Olefin Synthesis with Organic Phosphonate Carbanions

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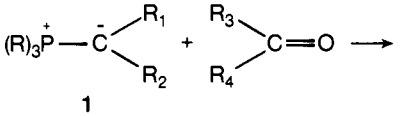
Contents

I. Forward

Many routes have been devised to enable the controlled introduction of carbon–carbon double bonds. The application of a selection of such routes has been recently reviewed by Reucroft and Sammes.[1] The present review deals with just one of the reactions mentioned in the review of Reucroft and Sammes, namely, the phosphonate modification of the Wittig reaction known also as the Wittig–Horner reaction. The present review is based on a search of *Chemical Abstracts* and the principal English language chemistry journals up until the end of 1971. Recent applications of the Wittig–Horner reaction have been considerable and are frequently described in the patent literature. The examples selected for discussion in this review are those which seem best to demonstrate either the mechanism or the versatility of the reaction.

II. Introduction

In recent years the reaction of carbonyl compounds with phosphorus ylides has had wide application in the synthesis of olefins. One of the first used forms of this group of reactions was the Wittig reaction in which carbonyl compounds were treated with phosphonium ylides (**1**) to form an olefin and phosphine oxide (eq **1**).[2] The



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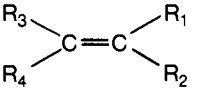
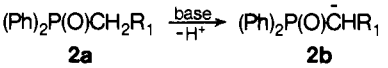


(1)

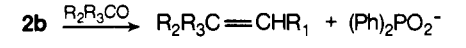
scope, mechanism, and stereochemistry of this reaction have been investigated in detail, and these studies have been the subject of many papers.[3-20]

There are, however, several limitations to the Wittig olefin synthesis, and this has led to the development of various modified forms of this reaction. These involve the use of other organophosphorus compounds which lend themselves to carbanion formation. The first of these studied utilized the carbanions of diphenylphosphine oxides (**2b**) which were found to undergo reaction with aldehydes and ketones to form olefins (eq 2)[21] (for a review of this reaction see ref 15, p 193).

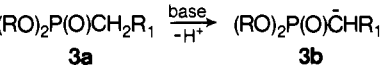


2a **2b**

R_1 = alkyl, alkoxycarbonyl, etc. (2)

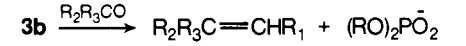


A further modification of the Wittig synthesis was developed by Horner, *et al.*,[22] and by Wadsworth and Emmons.[23] This reaction made use of resonance-stabilized phosphonate carbanions (**3b**), where R_1 is a group capable of stabilizing the adjacent anion. These carbanions were shown to undergo reaction with carbonyl compounds (eq 3) in a manner analogous to the phosphinoxy carbanions (**2b**).



3a **3b**

R = alkyl or phenyl; R_1 = resonance-stabilizing group (3)



This group of reactions (often referred to as the "modified Wittig" reaction, the "Wittig–Horner" reaction, or the "Horner–Emmons" reaction) possess the following advantages over the conventional Wittig reaction.

(a) Phosphonate carbanions are known to be more nucleophilic than the phosphonium ylides.[23,24] This is attributed to decreased stabilization of the negative charge by valence shell expansion of the phosphorus atom in the phosphonate. Hence the phosphonate carbanions react with a wider variety of aldehydes and ketones and under milder conditions. For example, phenacylidenetriphenylphosphorane (**1**, R = Ph; R_1 = H; R_2 = COPh) reacts with aldehydes only on prolonged refluxing in tetrahydrofuran, whereas the carbanion of diethyl phenacylphosphonate (**3b**, R = Et; R_1 = COPh)[23] reacts exothermally with aldehydes. Other examples of relative reactivity of the phosphonium and phosphonate carbanions has been demonstrated by Horner, *et al.*[24]

(b) The water-soluble phosphate ion formed from the phosphonates allows much easier separation of the olefin from the reaction mixture.

(c) The enhanced reactivity of the phosphonate carbanions allows the α-carbon to be elaborated by alkylation

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(eq 4), whereas the phosphonium ylides do not generally undergo smooth alkylation.[23,25]

$$\underset{\mathbf{3b}}{(RO)_2P(O)\bar{C}HR_1} + R_2X \longrightarrow (RO)_2P(O)CHR_1R_2 + X^- \quad (4)$$

(d) Phosphonates are readily available from the Arbuzov reaction[26,27] (see section IV) and are cheaper than the alkylphosphonium salts.

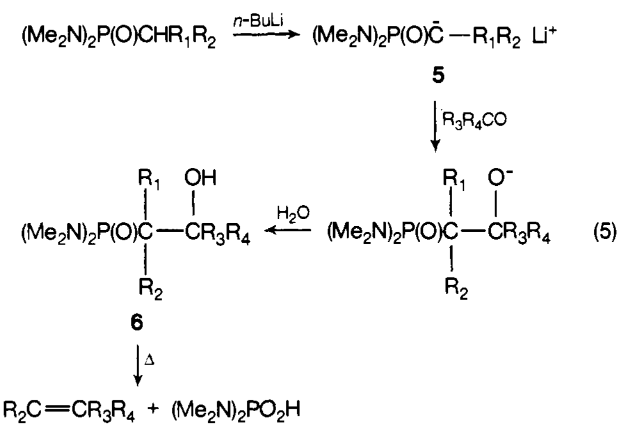
The phosphonates also possess advantages over the phosphine oxides in that the phosphonate anions are more reactive toward aldehydes and ketones, as well as being less sensitive to the nature of the base used or to atmospheric oxygen (see ref 15, p 195, and ref 23).

A newer variation of the phosphonate olefin synthesis involves the use of alkylthiophosphonate carbanions (**4**) which have been shown to react with aldehydes and ketones in a similar manner to the phosphonates to form olefins.[28] However, the experimental results indicated that these compounds have limited usefulness in olefin synthesis.

$$(RO)_2P(S)CHR_1R_2$$

4, R_1 and R_2 = H or alkyl groups

Other alternatives to the conventional Wittig synthesis exist in the use of α-lithio derivatives of phosphonic acid bisamides (**5**). Reaction of these carbanions with carbonyl compounds has recently been shown to yield olefins in a two-step reaction (eq 5).[29-33] The product of the first step, the β-hydroxy phosphonamide **6**, can be isolated and purified. Subsequent thermal decomposition of this product gives the olefin.



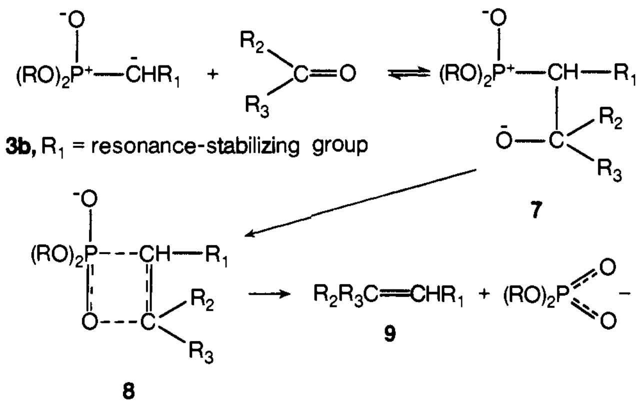
The phosphonamide route to the olefins appears to offer some advantages over the conventional Wittig reaction in that it is possible to isolate the pure diastereoisomers of the intermediate β-hydroxy phosphonamide **6**, and hence control the geometry of the resulting olefin. These reagents, however, have had little application in organic synthesis, and the full scope of this reaction is still to be evaluated.

The growing use of stabilized phosphonate carbanions in olefin synthesis is shown by the increasing number of publications involving this reaction. However, comparatively little experimental investigation has been done on the mechanism of this reaction, or on the effect of the structural nature of the phosphonate or the carbonyl compound on the stereochemical pathway. These factors will now be considered.

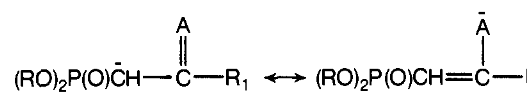
III. Mechanism and Stereochemistry

The mechanism proposed for olefin formation from stabilized phosphonate carbanions (see ref 15, p 203, ref 20, and ref 23) is analogous to the mechanism of the conventional Wittig reaction and comprises a two-step process in which the carbanion reacts with the carbonyl compound in a reversible first step to form an intermediate oxyanion (betaine) (**7**). The betaine **7** then decomposes irreversibly by oxygen transfer to the phosphorus atom to yield the olefin **9** and the dialkylphosphate ion (Scheme I). It is thought that the conversion of the betaine **7** to the olefin **9** proceeds by a cis elimination of the phosphate ion *via* a four-membered cyclic transition state **8** which has some double bond character. A similar mechanism has been proposed by Corey and Cane[32] for the formation of olefins from phosphonic acid bisamides.

SCHEME I. Proposed Mechanism of the Phosphonate Modification of the Wittig Reaction

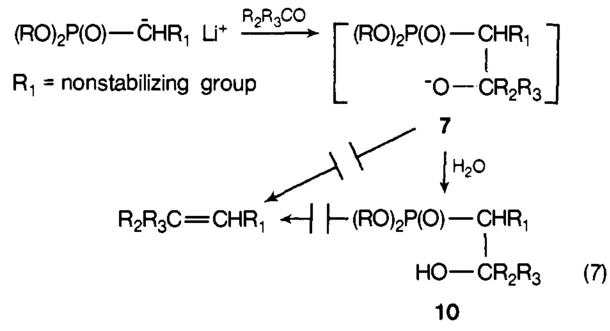


Only those phosphonates (**3a**) in which R_1 can further stabilize the carbanion by resonance can be employed successfully in olefin synthesis (that is, when R_1 = COR, CO_2R, CN, Ph, etc.) (eq 6).

