of the P-C bond under the action of HCl with the formation of phosphorochloridates. Full utilization of gaseous chlorine being handicapped by the sensitivity of the P-C bond in acid medium, an alternative procedure for the preparation of **121** in 90% yield is the chlorination of 2-ethoxyvinylphosphonates **6** in CCl_4 at r.t. followed by hydrolysis.¹²⁷ Preparation of

compound **121** has also been accomplished in high yield by reaction between the dialkyl 1-lithio-1-chloromethylphosphonates and HCO₂Et at low temperature (70-85%).³⁷ By carefully choosing the experimental conditions, it has been found that dialkyl 2,2-diethoxyethylphosphonates react in a similar manner with chlorine in refluxing CCl₄ to provide dichloro acetals.^{127f}

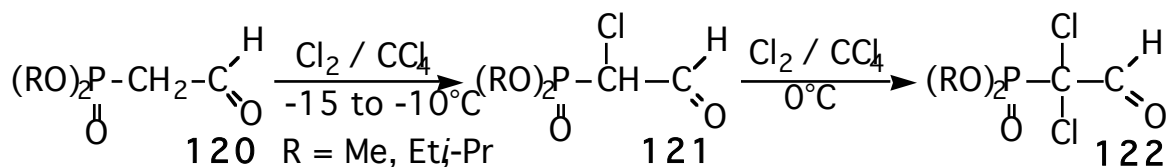


Fig. 48. Synthesis of chloroformyl- and dichloroformylmethylphosphonates¹²⁷.

Systematic studies on the chemistry of the chloroformyl- **121** and dichloroformyl- **122** methylphosphonates showed their high reactivity and extensive synthetic possibilities. For example, the nitration of **4** with acetyl nitrate gives a low yield of nitromethylphosphonate.¹⁹⁴ The nitrosation of **121** with HNO₂/HCl below 0°C results in hydrolytic rupture of the C-C bond in the initially formed 1-nitroso compound, loss of the formyl group and formation of the oximes of the dialkoxyphosphinylformyl chloride in 95% yield. With increasing reaction temperature, however, loss of chlorine and formation of the α-nitroso derivative of 1-formylmethylphosphonate takes over.^{127e,128} The oximes react with 1,4-phenylenediamine, 4-aminoantipyrine, benzhydrazide or thiosemicarbazide as a result of nucleophilic attack by a nitrogen atom on the electrophilic carbon center of the halo oxime to give products of amino- or thiosemicarbazide-oxime structure.¹²⁹ In the presence of NEt₃, these oximes can serve as a source of nitrile oxide, which easily enter into dipolar cycloaddition with terminal acetylenes at 20°C to give 3-phosphorylated isoxazoles in good yields (69-94%).^{18b,130} It has also been found that in the reactions between **121** and aryldiazonium salts (chlorides or tetrafluoroborates) in AcONa/H₂O, the formyl group is split off and the corresponding arylhydrazones of **121** are formed.¹³¹ A study of the kinetics of these reactions has been realized.¹³² The arylhydrazones react with a variety of nucleophiles (NH₄OH, R-NH₂, N₂H₄·H₂O, Na₂S, Na₂SO₃, Na₂S₂O₃, NaSCN, (H₂N)₂CS) with replacement of the halogen by the nucleophile.¹³³

The diethyl 1,1-dichloro-1-formylmethylphosphonate **122** readily takes part in the Abramov reaction with diethyl phosphite to form the 1,1-dichloro-2-hydroxyethyldiphosphonate in 70% yield.^{127d} Under the action of alcoholic solutions of alkalis or secondary amines, **122** undergoes decomposition in the manner of the haloform reaction with the formation of diethyl dichloromethylphosphonate (88% or 72%).^{127d} The diethyl 1,1-dichloro-1-formylmethylphosphonate **122** reacts with HC(OEt)₃/H₂SO₄ to give the acetal in almost quantitative yield (92%).^{127c} Reaction of **122** with Ph₃P in benzene or toluene results in the formation of diethyl 1,2-dichloro-vinylphosphonate (51%).¹³⁴ The reaction of **122** with isocyanates of trivalent phosphorus compounds proceeds by a [3+2] cycloaddition reaction with formation of oxazaphospholines (72-75%).¹³⁵ With *iso*-PrSH, **122** forms a hemithioacetal, the trimethylsilyl derivative of which, in boiling xylene, undergoes a transposition of the (original) carbonyl group to the α-position via an epoxyphosphonate.¹³⁶

3.3. Heterocyclic systems with phosphorylated substituents

One of the most thoroughly investigated synthetic applications of phosphorylated aldehydes is the synthesis of heterocyclic compounds containing a phosphoryl group in the side chain.¹³⁷ Historically, the first attempt to synthesise the diethyl 1-formylmethylphosphonate **4** was undertaken with the aim of its subsequent

employment in the synthesis of phosphorylated heterocycles.² In many cases phosphorylated acetals or enamines were used instead of phosphorylated aldehydes.

Diethyl 1,1-diethoxymethylphosphonate has been utilized in condensation with amino, hydroxy or mercapto 1,2-disubstituted benzene derivatives to produce a series of benzoheterocyclic phosphorus compounds. The yields of benzoxazole and benzothiazole derivatives are acceptable (68% and 30%),¹³⁸⁻¹⁴⁰ but benzimidazoles are obtained in poor yields (7%).¹⁴¹ The yield of benzimidazoles has been since improved to 65% by reacting the hydrazone derivative of **121** with *o*-phenylenediamine in refluxing CHCl₃ for 2.5h.¹⁴² Catechol and naphthalene-2,3-diol upon reaction with diethyl 1,1-diethoxymethylphosphonate are converted into dioxolane phosphonates in a similar manner.¹⁴³ Under Fischer indole synthesis conditions, diethyl 2,2-diethoxyethyl-phosphonate **5** reacts with phenylhydrazine to afford the 2-indolylphosphonate in low yield. It has been postulated that the initially formed product is the indolyl-3-phosphonate, which rearranges to the 2-derivative in the presence of an excess of ZnCl₂.^{14f,144} By a similar procedure, diethyl 1-formylmethylphosphonate **4** reacts with a variety of arylhydrazines in refluxing toluene in the presence of PPA to give the indolyl-3-phosphonates in moderate yields (35-45%).¹⁴⁵ A wide range of heterocycles can also be obtained by the condensation of diethyl 2,2-diethoxyethylphosphonate **5** with aromatic *o*-disubstituted compounds containing mobile hydrogen atoms such as *o*-phenylenediamine, *o*-aminophenol, *o*-aminothiophenol and others. These reactions, which are common to a large class of phosphorylated acetals, were carried out by heating equimolecular amounts of reactants at 160-180°C, whereupon alcohol was evolved. The yields of benzimidazoles, benzoxazoles and benzothiazoles are commonly in the range 30-50%.¹³⁸⁻¹⁴¹ Further applications of the Fischer reaction have been demonstrated in the reaction of diethyl 2-formylethylphosphonate **36** (R¹=H) with a large number of arylhydrazine chlorohydrates in anhydrous ethanol at reflux for 2 to 12 h. The indolyl-3-methylphosphonates are isolated in variable yields from 4 to 83%.¹⁴⁵ The diethyl 1-chloro-1-formylmethylphosphonate **121** is also a precursor to heterocycles via the intermediacy of the phenylhydrazones. Treatment of hydrazones of **121** with benzylamine gives the N³-benzyl-amidrazones, which on oxidation using H₂O₂, KMnO₄ or Ag₂O in biphasic medium yields the 3-phosphorylated-1,2,4-triazoles in 40-80%.^{133d} In a similar way, the oxime of **121** is a precursor of 3-phosphorylated isoxazoles via the nitrile oxide.¹³⁰

Enamine phosphonates bearing a functional group (CHO, COMe, COPh, CO₂Et) in α -position **123** have been shown to undergo similar nucleophilic cyclisation reactions with compounds containing mobile hydrogen atoms, providing the basis of another synthesis of phosphorylated heterocycles (Fig. 49). The dimethylamino group of enamine phosphonates **123** can be selectively and totally transaminated by treatment with symmetrical or unsymmetrical hydrazines, guanidine, acetamidine and methylisothiourea in refluxing ethanol. The corresponding phosphorylated pyrazolones **124** (R¹=OH, R²=H), pyrazoles **124a,b** and pyrimidines **125a,b** are isolated in excellent yield (90-95%).³⁵ The ethyl dialkylphosphonylformylacetates were also used as precursors of phosphorylated pyrazolones in moderate to good yields.¹⁹⁰

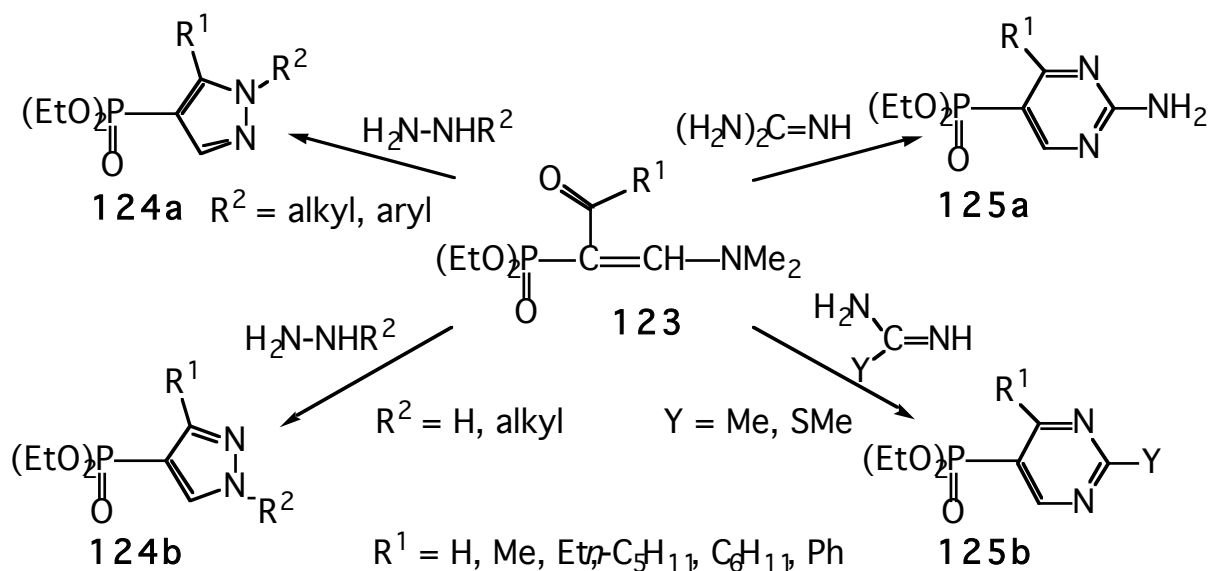


Fig. 49. Synthesis of phosphorylated pyrazoles and pyrimidines³⁵.