 (6)

A = heteroatom

On the other hand, phosphonates **3a** in which R_1 = H, alkyl, or other nonstabilizing groups can form nonstabilized carbanions by treatment with *n*-butyllithium, but reaction of these with aldehydes or ketones does not yield olefins in significant amounts.[28] Instead the conjugate acid (**10**) of the betaine intermediate is formed and can be isolated in good yield. The isolated betaine cannot be induced to undergo efficient Wittig-type elimination either as the conjugate acid **10** or as the oxyanion (eq 7). The slowness of the decomposition of the oxyanion **7** (R_1 = H or alkyl) relative to **7** (R_1 = resonance-stabilizing group) appears to indicate that in the former case considerable negative charge accumulates on the carbon α to the phosphorus atom in the transition state making Wittig elimination unfavorable. Therefore, efficient Wittig elimination of the β-alkoxyphosphonate **7** can only be brought about if the intermediate is activated at the position α to the phosphorus atom by an electron-withdrawing group.



Although the stereochemical pathway of the conventional Wittig reaction is now well documented (see ref 3–20), that of reactions involving phosphonate carbanions in olefin formation has not been as extensively studied. Olefin formation was initially observed to yield only the trans-disubstituted olefin.[22-24] It was originally thought that a mixture of cis and trans isomers was first formed and that base-catalyzed isomerization of the cis olefin occurred under the reaction conditions to form the more thermodynamically stable trans isomer.[23,24] Attempts by Bergelson and Shemyakin[8] and by Wadsworth, *et al.*,[35] to increase the proportion of cis olefin have been unsuccessful. The latter workers showed that no appreciable isomerization of the cis olefin to the trans isomer occurred under the conditions used. These findings were in contrast to those observed for the conventional Wittig reaction where the olefin isomer ratio is readily affected by structural changes of both the ylide and the carbonyl components of the reaction, and also by the reaction conditions.[8,17] Many of the subsequent reports of olefin synthesis from phosphonate carbanions have shown that where isomer formation is possible the stereochemistry of the reaction favors the formation of the trans olefin. In most cases the trans olefin is the sole isomer produced (a review of these reactions is contained in section VI).

Although early attempts at cis olefination from phosphonate carbanions were unsuccessful, it has recently become apparent that in some cases this reaction is not stereospecific and that a mixture of geometric isomers can be produced. Sasaki[36-38] found that treatment of the aldehyde citral (**11**) with carbanions of diethyl 2-oxoalkylphosphonate (**12**, R_1 = CH_3 or C_2H_5) gave the ester **13** which consisted entirely of the trans isomer when the substituent on the α-carbon of the phosphonate (R_2) was hydrogen or methyl. However, increasing the size of the phosphonate side chain to R_2 = Et gave small but appreciable amounts of the cis isomer (eq 8). Similar results

$$(CH_3)_2C{=}CH(CH_2)_2C(CH_3){=}CHCHO + (EtO)_2P(O)\bar{C}R_2COR_1 \quad (8)$$

11 **12** → $C_9H_{15}CH{=}C(R_2)COR_1$ **13**

were obtained with citronellal (**14**) where reaction with diethyl 1-ethoxycarbonylpropylphosphonate carbanion (**15**) gave the product **16** which contained 44% of the cis isomer (eq 9).[39] Yanovskaya and Kucherov[40] showed

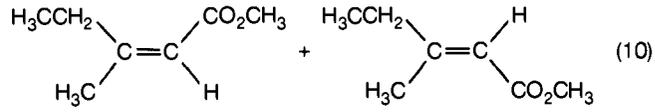
$$(CH_3)_2C{=}CH(CH_2)_2CH(CH_3)CH_2CHO + (EtO)_2P(O)\bar{C}(C_2H_5)CO_2Et \longrightarrow C_9H_{17}CH{=}C(C_2H_5)CO_2Et \quad (9)$$

14 **15** **16**

that reaction between the ketone α-ionone and diethyl ethoxycarbonylmethylphosphonate carbanion gave a mixture of ethyl *cis*- and *trans*-α-ionylideneacetate. Dahm, *et al.*,[41] utilized three condensation reactions of the dimethyl methoxycarbonylmethylphosphonate anion with appropriate ketones in a synthetic route to racemic juvenile hormone. From each reaction a mixture of cis and trans isomers of the new double bond was produced, from which the desired pure cis or trans isomer was isolated. For example, the reaction of dimethyl methoxycarbonylmethylphosphonate anion and 2-butanone (**17**) gave an isomer mixture containing 43% methyl *cis*-3-methylpent-2-enoate (**18a**) (eq 10).

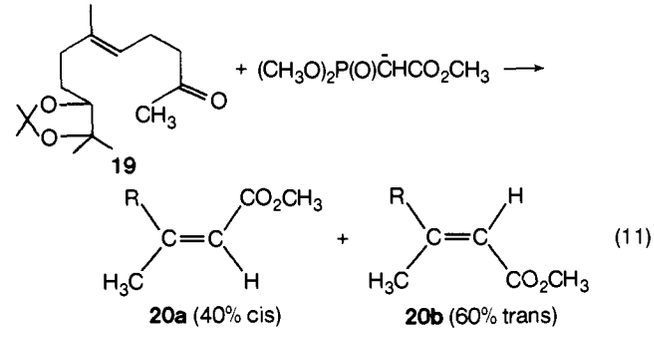
$$CH_3CH_2COCH_3 + (CH_3O)_2P(O)\bar{C}HCO_2CH_3 \longrightarrow$$

17



18a (43% cis) + **18b** (57% trans) (10)

In similar synthetic studies leading to juvenile hormone, Cavill, *et al.*,[42,43] found that the reaction between the dimethyl methoxycarbonylmethylphosphonate anion and the methyl ketone **19** gave an isomeric mixture of esters **20a** and **20b** in the proportions indicated (eq **11**). Mori, *et al.*,[44] have also shown nonstereospecific condensation of diethyl methoxycarbonylmethylphosphonate carbanion with methyl ketones in the synthetic route to C_{18} *Cecropia* juvenile hormone.

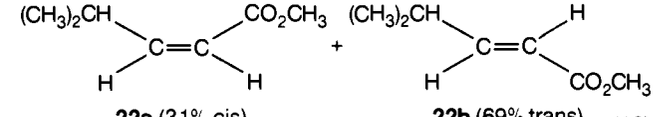


19 + $(CH_3O)_2P(O)\bar{C}HCO_2CH_3$ → **20a** (40% cis) + **20b** (60% trans) (11)

McGreer and Chiu[45] produced an isomeric mixture containing 31% cis isomer **22a** from the reaction of 2-methylpropanal (**21**) and dimethyl methoxycarbonylmethylphosphonate carbanion (eq 12).

$$(CH_3)_2CHCHO + (CH_3O)_2P(O)\bar{C}HCO_2CH_3 \longrightarrow$$

21

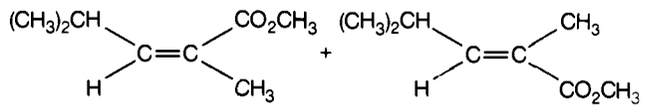


22a (31% cis) + **22b** (69% trans) (12)

Similarly,[45] reaction of **21** with the diethyl 1-methoxycarbonylethylphosphonate anion (**23**) gave a product containing 40% cis isomer **24a** (eq 13). There was no attempt by any of these workers to explain the presence of substantial proportions of cis isomers in the olefin mixture.

$$(CH_3)_2CHCHO + (C_2H_5O)_2P(O)\bar{C}(CH_3)CO_2CH_3 \longrightarrow$$

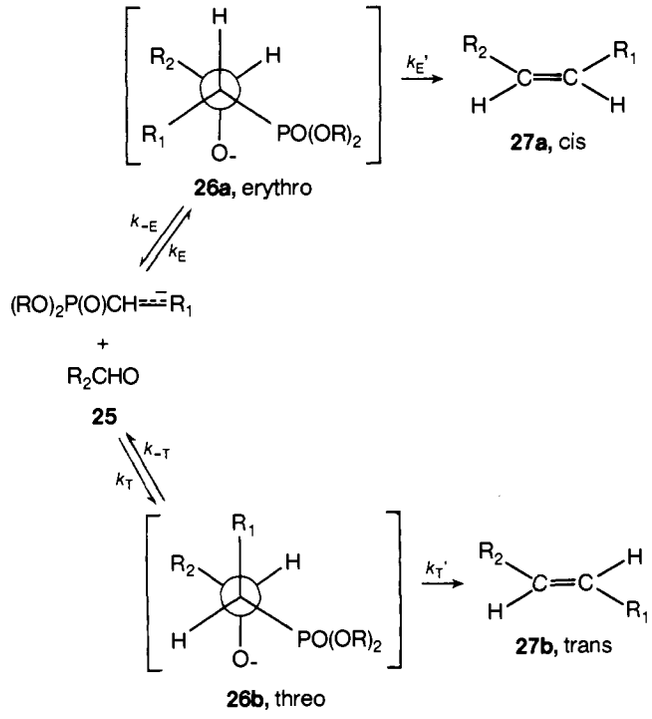
21 **23**



24a (40% cis) + **24b** (60% trans) (13)

The observed stereochemistry of reactions between stabilized phosphonate carbanions and carbonyl compounds can be accounted for on the basis of the previously proposed mechanism. It appears that the stereochemical course of the reaction (Scheme II) is governed by the same steric effects at the intermediate level as that of the conventional Wittig reaction. The intermediate oxyanions, formed reversibly by reaction of the phosphonate carbanion and the aldehyde **25**, can exist as two diastereoisomers, where the erythro betaine **26a** is the pre-

SCHEME II. Proposed Stereochemical Course of the Phosphonate Modification of the Wittig Reaction Showing Formation of Cis and Trans Isomers