Of special interest is the report of an efficient, one-pot procedure for the preparation of 3-phosphorylated indole **127** in 88% yield using **126** (Fig. 50). The presence of a nitro group in the *ortho* position promotes, after reduction, a spontaneous transamination offering an easy approach to 3-phosphorylated indole derivatives.^{35a}

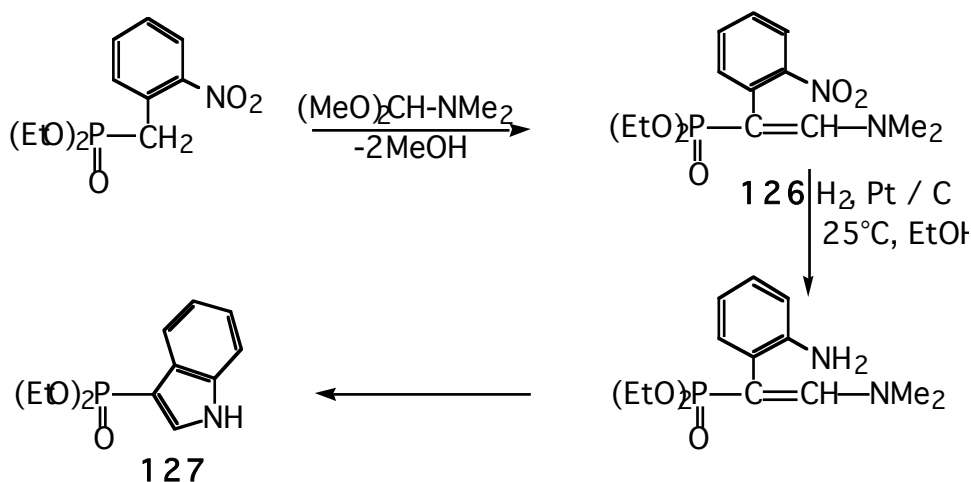


Fig. 50. Synthesis of 3-(diethoxyphosphinyl)indole^{35a}.

The addition of tosylazide to diethyl 1-formylalkylphosphonate **4** yields the triazolone which under the reaction conditions produces the diethyl diazomethylphosphonate and the triazole, respectively, according to the nature of α -substituent.¹⁴⁶

3.4. Horner–Wadsworth–Emmons (HWE) reaction

The Wittig and the Horner–Wadsworth–Emmons reactions are among the most important reactions for the two carbon elongation of a carbonyl functional group to a more complex aldehyde or ketone.¹⁵⁰ They can be described as a general synthetic protocol for the conversion of aldehydes and ketones into α,β -unsaturated carbonyl compounds **131** ($\text{R}=\text{H}$ or $\neq\text{H}$) and their derivatives. But whereas the reaction of the resonance-stabilized phosphonium ylids (Wittig reaction) proceeds readily with aldehydes, the reaction with ketones is more effectively achieved using the more nucleophilic anions of phosphonate reagents (HWE reaction).¹⁵¹ The

first reagent for the formylolation of ketones as well as aldehydes, diethyl 2-(cyclohexylimino)ethylphosphonate **128** was described in 1968 (Fig. 51).^{23,152} The carbanion **129** is generated conveniently by treatment of **128** with NaH then coupled with a variety of aldehydes and ketones. Satisfactory results were obtained when hydrolysis of the intermediate aldimines **130** was carried out in a two-phase system. Other procedures were reported for the hydrolysis of imines such as dilute oxalic acid or acetate buffer and SiO₂ / weak acid. Several variations on the formylolation reaction have been reported utilizing protecting reagents for aldehydes such as oxazine (Fig. 5)²⁵ semicarbazide¹⁵³ and 1,1-dimethylhydrazine.¹⁵⁴