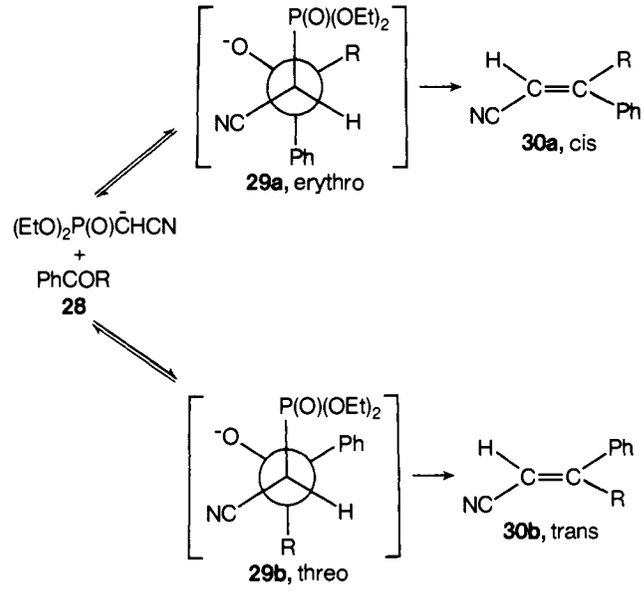


cursor of the cis olefin **27a** *via* a cis elimination, and similarly the threo betaine **26b** leads to the trans product **27b.** The ratio of isomeric olefins would then be expected to be determined by the degree of reversibility of the formation of the two oxyanions **26a** and **26b** if they do not interconvert directly, and of the rates of their decomposition into olefins **27a** and **27b.**

Because the stereochemistry of the reaction generally favors the trans olefin, it can be supposed that the formation and decomposition of the threo betaine **26b** is more rapid than that of the erythro betaine **26a.** This would be expected on steric grounds since the erythro betaine **26a,** which is more sterically hindered in the eclipsed conformation, will be formed at a slower rate than the threo betaine **26b.** Similarly the rate of decomposition of the threo betaine **26b** to the trans olefin **27b** is usually greater than that of the erythro betaine **26a** to the cis olefin **27a** because the threo betaine is less sterically hindered and provides better conjugative stabilization of the incipient double bond in the transition state. Such conjugation should be more difficult in the transition state from the erythro betaine since the R_1 and R_2 groups could not become coplanar with the incipient double bond.

The findings of Jones and Maisey,[46] who quantitatively studied the stereochemistry of the α,β-unsaturated nitriles produced from the reaction between diethyl cyanomethylphosphonate carbanion and a series of alkyl aryl ketones (**28**) in dimethoxyethane, added further evidence to support the proposed stereochemical pathway (Scheme III). When the alkyl chain (R) of the ketone **28** was unbranched and the phenyl ring unsubstituted in the ortho position, then the trans isomer **30b** predominated in the olefin mixture. (The trans isomer resulting from the interaction of an unsymmetrical ketone and an unbranched phosphonate contains the larger ketone residue and the ylide side chain on opposite sides of the double bond.) Branching of the alkyl chain or substitution in the ortho position of the phenyl ring gave increased proportions of cis isomer **30a.** Where the alkyl group was tertiary (*i.e.*, R = *tert*-butyl), the cis isomer **30a** predominat-

SCHEME III. Reaction of Diethyl Cyanomethylphosphonate Carbanion with Alkyl Aryl Ketones (Jones and Maisey[46])



ed in the olefin mixture. Substitution in the meta or para position of the phenyl ring had little effect on the isomer ratio compared with the unsubstituted phenyl ring. These workers suggest that branching of the alkyl chain of the ketone increases the steric hindrance in the threo betaine **29b.** The rate of formation of the threo betaine **29b** and the rate of its decomposition to the trans olefin **30b** are thus reduced. They further suggest that ortho substitution on the phenyl ring decreases conjugative stabilization of the incipient double bonds in the transition states, and, since conjugative stabilization is usually greater in the transition state leading to the trans olefin **30b,** the proportion of the trans isomer in the reaction mixture is decreased.

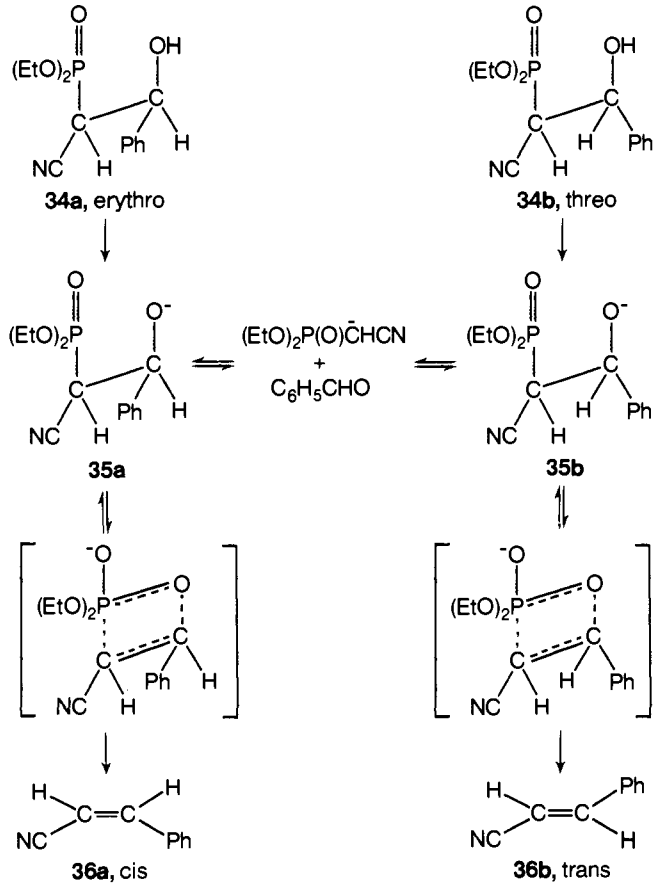
Similar findings were obtained from the stereochemical studies of Kinstle and Mandanas[47] on the reaction between aliphatic aldehydes (**32**) and diethyl 1-ethoxycarbonylalkylphosphonate (**31**) carbanions in dimethoxyethane (eq 14). The isomer ratio of the resulting α,β-unsatu-

$$(EtO)_2P(O)CHCO_2Et + R_2CHO \xrightarrow[DMe]{NaH} R_2CH{=}CR_1CO_2Et \quad (14)$$
$$\quad\quad R_1 \quad\quad\quad\quad 32 \quad\quad\quad\quad 33$$
$$31$$

rated esters (**33**) depended on the size of R_1 and R_2. When the side chain on the phosphonate (R_1) was hydrogen, only the trans isomer was obtained from all the aldehydes used. With increasing size of R_1 together with branching of the alkyl chain (R_2) of the aldehyde **32,** the proportion of cis isomer of the ester **33** was increased. When R_1 = isopropyl, 84% of the cis-unsaturated ester (**33**) was produced.[47a] It was concluded by these workers that steric factors were responsible for the trends observed, but the precise nature of these factors was not stated.

More recent suggestions on the mechanism of the phosphonate modification of the Wittig reaction were put forward by Lefèbvre and Seyden-Penne[48] who isolated the erythro and the threo isomers of diethyl 1-cyano-2-hydroxy-2-phenylethylphosphonate (**34a** and **34b**) after treatment of benzaldehyde with diethyl cyanomethylphosphonate and isopropylmagnesium chloride in tetrahydrofuran at −70°. Decomposition of each isomer of this compound under basic conditions in the presence of *p*-chlorobenzaldehyde gave a mixture of cinnamonitrile and *p*-chlorocinnamonitrile, the ratio of which was solvent de-

SCHEME IV. Decomposition of *erythro*- and *threo*-β-Hydroxyphosphonates in Basic Medium (Lefèbvre and Seyden-Penne[48])

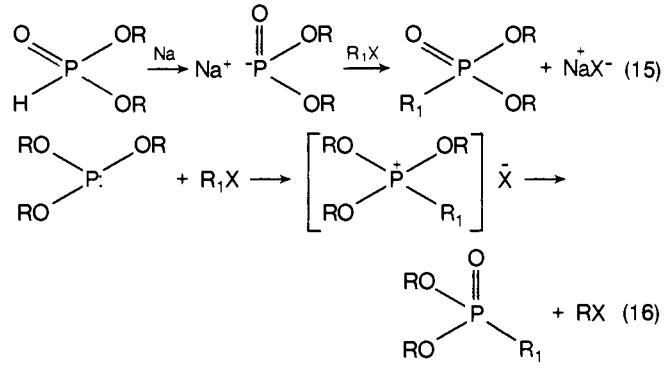


pendent. This is good evidence that the oxyanions **35a** and **35b** are intermediates in the direct reaction between benzaldehyde and diethyl cyanomethylphosphonate carbanion (Scheme IV), and that betaine formation is reversible to an extent depending on the solvent. (The reversibility of the first step of the reaction between phosphonate carbanions and carbonyl compounds has been previously evidenced in polar solvents by Danion and Carrie.[49])

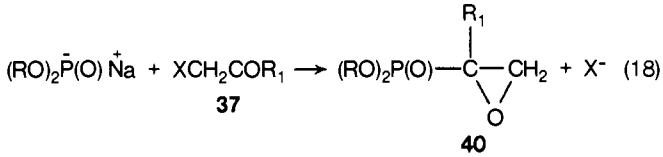
The ratio of *cis*- (**36a**) to *trans*-cinnamonitrile (**36b**) produced in tetrahydrofuran either from the direct reaction between diethyl cyanomethylphosphonate carbanion and benzaldehyde,[50] or from the decomposition of either the *erythro*- (**34a**) or the *threo*-β-hydroxyphosphonate (**34b**), with and without the presence of the competing *p*-chlorobenzaldehyde, was found to be the same. These results indicate that the two epimeric oxyanions (**35a** and **35b**) of the β-hydroxyphosphonate should partly interconvert directly, as well as epimerize *via* dissociation into benzaldehyde and the phosphonate carbanion. This is a finding which is different from that observed for the reaction involving stabilized phosphonium ylides. The process involved in the direct interconversion is not clear, but it was suggested that this may involve either pseudorotation or rapid bond-making–bond-breaking of a five-coordinate intermediate as well as direct interconversion of the two oxyanions.