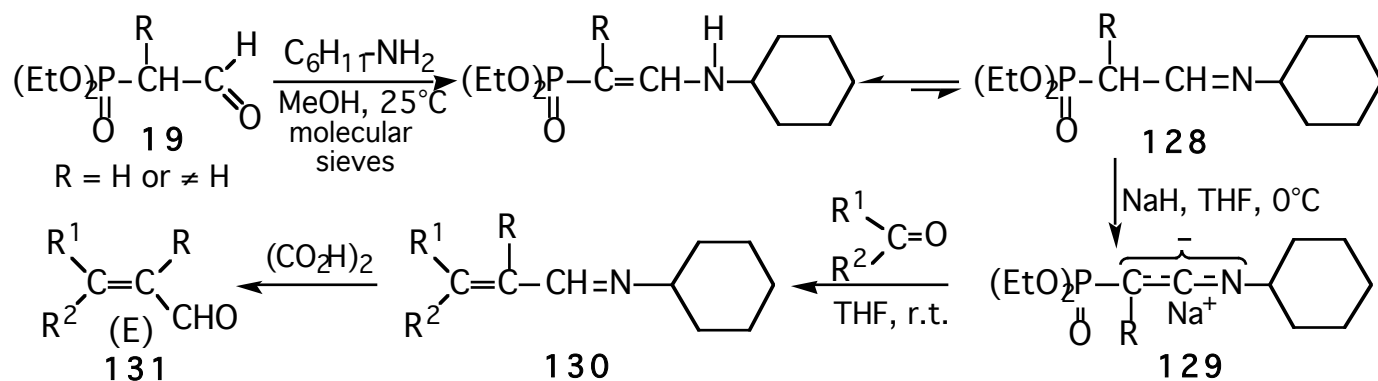


Fig. 51. Synthesis of α,β -unsaturated aldehydes¹⁵².

An alternative and efficient route leading to E - α,β -unsaturated aldehydes **131** ($R=H$) is based upon the metallation of the *N-tert*-Butylacetalimine **132** (Fig. 52). In this attractive one-pot procedure, **132** was treated with LDA and then with diethyl chlorophosphate to give the lithiated enamine phosphonate **133**, thus avoiding the preparation of the phosphonate imine reagent, which required three steps from commercial materials.¹⁵⁵

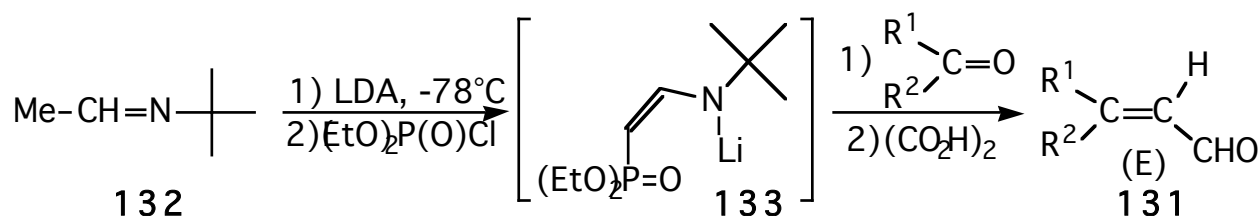


Fig. 52. One-pot synthesis of α,β -unsaturated aldehydes¹⁵⁵.

In addition to the previous methods for generating E - α,β -unsaturated aldehydes **131**, an advantageous one-pot preparation of α,β -unsaturated- α -substituted aldehydes **135** was reported (Fig. 53). The procedure involves the intermediacy of the lithiated α,β -enamine phosphonate **134** prepared by nucleophilic addition of diethyl α -lithioalkylphosphonates to ethyl *N*-phenyl-formimidate.¹⁵⁶ On reaction with aliphatic or aromatic aldehydes **134** produces α,β -unsaturated- α -substituted imines, which may be efficiently converted to α,β -unsaturated- α -substituted aldehydes **135** by acid hydrolysis in yields ranging from 45 to 78%.¹⁵⁷

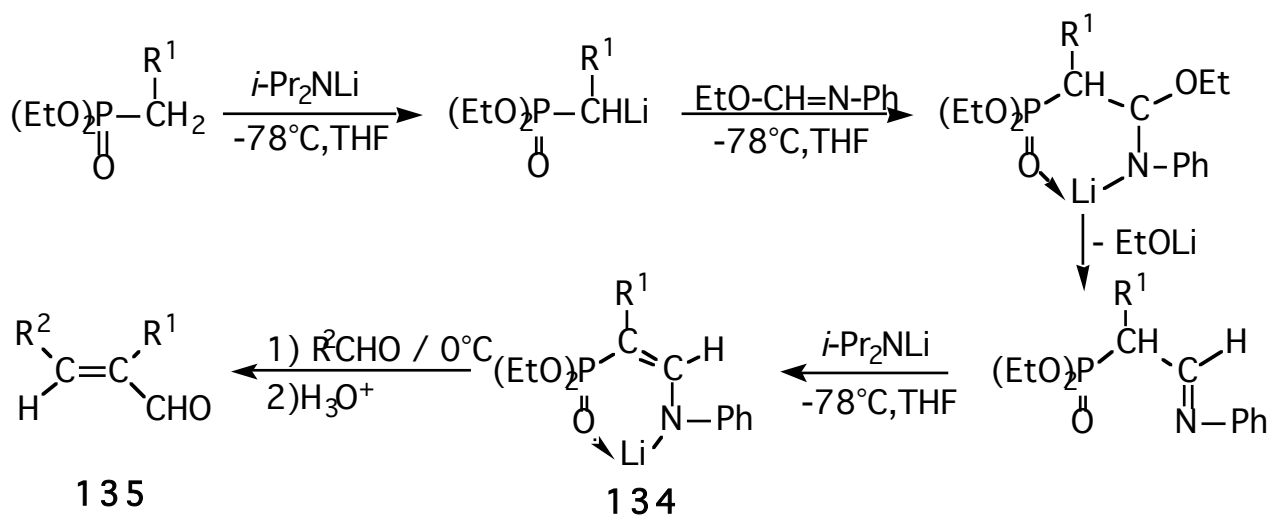


Fig. 53. One-pot synthesis of α,β -unsaturated- α -substituted aldehydes¹⁵⁷.

Of significant synthetic importance is the intramolecular version of the HWE methodology. It has been recognized as the method of choice for preparing five-,⁸⁸ six-¹⁵⁸⁻¹⁶¹ and seven-¹⁶² membered ring systems as well as macrocyclic ring systems, including rings containing 11,¹⁶³ 12,^{105,110} 14,^{105-109,111} 15,^{112,164} 16,¹¹² and 17^{75,164} atoms. In the preparation of larger ring sizes high-dilution procedures have usually been required to achieve satisfactory yields. The use of a mild base (LiCl / DBU) or crown ether catalysis has also been shown to be of importance. As an illustration of the utility of this technique, some typical macrocyclisations providing biologically active compounds (with conditions in brackets) are given : 11-membered ring (-)-bertyadionol (NaH / toluene / 42°C, 28-32%),¹⁶³ 12-membered ring (+)-cleomeolide (K₂CO₃ / 18-crown-6 / toluene / r.t., 38%),¹¹⁰ 12-membered ring pseudopterane and 14-membered ring furanocembrane systems (LiCl / DBU / MeCN / r.t., 50% and 42%),¹⁰⁵ 14-membered ring (-)-asperdiol and (+)-desepoxyasperdiol (LiCl / DBU / MeCN / r.t., 61% and 30%),¹⁰⁶ 14-membered ring (\pm)-methyl ceriferate-I (NaH / DME / 80°C, 24%),¹⁰⁷ 14-membered ring anisomelic acid (LiCl / DBU / MeCN / r.t., 71%),¹⁰⁸ 14-membered ring cembratrienediols and thunbergols (LiCl / DBU / MeCN / 40°C, 63%),¹⁰⁹ 14-membered ring macrocyclic trienone (LiCl / DBU / MeCN / r.t., 63%),¹¹¹ 15-membered ring muscone precursor (NaH / DME / high dilution, 50%),¹¹² 17-membered ring civetone precursor (*tert*-BuOH / H₂O / KHCO₃ / reflux, 56%)¹⁶⁴ and 17-membered ring lankacidin (K₂CO₃ / 18-crown-6 / toluene / 100°C, 37%).⁷⁵ The stereochemistry, as well as the ease of the intramolecular reaction is largely determined by the nature of the carbon chain that forms the ring. In a paper appearing in 1987 the authors concluded that "*the intramolecular ketophosphonate-aldehyde condensation reaction is a most powerful method for constructing macrorings, and, therefore, it should be placed high on the list of choices for such operations when applicable*".¹⁶⁵

3.5. Phosphonoacetaldehyde in nature

In 1972 it was demonstrated that not only phosphoenolpyruvate (PEP) is the immediate precursor of phosphonates in *Tetrahymena*, but that phosphonoacetaldehyde (PAAI) is a direct precursor of 2-aminoethylphosphonate (AEP) (Fig. 54).¹⁶⁶⁻¹⁶⁹ Phosphonoalanine (PALa) is a side product in the synthesis and apparently is not directly converted to AEP. In *Tetrahymena* the radioactive carbon atom in phosphoenol [3-¹⁴C] pyruvate is incorporated into the phosphonate carbon atom in 2-aminoethylphosphonic acid (AEP) confirming that an intramolecular rearrangement of PEP takes place during the biosynthesis of AEP. The incorporation of

label into AEP is inhibited to a greater extent by PAAI than by PAIa : hence the latter may not be on the main biosynthetic pathway to AEP. The phosphonopyruvate (PnPyr) initially formed by the intramolecular rearrangement of PEP is probably decarboxylated to phosphonoacetaldehyde before amination to AEP occurs and the latter is then incorporated into phosphonolipids. Since the discovery of enzymes, PEP phosphonotransferases, responsible for C-P bond formation from *Tetrahymena* or from *Streptomyces hygroscopicus*, new systems have been reported.¹⁷⁰ Recently, another enzyme (phosphonoacetaldehyde hydrolase (phosphonatase) from *Bacillus cereus*), which catalyzes the dephosphonylation reaction of phosphonoacetaldehyde (PAAI) to inorganic phosphate and acetaldehyde, was highlighted. This enzymatic process involves activation of C-P bond cleavage by formation of a Schiff base between PAAI and an active site lysine in phosphonatase.¹⁷¹ All these results clearly demonstrate the importance of phosphorylated aldehydes in biological processes.