IV. Preparation of Phosphonates

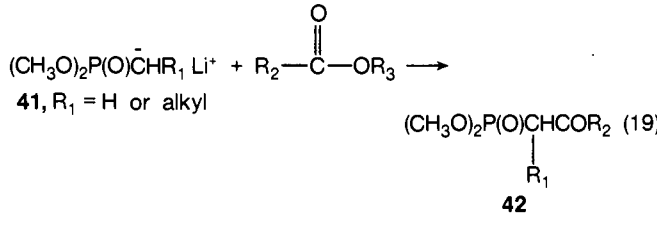
Phosphonates have generally been prepared by the Michaelis reaction or by the Arbuzov reaction.[26,27] The former involves the treatment of alkylmetal derivatives of dialkyl phosphites with alkyl halides (eq 15), while the Arbuzov reaction involves treatment of trialkyl phosphites with alkyl halides (eq 16).



In recent years the Arbuzov reaction (eq 16) has been more widely adopted owing to the simpler reaction conditions required and the greater yield of phosphonate obtained. Difficulty, however, is encountered in the use of either of these reactions in the preparation of α-ketophosphonates, which are valuable reagents in olefin synthesis.[51] The reaction of trivalent phosphorus compounds with α-halo ketones (**37**) (known as the Perkow reaction) is complex and usually gives both the products of the normal Arbuzov or Michaelis reactions as well as anomalous products (eq 17). With trialkyl phosphites the yield of the α-ketophosphonate **38** is usually higher at temperatures of 150°, while at low temperatures (30–50°) the reaction yields predominantly the enol phosphate **39.** Reaction of dialkyl phosphite ions with α-halo ketones **37** (X = halogen) gives a mixture of products of which the dialkyl 1,2-epoxyalkylphosphonate (**40**) predominates (eq 18). (Reviews on the mechanism of the reaction of dialkyl phosphite ions and trialkyl phosphites with α-halo ketones and α-halo aldehydes are found in ref 27, 52, and 53.)



An alternate and more useful method of synthesis of α-ketophosphonates was reported by Corey and Kwiatkowski[28] where α-lithio derivatives of alkylphosphonates **41** on treatment with esters gave α-ketophosphonates **42** in good yield (eq 19).

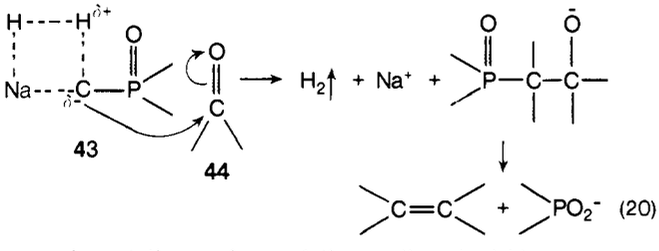


V. Experimental Conditions

The conditions for olefin formation by phosphonate carbanions have essentially remained unchanged from those first employed by Horner, *et al.*,[22] and by Wadsworth and Emmons.[23] Where phosphonates **3a** have a

strong electron-withdrawing group of the type R_1 = CO_2R, COR, CONHR, SO_2R, CN, $PO(OR)_2$, on the carbon α to the phosphorus atom, anion formation proceeds exothermally at room temperature with bases such as sodium hydride, sodium amide, or the metal alkoxides. Condensation is brought about by the addition of the carbonyl compound to the carbanion, and in many cases the reaction proceeds smoothly at room temperature. Solvents employed range in polarity from benzene through diglyme, tetrahydrofuran, and ethanol to dimethylformamide and dimethyl sulfoxide. On the other hand, alkyl phosphonates **3a** of the type where R_1 = H, alkyl, or O-alkyl are unreactive in conditions which will suffice for carbanion formation of the more stabilized phosphonates.[28,54] However, as previously mentioned, these form unstabilized carbanions when treated with *n*-butyllithium at −78° in tetrahydrofuran but have not been shown to form olefins from aldehydes or ketones.

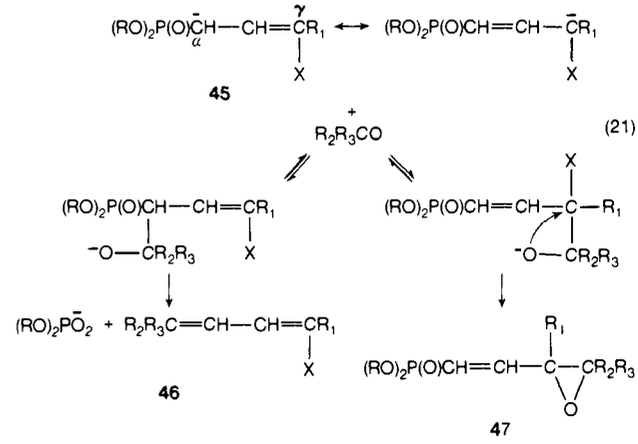
Phosphonates **3a** of the type where R_1 = Ph, CH=CHR, SR, or $CH(OR)_2$ are intermediate in their ability to form stable carbanions. These react slowly with sodium hydride, and the use of elevated temperatures leads to their decomposition. Detachment of the proton by a base is facilitated by use of basic media such as hexamethylphosphoramide.[55] For condensation to take place, it is necessary to generate the carbanion in the presence of the aldehyde or ketone.[23] In fact, recent studies by the French workers Lavielle and Sturtz[56] on olefin formation with allylic phosphonates **3a** of the type where R_1 = $C(R)_2$=$C(R_3)_2$ in hexamethylphosphoramide–benzene mixtures using sodium hydride as base showed that carbanion formation only occurred when the aldehyde or ketone was present. The phosphonates failed to react with sodium hydride in the absence of the carbonyl compound. Since, in the presence of the carbonyl compound, the rate of evolution of hydrogen from the sodium hydride is a measure of the reaction rate, a quantitative study was made on the influence of the nature of the carbonyl group on the rate of reaction. From a series of aldehydes and ketones it was shown that sodium hydride was more rapidly consumed with the more electrophilic carbonyl groups. It was postulated that a complex was formed between the base and the phosphonate at the surface of the sodium hydride **43.** Such a postulate was based on similar findings by Caubère and Loubinoun.[57] Evolution of hydrogen only occurs when the electrophile destroys the complex. The oxyanion produced then undergoes elimination to form the olefin (eq 20). The formation of such a



(20)

complex at the surface of the sodium hydride was considered to be in accord with the observation that the destruction of the complex **43** is more rapid when the carbonyl group **44** of the aldehyde or ketone is electrophilic. Similarly, the stability of the complex is less when the α-carbon of the phosphonate is more acidic. In the extreme case the carbanion of the phosphonate is formed quantitatively in the absence of the aldehyde or ketone when the α-carbon of the phosphonate bears a strong electron-attracting group (*e.g.*, **3a,** R_1 = CO_2Et).

Phosphonates of the allylic type **3a,** where R_1 = $C(R_2)$=$C(R_3)_2$, have the charge of the carbanion delocalized by resonance. These can be expected, by analogy to the allylic phosphoranes,[58] to react with carbonyl compounds by electrophilic attack on either the α- or γ-carbons. As the greatest degree of negative charge resides on the α-carbon,[32] attack at this position to form the olefin in the normal manner predominantly takes place. Evidence, however, for attack on the γ-carbon has been shown by Lavielle[59] who isolated both the halodiene **46** and allylic epoxide **47** from treatment of the γ-haloallylic phosphonate (**45,** X = halogen) with an aldehyde or ketone according to the scheme in eq 21. The controlling

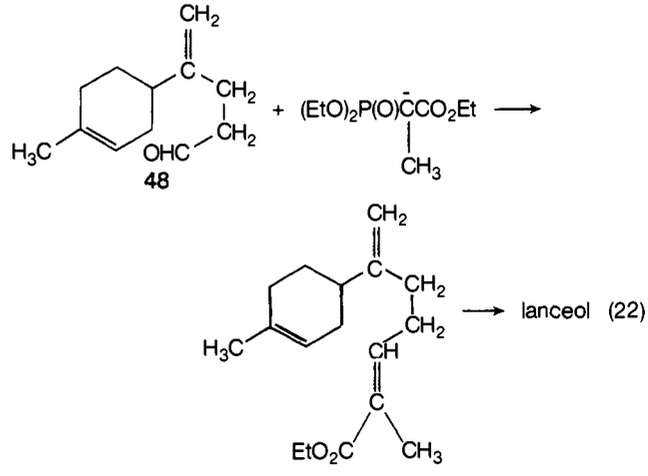


(21)

factor governing the ratio of α- to γ-additions is not clear, but in the case of allylic phosphonamides it was proposed by Corey and Cane[32] that these factors are steric in nature.

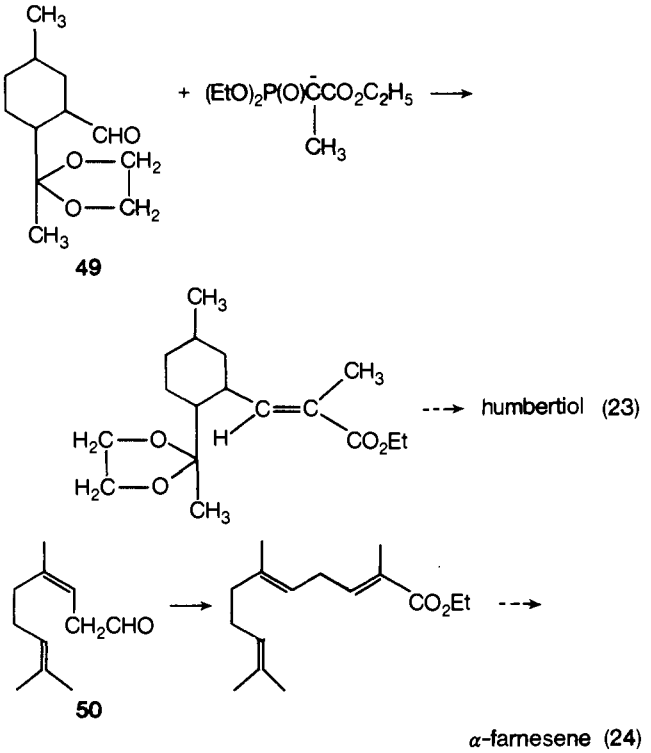
VI. Application and Scope

The advantages of using phosphonate carbanions in olefin synthesis over the conventional Wittig reaction has resulted in their increasing application in the synthesis of a wide range of compounds.[59a] Particular advantage has been made of the fact that the steric requirements at the intermediate stage of the reaction often permit the reaction to proceed stereoselectively to produce predominantly the trans olefin. Syntheses involving natural products illustrate this point. Vig, *et al.*,[60-63] showed that trans-olefination from diethyl **1**-ethoxycarbonylethylphosphonate carbanion with aldehydes **48, 49,** and **50** was a key step in the synthesis of the sesquiterpenoids (±)-lanceol, humbertiol, and α-farnesene (eq 22–24).

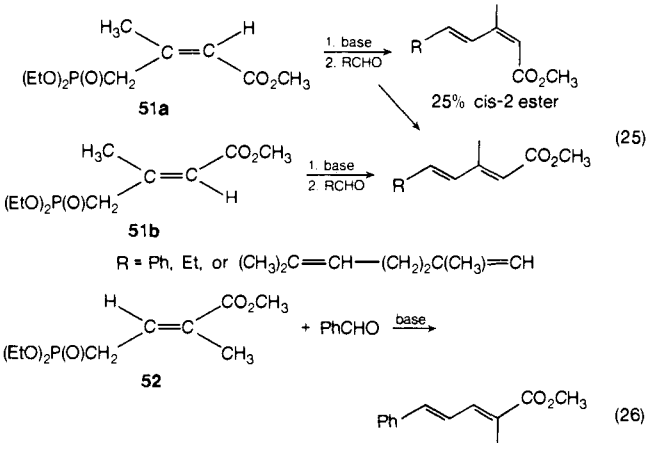


(22)

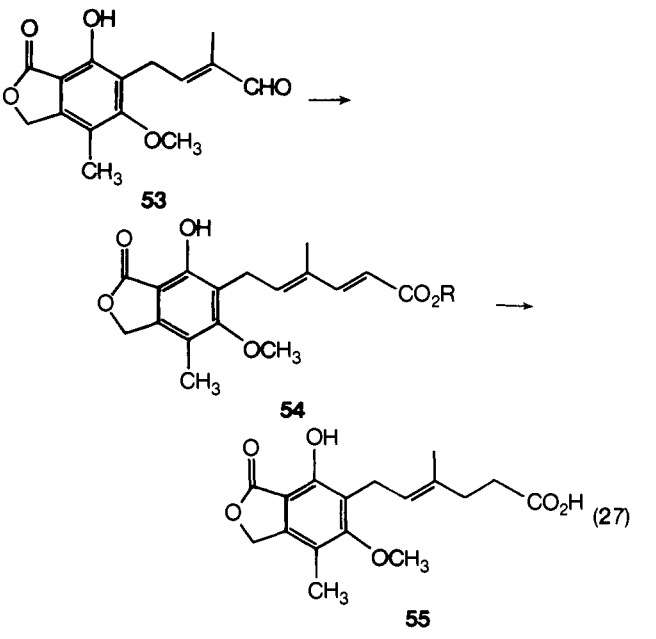
Pattenden and Weedon,[64,65] in synthetic studies of carotenoids and related compounds, prepared pure diethyl *cis*- and *trans*-3-methoxycarbonyl-2-methylprop-2-enylphosphonates (**51a** and **51b**), and also the 3-methyl ana-

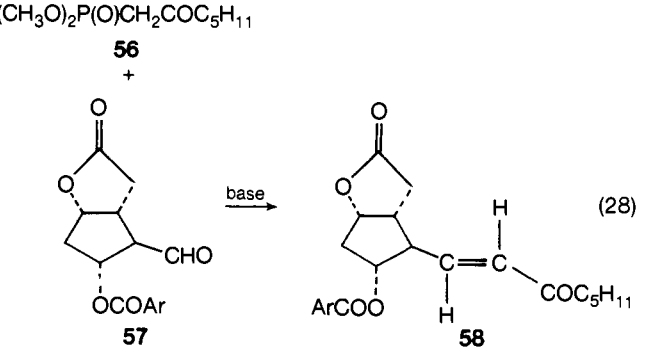


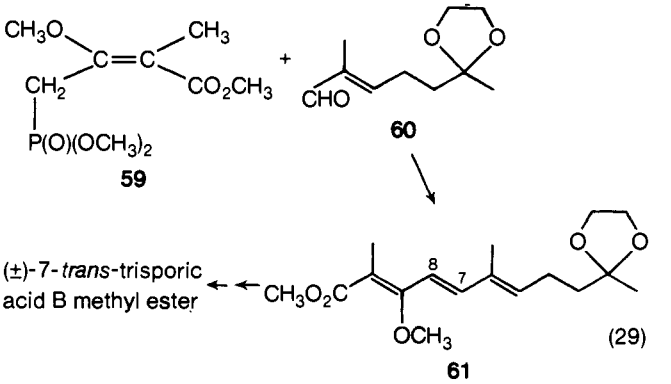
log (**52**). Condensation of the anions of these compounds with various aldehydes (eq 25 and 26) was valuable as



model reactions in the synthesis of cis polyenes. In all the phosphonate condensations trans-olefination occurred and the newly formed double bond had the trans-configuration. The cis-phosphonate **51a** underwent extensive stereomutation on condensation of the carbanion with the aldehydes with only 25% of the resulting ester possessing the cis-2 configuration. Similar syntheses of polyenes involving the use of phosphonates was reported by Kjoesen and Liaaen Jensen.[66] Birch and Wright[67] prepared the fungal metabolite mycophenolic acid (**55**) by treatment of the aldehyde **53** with diethyl ethoxycarbonylmethylphosphonate anion to give exclusively the trans-2 ester (**54**, R = Et). Selective reduction of the corresponding dienoic acid (**54**, R = H) gave mycophenolic acid (**55**) (eq 27). Corey, *et al.*,[68] prepared a new phosphonate, dimethyl 2-oxo-*n*-heptylphosphonate (**56**), whose carbon skeleton and the geometry of the olefin formed on condensation with a suitable aldehyde gave the required intermediate in prostaglandin synthesis. For example, the lactone aldehyde **57** when condensed with the anion of **56** gave the trans enone lactone **58** which was the required intermediate in the synthesis of prostaglandins F and E (eq 28).[69-71] The phosphonate condensation reaction formed the trans-12,13 double bond of the prostaglandin E. The synthesis of the *all-trans*-(±)-trisporic acid B methyl ester by Edwards, *et al.*,[72] involved the use of a more novel phosphonate reagent (**59**) as an acetoacetic acid synthon. Condensation of the carbanion of **59** with the aldehyde **60** gave the *all-trans*-trienyl ester **61** (eq 29) as an intermediate from which the trisporic acid B methyl ester was obtained. This reaction incorporated the trans-7-ene function into the molecule.





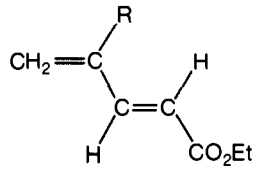


In some instances the phosphonate modification of the Wittig reaction provides a more suitable alternative to older established procedures by giving more satisfactory results. The direct formation of α,β-unsaturated esters from the reaction between diethyl ethoxycarbonylmethylphosphonate and aldehydes or ketones is an example of an alternative to the Reformatsky route to the acrylates. Similarly, Sundberg, *et al.*,[73] found that derivatives of vinylacrylic acid can be prepared by the action diethyl ethoxycarbonylmethylphosphonate anion on 2-alkylacroleins (**62**). The 2-alkylacroleins were converted exclu-

sively to the *trans*-4-alkyl-2,4-pentadienoates (**63**) in moderate yield (eq 30). This method provides a suitable replacement for the amine-catalyzed decarboxylative condensation of α,β-unsaturated aldehydes with malonic acid.

$$CH_2{=}CR{-}CHO + (EtO)_2P(O)CH_2CO_2Et \xrightarrow{base}$$

62



(30)

63

Phosphonates containing amide groups (**64**) number among the new ylides recently reported.[74] These readily form anions which react with aldehydes and ketones in the normal manner to provide a useful route to α,β-unsaturated amides (eq 31).

$$(EtO)_2P(O)\bar{C}HCONR_1R_2 + R_3R_4CO \longrightarrow$$

64

$$R_3R_4C{=}CHCONR_1R_2 \quad (31)$$

A new two-step process was described by Nagata and Hayase[75] for the conversion of ketones (or aldehydes) into α,β-unsaturated aldehydes according to the scheme in eq 32. This sequence is stereoselective giving the *trans*-formyl olefin **65** in good yields.

$$R_1R_2CO + (EtO)_2P(O)\underset{R}{C}HCH{=}NC_6H_{11} \xrightarrow{NaH}$$

$$R_1R_2C{=}\underset{R}{C}CH{=}NC_6H_{11} \xrightarrow{H^+} \underset{R_2}{\overset{R_1}{C{=}C}}\overset{R}{\diagdown}\!\!\diagup\overset{}{CHO} \quad (32)$$

65

The ability of bivalent sulfur to stabilize an adjacent carbanion lends further scope to the phosphonate Wittig synthesis. Alkyl and aryl thiomethylphosphonates (**66**) have been originally shown by Green[76] to form vinyl sulfides (**67**) when the carbanion is generated in the presence of the carbonyl compound (eq 33). The adjacent thiomethyl group confers some stabilization to the carbanion, whereas alkyl (**3a**, R_1 = H, CH_3, etc.)[28] and alkoxy phosphonates (**3a**, R_1 = OCH_3, etc.)[54] are relatively inactive.