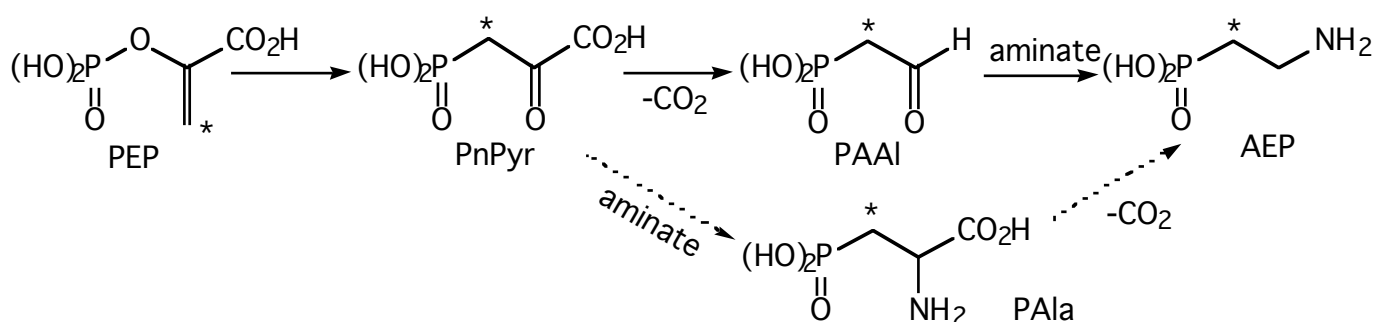


Fig. 54. Pathway for the biosynthesis of AEP.

Fosfomicin, a clinically used antibiotic, is biosynthetically derived from a P-C₂ unit, most likely to be phosphonoacetaldehyde, and a methyl group from L-methionine (Fig.55). As shown above for AEP, the phosphoenolpyruvate (PEP) was suggested as the most likely precursor of carbons 1 and 2 of fosfomicin.¹⁷²

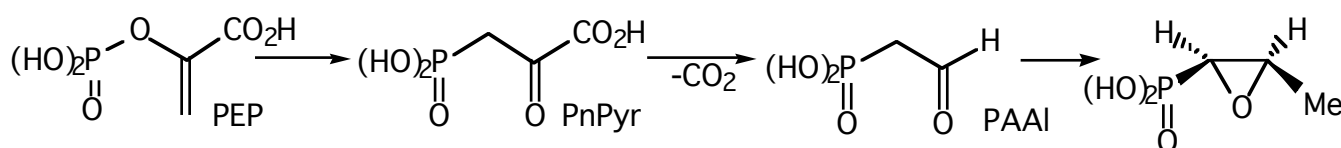


Fig. 55. Pathway for the biosynthesis of fosfomicin¹⁷².

3.6. Reductive amination

Since the phosphonoacetaldehyde is an ideal precursor for the generation of AEP, an attractive procedure for the preparation of 2-aminoalkylphosphonic acids **137** from 1-formylalkyl-phosphonates **4** (R¹=H) and **19** (R¹=Me) has been developed using reductive amination of the carbonyl in the presence of NaBH₃CN (Fig. 56). This method appears to be fairly general and may be used for the preparation of 2-aminoalkylphosphonates **136** containing primary, secondary or tertiary amino groups simply by treating the carbonyl compound at room temperature with a primary or secondary aliphatic or aromatic amine.^{17a} When AcONH₄, as a source of ammonia, was subjected to this reaction it required lengthy reaction times and produced a mixture of primary aminophosphonate (7%) and iminobis(ethylphosphonate) (30%).¹⁷³ The primary aminophosphonate being considerably more nucleophilic than ammonia, the second attack upon the carbonyl group is an unavoidable competing side reaction. Finally, hydrolysis of **136** with 8M HCl followed by

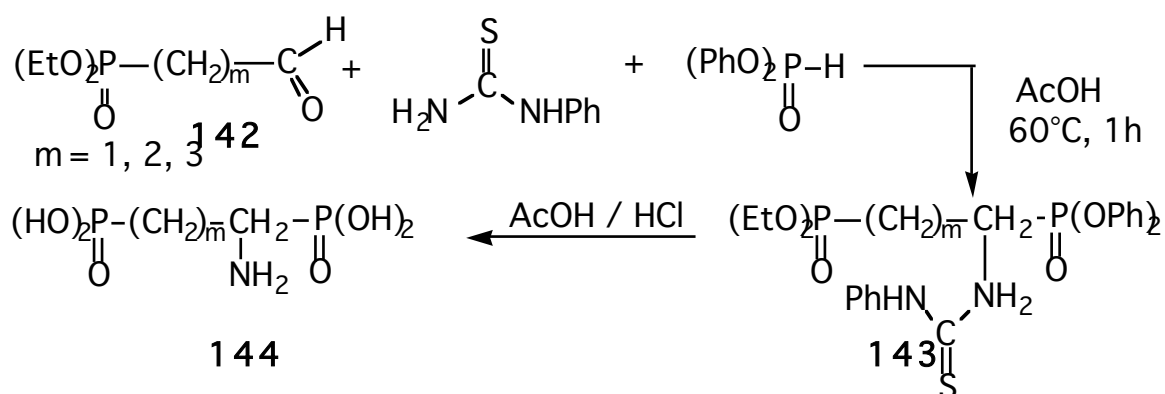


Fig. 58. Synthesis of 1-aminoalkyldiphosphonic acids^{18a}.