$$(RO)_2P(O)CH_2SR_1 + R_2R_3CO \xrightarrow{NaH} R_2R_3C{=}CHSR_1 \quad (33)$$

66 (R_1 = alkyl or aryl) **67**

Similarly, Shahak and Almog[77,78] showed more recently that, though alkyl and aryl thiomethylphosphonates (**66**) react slowly with sodium hydride, condensation with aldehydes proceeds exothermally when the aldehyde is present together with the sodium hydride and the phosphonate. The vinyl sulfide produced, as expected from previous results, has the trans configuration. Ketones underwent condensation with more difficulty. This group of reactions was extended by Corey and Shulman[79] with the use of lithium salts of branched thioalkylphosphonates (**68**). These underwent facile condensation with both aldehydes and ketones to produce the β-alkoxyphosphonate adducts (**69**) which decomposed upon warming to form substituted vinyl methyl sulfides (**70**) in good yield (eq 34). Where formation of isomeric vinyl sulfides was possible, the trans product predominated. The vinyl sulfides proved a convenient precursor to unsymmetrical ketones (**71**) through mercury(II)-promoted hydrolysis (eq 35).

$$(EtO)_2P(O)\underset{R_1}{C}HSCH_3 \xrightarrow[2.\ R_2R_3CO]{1.\ n\text{-BuLi}} R_2R_3C(Li^+\ {}^-O)\text{–}C(P(O)(OEt)_2)\text{–}R_1 \longrightarrow$$

68 **69**

$$R_2R_3C{=}\underset{R_1}{C}SCH_3 + (EtO)_2P\bar{O}_2\ Li^+ \quad (34)$$

70

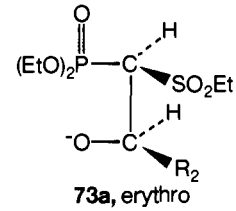
$$R_2R_3C{=}\underset{R_1}{C}SCH_3 \xrightarrow[Hg^{2+}]{H_2O} R_2R_3CHCOR_1 \quad (35)$$

71

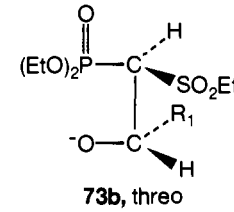
In the same way α,β-unsaturated sulfones (**74**) are prepared by reaction of alkyl- or arylsulfonylmethylphosphonate carbanions (**72**) with aldehydes[77,78,80] (eq 36). The more electronegative sulfonyl group renders the phosphonate very reactive toward base, and the carbanion generated reacts readily with aldehydes under mild conditions. This route provides a more suitable alternative to previously existing methods for the preparation of unsaturated sulfones and, in general, better yields are obtained. For example, ethyl styryl sulfone (**74**, R_1 = Et; R_2 = C_6H_5) was prepared from benzaldehyde and diethyl ethylsulfonylmethylphosphonate (**72**, R_1 = Et) in 84% yield and consisted exclusively of the trans isomer, while the Knoevenagel-type reaction gave 12% of ethyl styryl sulfone with unknown stereoisomerism.[73] The reactions so far observed between aldehydes and sulfonylmethylphosphonate carbanions have yielded predominantly the trans-unsaturated sulfone. This is expected from the mechanism previously outlined where the steric factors at the intermediate stage (**73a** and **73b**) of the reactions studied favor trans isomer formation. The reaction between sulfonyl phosphonates and ketones has not been adequately studied.

$$(EtO)_2P(O)CH_2SO_2R_1 + R_2CHO \xrightarrow{NaH} \overset{R_2}{\underset{H}{C{=}C}}\overset{H}{\diagdown}\!\!\diagup\overset{}{SO_2R_1} \quad (36)$$

72 **74**



73a, erythro

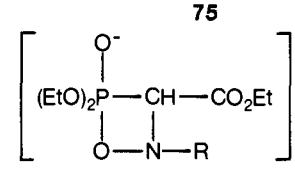


73b, threo

A more novel synthesis has been reported by Zimmer, *et al.*,[81] where phosphonate carbanions have been shown to condense with nitroso compounds (**75**) to give the imine **76** (eq 37). This appears to be analogous to the

$$(EtO)_2P(O)\bar{C}HCO_2Et + RN{=}O \longrightarrow$$

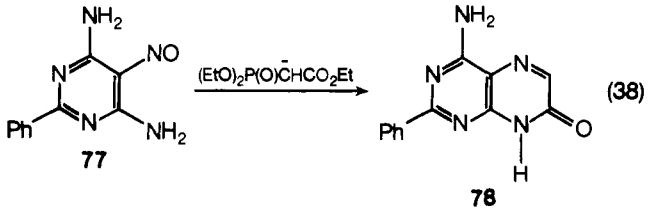
75



$$\longrightarrow RN{=}CHCO_2Et \quad (37)$$

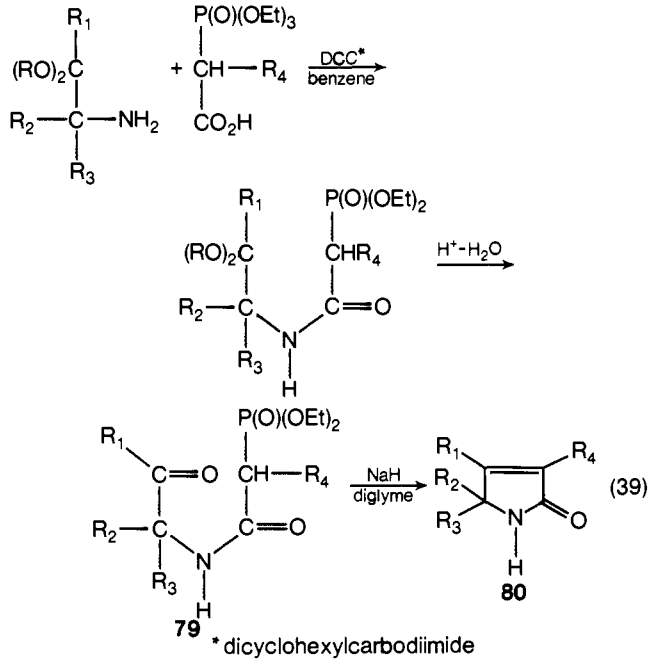
76

condensation of phosphonates with carbonyl groups. More recently this reaction was successfully applied in the development of a new synthetic route to the pteridines from nitrosopyrimidines.[82,83] For example, the 4-amino-5-nitrosopyrimidine **77** reacted readily with diethyl ethoxycarbonylmethylphosphonate to form the pteridine **78** in good yield (eq 38). The reaction probably involves an initial reaction of the ylide with the nitroso group to form the unsaturated ester, such as **76** above, which undergoes cyclization to give the lactam.



(38)

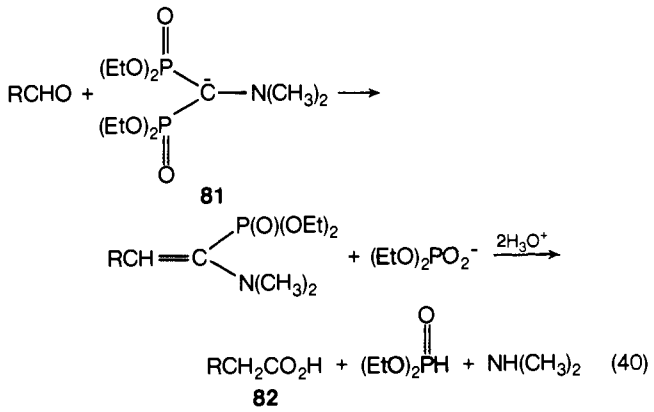
Stork and Matthews[84] used a similar approach in the synthesis of alkylpyrrolones from alkylamines, where an intramolecular phosphonate condensation was successfully employed to close the five-membered ring. The general scheme is depicted in eq 39. The amino ketone intermediate **79** readily underwent cyclization under modified Wittig conditions to give the desired pyrrolone **80.**



(39)

*dicyclohexylcarbodiimide

Bisphosphonates containing an acidic hydrogen have also been observed to undergo carbanionic reactions. Gross and Costisella,[85] in a recent example, showed that carboxylic acids **82** could be synthesized from aldehydes



(40)

containing one carbon atom less *via* olefination with tetraethyl dimethylaminomethylenediphosphonate (**81**) (eq 40).

Other recent applications of the phosphonate modification of the Wittig reaction in synthetic chemistry are listed below.

i. The synthesis of potential biologically active semisynthetic derivatives of cassaine and related compounds[86,87]
ii. The total synthesis of emetine[88,89]
iii. Synthetic routes to the fulvenes and fulvene analogs[90]
iv. The synthesis of isomeric (±)-pyrethric acid[91]
v. The synthesis of branched-chain sugars from carbohydrate ketones[92]
vi. The synthesis of α-fluorostilbenes[93]
vii. Unsaturated derivatives of piperidine[94]
viii. Synthesis of α,β-unsaturated esters from cyclopropyl aldehydes and ketones[95]
ix. The synthesis of aminoalkoxycarbonylmethyl derivatives **83** of dialkylphosphonates as reagents for the preparation of biologically active aminoalkoxycarbonylmethylene derivatives of steroids and related compounds[96]

$$(EtO)_2P(O)CH_2CO_2CH_2CH_2N(CH_3)_2$$

83

x. The preparation of cyclic α,β-unsaturated ketones from enol lactones[97] (see below)