3.7. Aminocarboxylation (Strecker and related reactions)

Receptors for glutamic and aspartic acids^{175,176} have been implicated in the pathology of several neurological and neurodegenerative illnesses, including, for example, epilepsy, cerebral ischemia, hypoglycaemia, Huntington's and Alzheimer's diseases, and Parkinsonism. The growing number of these disorders, in which excitatory amino acids (EAA) have been implicated, has resulted in considerable attention being focused on the development of compounds which antagonize excitatory amino acids neurotransmission. Compounds which act selectively and competitively at the subclass of EAA receptor selectively activated by N-methyl-D-aspartate (NMDA) have received particular attention.¹⁷⁷ Several amino phosphonocarboxylic acids have been characterized as being potent and selective competitive NMDA antagonists¹⁷⁸⁻¹⁸² (Fig. 59) and have been found to be efficacious against neuronal damage. With these considerations in mind, the Strecker and Bucherer–Bergs reactions for the synthesis of ω -amino- ω -carboxyalkylphosphonic acids have been applied to a variety of phosphorylated aldehydes.

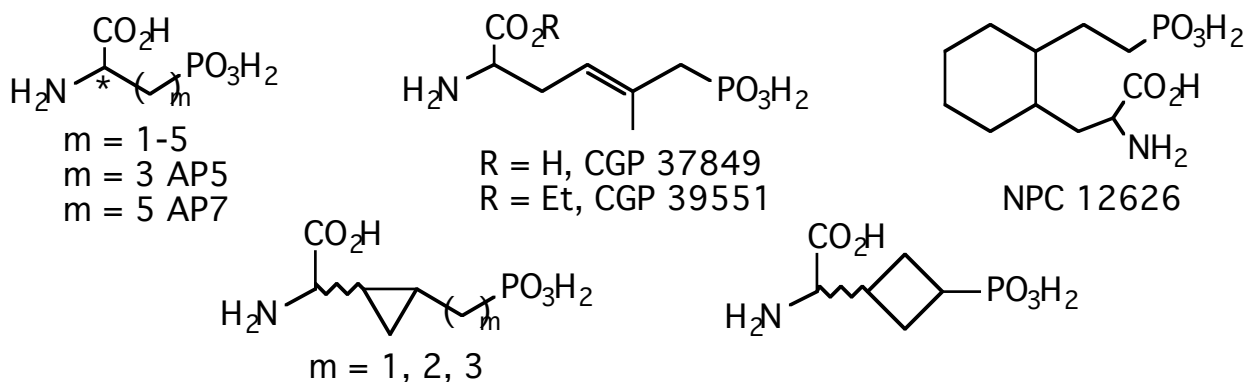


Fig. 59. Structures of some NMDA antagonists.

Phosphorylated aldehydes **138** are first smoothly converted to amino nitriles **145**, which are further treated with concentrated HCl to provide the amino acids **146** (Fig. 60). In this method, treatment (in the absence of light) of freshly purified phosphorylated aldehydes at room temperature in water (or MeOH/water or MeCN) with NaCN (or KCN) and NH₄Cl (or NH₄OH or HCO₂NH₄) (or (NH₄)₂CO₃) at 50-60°C in the Bucherer–Bergs reaction^{79,85} produces selectively the amino nitriles in moderate to high yields (44-91%).^{17b,71,72a,83,85,93,183} Improved yields have been reported through the use of alumina/ultrasound⁷¹ or a modified Strecker reaction.¹⁹⁶ Hydrolysis of the amino nitriles **145** with 6-8M HCl at reflux delivers the crude amino acids **146**, which were purified by ion-exchange chromatography using strongly acidic resin (Dowex 1 8x100). The Bucherer–Bergs route is not so efficacious because of difficulties in the hydrolysis of the hydantoin.^{17b}

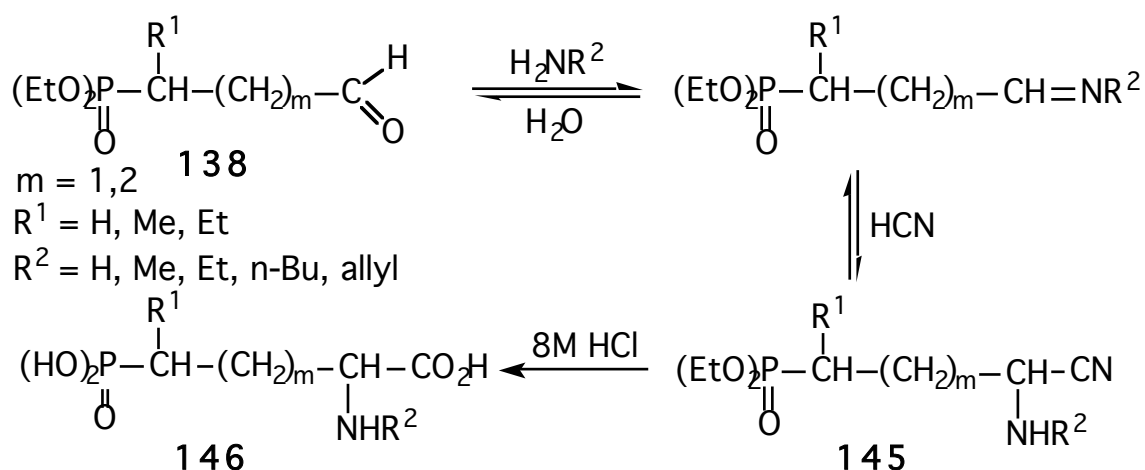


Fig. 60. Synthesis of amino carboxyalkylphosphonic acids via the Strecker reaction.

Though initially prepared and evaluated as a racemic, it was recognized that the NMDA antagonist activity was likely to reside primarily in a single enantiomer. The stereoselective nature of the NDMA receptor is well established, albeit not completely understood. Consequently, several attempts were undertaken to develop synthetic protocol which would allow to prepare optically active compounds. Early reported preparations of optically active ω -amino- ω -carboxyalkylphosphonic acids included a Strecker reaction using (*S*)(-)- α -methyl-benzylamine as the amination agent. However, the enantiomeric excess was only 50%.¹⁸⁴ Recently reported procedures, which use chemoenzymatic processes, offer a more convenient approach for the mild obtention of optically pure aminophosphonic acids. The enzymatic hydrolysis either of amide (using penicillinacylase, EC 3.5.1.11, from *Escherichia coli*)⁸³ or ester (with Subtilisin A⁸⁵ or Carlsberg esterase¹⁸⁵) groups provides a high yielding method of resolution of the racemic mixture. In the case of the hydantoin resulting from Bucherer–Bergs reaction, the resolution of two diastereomeric compounds, epimeric at the C-5 hydantoin carbon atom, was made using D-hydantoinase from *Agrobacterium*, in alkaline buffer.⁸⁵

Another attractive route to aminocarboxylalkylphosphonic acids involves the intermediacy of the ethyl α -azidoacetate (Fig. 61). Addition of methanolic sodium methoxide to a solution of **147** and ethyl α -azidoacetate in methanol at -30°C , provides the vinyl azide **148**. Hydrogenation of **148** (10% Pd/C/MeOH) gives the aminoester **149**, which at reflux with 3M HCl delivers the free amino acid **150**.^{95b,c}

The copper(I) catalyzed cycloaddition of an aldehyde with ethyl isocyanoacetate¹⁹⁷ to form the corresponding oxazoline has also been found to be an interesting method for introducing the amino acid group. However, this procedure is not diastereoselective and the yield is moderate (33%).¹⁹⁸

Similarly, a promising methodology using an Horner–Wadsworth–Emmons reaction between an aldehyde and the sodium derivative of N-acyl-2-(dialkoxyphosphinyl)glycine ester has been described.¹⁹⁹ Unfortunately, the dehydro amino acid is obtained in poor yield.⁸⁵ By contrast, the use of diethyl 2,4-dioximidazoline-5-phosphonate²⁰⁰ and LiOH/MeOH leads to a rapid and high yielding conversion of aldehyde to dehydrohydantoin as a mixture of *E*- and *Z*- isomers.⁸⁵

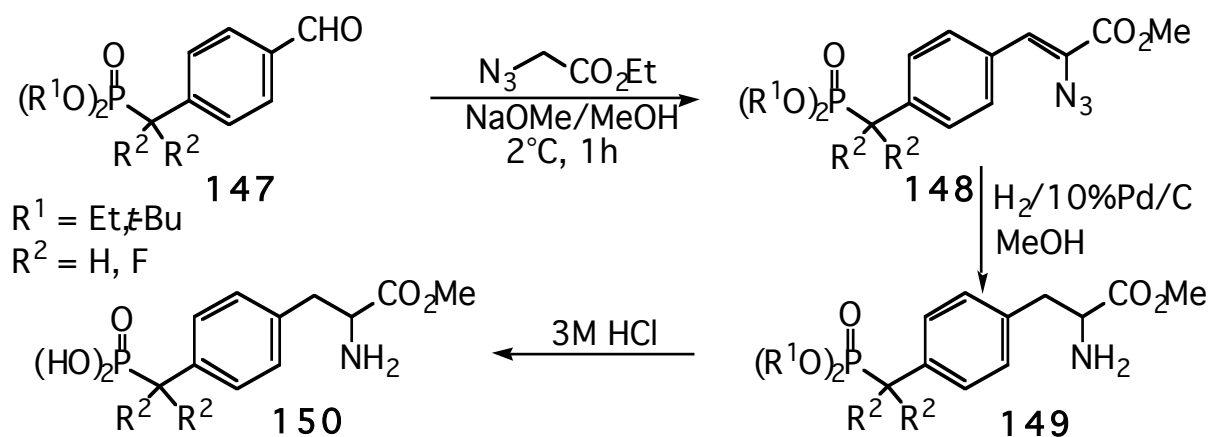


Fig. 61. Synthesis of amino carboxyalkylphosphonic acids via α -azidoacetate^{95b}.

4. CONCLUSION

Since their discovery in 1952, phosphorylated aldehydes have found widespread prominence in organic chemistry and their popularity emanates from their efficiency and versatility. They are functionally rich molecules very useful in organic synthesis and frequently involved in biological processes. The present review highlights three major developments of this chemistry. First, significant progress in the preparation of phosphorylated aldehydes has been achieved resulting in various new reactions to arrive at a high level of structural diversity and complexity. Second, olefination reaction based on the Horner–Wadsworth–Emmons reaction is an ever-growing area and the intramolecular version has become the most powerful tool for the construction of macrorings. Finally, the utility of phosphorylated aldehydes for the synthesis of biologically active compounds has blossomed during the last ten years. The diversity of phosphono amino acid analogues prepared attests to the wide acceptance and general utility of phosphorylated aldehydes.

5. ACKNOWLEDGEMENTS

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