VII. Steroids

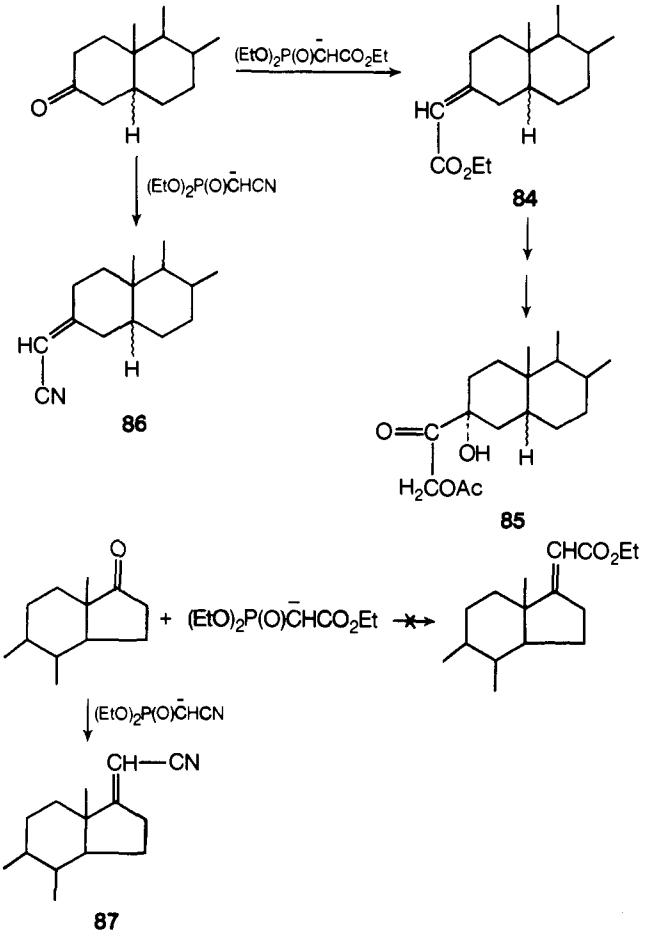
Carbonyl olefination has received significant application in the field of steroid chemistry. This is illustrated by the use of phosphonate carbanions in the transformation of steroid aldehydes and ketones to potential biologically active compounds.

The general reaction between diethyl ethoxycarbonylmethylphosphonate and diethyl cyanomethylphosphonate carbanions with various steroid ketones was first studied by Bose and Dahill.[98] The ethoxycarbonyl phosphonate was found to react only with 3-oxo steroids to give the α,β-unsaturated ester **84,** which could subsequently be transformed to a cortical side chain at C-3 (**85**). The more linear diethyl cyanomethylphosphonate is less selective and gave the unsaturated nitriles **86** and **87** from steroid ketones with keto groups at other positions as well as C-3 (Scheme V). Since nitriles can be converted to other functional groups, the cyanomethylene derivatives obtained from steroid ketones can serve as intermediates for various types of substituted steroids.

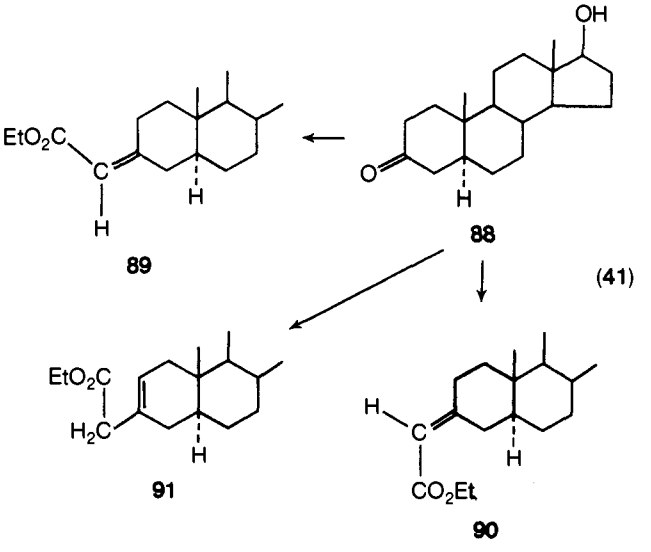
The stereochemistry of the reaction between phosphonate carbanions and cyclic ketones has not been extensively studied. Bose, *et al.*,[98-100] reported that the reaction between diethyl ethoxycarbonylmethylphosphonate anion and 3-oxo steroids gave exclusively one isomer which was assigned a configuration of trans to C-4. Similarly Kaneko and Okazaki[101] obtained the trans isomer **89** from the reaction between dihydrotestosterone (**88**) and diethyl ethoxycarbonylmethylphosphonate using equimolar quantities of sodium hydride as base (eq 41).

However, the same reaction carried out in the presence of any added Lewis acid or base (for example, boron trifluoride or potassium *tert*-butoxide) gave a preponderance of the cis isomer **90.** The structures of the geometrical isomers were assigned from chemical data. There was no explanation given for the difference in the stereochemistry of the two reactions. These workers further noted that reaction of dihydrotestosterone (**88**) with diethyl ethoxycarbonylmethylphosphonate in the presence

SCHEME V. Reaction of Steroid Ketones with Phosphonate Carbanions

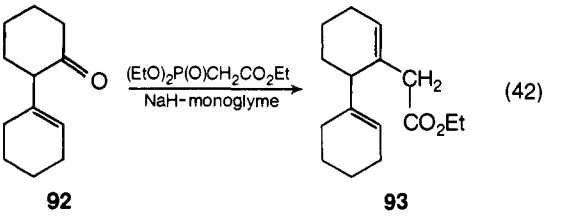


of 2 molar equiv of sodium hydride at 80° gave the β,γ-unsaturated ester **91** in quantitative yield. The mechanism for the reaction leading to this compound is unknown. Double bond migration under the reaction conditions was excluded as the α,β-unsaturated ester **89** or **90** did not isomerize when treated with sodium hydride, alkali, or acid.



(41)

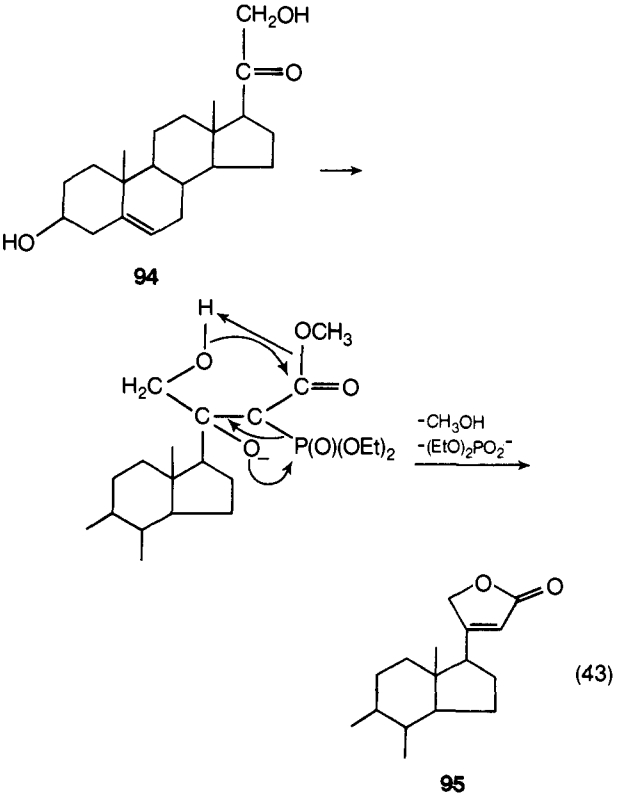
A similar observation has been made by Gupta, *et al.*,[102] who showed that reaction of diethyl ethoxycarbonylmethylphosphonate in the presence of sodium hydride in monoglyme with 2-(cyclohexen-1-yl)cyclohexanone (**92**) gave the product containing the endocyclic nonconjugated double bond (**93**) (eq 42). Details of the experimental procedure are not given.



(42)

Less is known about the stereochemistry of unsaturated nitriles derived from the reaction between diethyl cyanomethylphosphonate carbanion and steroid ketones. Some steroid ketones have been shown to yield a single isomer, while others have given a mixture of geometric isomers.[98,103,104] The geometry of the products has not been ascertained.

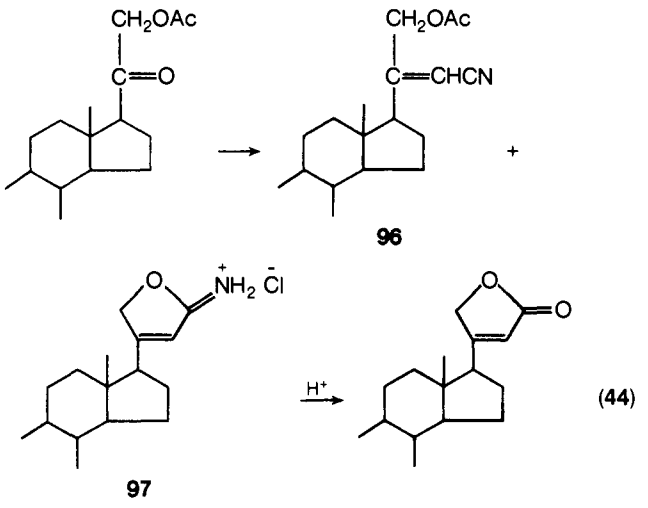
Though 20-oxo-21-methyl steroids were unreactive to carbanions of alkoxycarbonylmethylphosphonates,[98] it was shown that 20-oxo-21-hydroxypregnanes (**94**) reacted exothermally with diethyl methoxycarbonylmethylphosphonate in the presence of sodium hydride to yield the corresponding cardenolide (**95**) (eq 43).[105,106] It was considered that the 21-hydroxy group has a strong orientating effect on the approaching phosphonate carbanion, and combined with a thermodynamically favorable ring formation leads to a very efficient (95% yield) reaction.



(43)

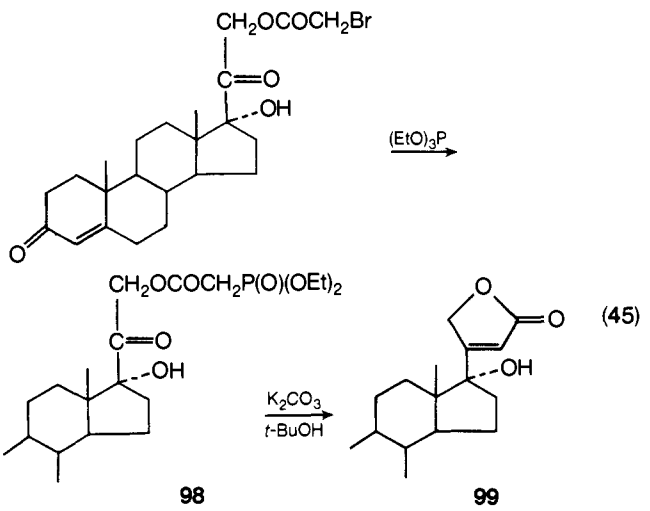
Similarly the reaction of diethyl cyanomethylphosphonate carbanion with 20-oxo-21-acetoxy steroids and subsequent treatment with hydrochloric acid gave a mixture of the unsaturated nitrile **96** and the imino lactone **95**.[104] Acid hydrolysis of the imino lactone **97** gave the cardenolide (eq 44).

On the basis of the reactions discussed above, Farbwerke Hoechst A.-G. and other workers[107-111] have patented numerous alkoxycarbonylmethylene and cyanomethylene derivatives of steroids ketones in a search for biologically active compounds. Similarly the patent literature gives several examples of new cardenolides prepared as potential cardioactive compounds by reaction of



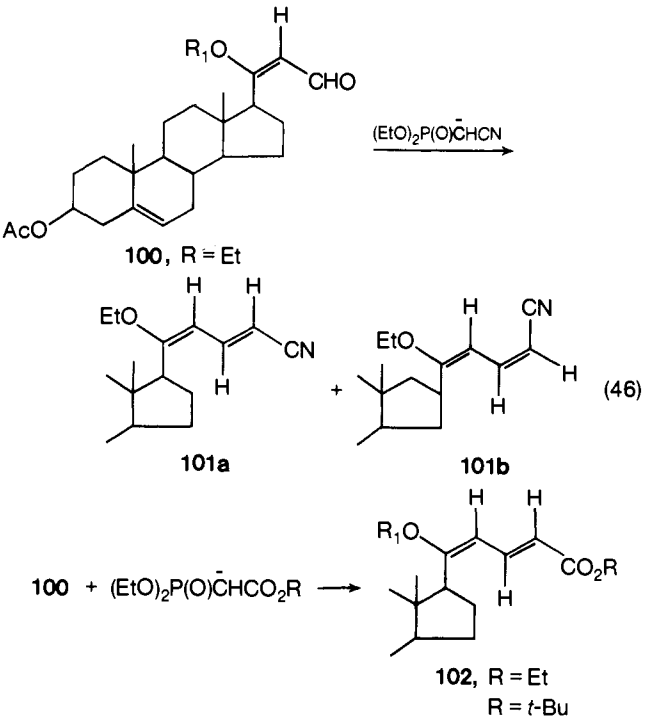
diethyl methoxycarbonylmethylphosphonate carbanion with 20-oxo-21-hydroxy steroids.[112]

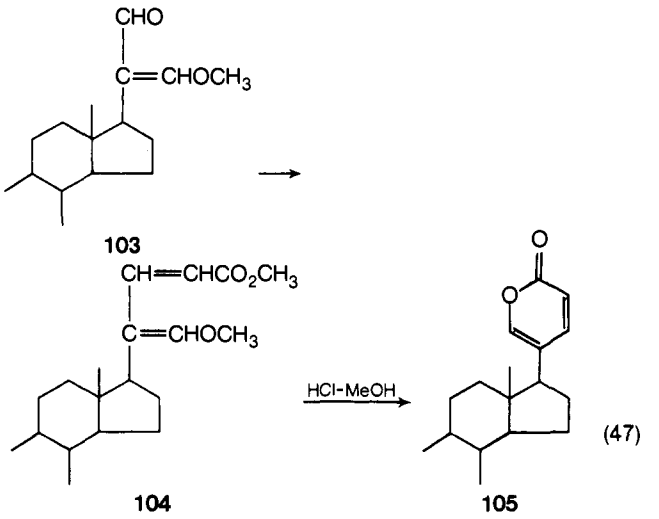
A more novel method for synthesis of unsaturated lactones was recently reported by Lehmann and Wiechert[113] where 20-oxo-21-acyloxy steroids (**98**) underwent intramolecular phosphonate condensation to form cardenolides (**99**) (eq 45). This method also opens up new possibilities for preparing unsaturated lactone derivatives of steroids with differing stereochemical features, and several compounds synthesized by this process have recently been patented.[114]



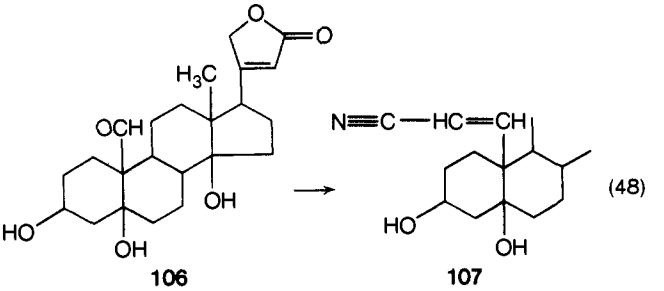
The reaction between phosphonate carbanions and some steroid aldehydes has been reported. Pettit, *et al.*,[115] examined the reaction between 20-alkoxy-21-formyl-c*i*s-20-pregnenes (**100**) and various phosphonate carbanions (eq 46) as part of the study in the synthesis of 14α-6′-isobufadienolides. It was noted that treatment of the aldehyde **100** with diethyl cyanomethylphosphonate anion gave the diene **101** as a mixture of cis and trans isomers of the new double bond in near equal proportions, while the more bulky phosphonate esters gave solely the corresponding trans isomer **102** (eq 46). By use of the modified Wittig condensation the syntheses of several steroids with a dienyl ester function at C-20, such as **102**, have been reported as potential antigonadotrophic and anabolic compounds.[116]

Radscheit, *et al.*,[117] have described a short synthesis of 14α-bufadienolides in which aldehyde **103** is treated with diethyl methoxycarbonylmethylphosphonate anion to give the unsaturated ester **104** which is then cyclized to the bufadienolide **105** (eq 47).



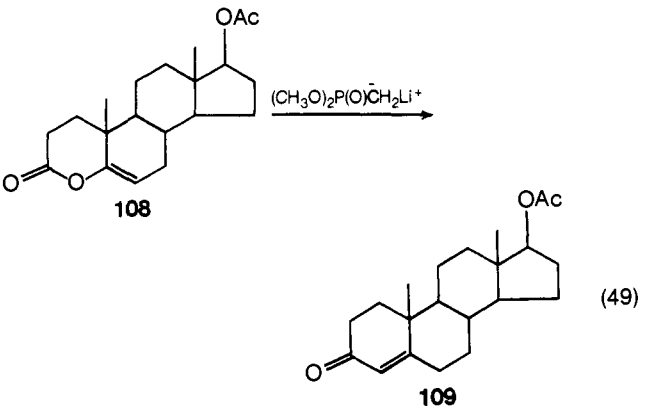


The C-10 cyanomethylene derivative (**107**) of strophanthidin obtained by olefination of the C-10 formyl group of strophanthidin (**106**) with diethyl cyanomethylphosphonate anion (eq 48) has recently been reported in the patent literature.[118] This compound was studied for its cardiotonic activity. The geometry of the C-19 cyanomethylene group was not stated.



The transformation of enol lactones to cyclic unsaturated ketones by reaction with phosphonium ylides, or phosphonate carbanions, as previously mentioned (Fried, *et al.*[97]), provides a useful method for the synthesis of steroids. A particular example is seen where the enol lac-

tone **108** is converted to testosterone acetate **109** by treatment with the unstabilized dimethyl methylphosphonate anion[28] in tetrahydrofuran at −78° (eq 49). A mechanism for the general reaction governing the transformation has been postulated by the authors. The potential utility for synthesis of 4-^{14}C steroids should be noted.



(49)

The authors of this review have recently made use of phosphonate carbanions to prepare a series of semisynthetic analogs of digitoxigenin in which the 17β-lactone ring has been replaced by a variety of α,β-unsaturated ester side chains and related structures with steric and electronic properties similar to those of the lactone moiety.[119-121] Further publications are being prepared, and this work will also be discussed in the review entitled Semi-Synthetic Cardenolides and Related Compounds which will be published in the *Journal of Pharmaceutical Sciences* during 1974.

VIII. Some Recent Applications

The following are a selection of significant reports which have come to the authors' notice subsequent to the submission of the original manuscript.

The preparation of α-bromo-4-nitrostilbenes by treatment of diethyl α-bromo-*p*-nitrobenzylphosphonate with aromatic aldehydes in the presence of an equivalent of sodium alkoxide in alcohol at room temperature has been reported.[122] A similar reaction with the use of 2 equiv of base gave the diphenylacetylene.

Keto olefins have been prepared by reaction of keto aldehydes with phosphonate carbanions.[123]

$$MeCO(CH_2)_nCHO + (EtO)_2P(O)\bar{C}HR \longrightarrow MeCO(CH_2)_nCH{=}CHR$$

$$n = 3,4;\ R = MeCO \text{ or } CH{=}CHCO_2Et$$

Condensation with the keto carbonyl group occurred when the corresponding keto acetal was treated with the phosphonate carbanion.

$$MeCO(CH_2)_nCH(OEt)_2 + (EtO)_2P(O)\bar{C}HR \longrightarrow RCH{=}CMe(CH_2)_nCH(OEt)_2$$

The stereochemistry of the reaction between fulvenic and related ketones with selected phosphonate carbanions has been studied by Rabinovitz, *et al.*[124] The product of condensation was found to contain a mixture of geometric isomers.

Endocylic and exocylic olefin formation from 4-piperidones *via* reaction with phosphonate carbanions (previously reported by other workers[94,125]) has been investigated by Borne and Aboul-Enein.[126] Factors affecting isomer distribution during the course of the reaction were discussed.

Popplestone and Unrau[127] have utilized a stereoselective reaction (trans olefination) between diethyl ethoxycarbonylmethylphosphonate and a steroidal ketone in the synthetic sequence to isoantheridiol.

IX. References and Notes

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