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Studies on the mechanism and stereochemistry of phosphonate anion condensations

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by

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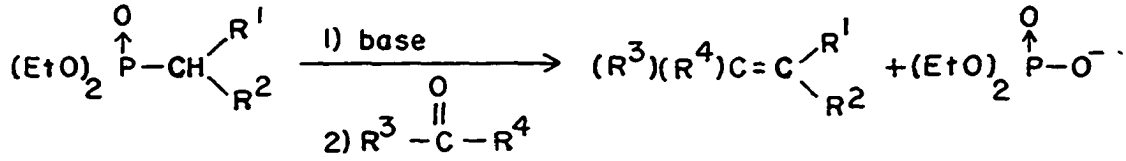
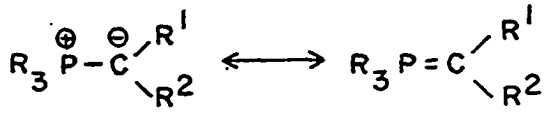
INTRODUCTION

The preparation of olefins by a convenient, general procedure has long been of interest. The Wittig reaction (1-7) has proved to be quite versatile in this respect.

In 1961, Wadsworth and Emmons (8) reported a synthesis which has a useful supplement to the well known Wittig reaction. They studied the reaction of phosphonate carbanions with aldehydes and ketones to produce olefins.



The phosphonate modification of the Wittig reaction has proved to be useful in preparing sensitive olefins not preparable by the standard Wittig reaction. The phosphonate anions have in many instances, advantages over the Wittig reagents (2). They are in most cases, much less expensive and they react with a wider variety of ketones and aldehydes usually under much milder conditions.



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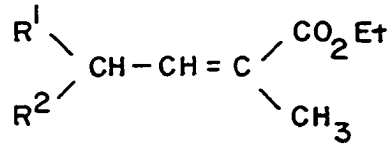
The stereochemistry of phosphonate ester condensations is of some interest. In their study, Wadsworth and Emmons did not attempt to determine the stereochemistry of their products but assumed that a mixture of cis- and trans-isomers were formed with subsequent equilibration of the mixture to the more stable trans-isomer. Since then several studies had

been made on the stereochemistry of this reaction. It has been reported (9) to invariably yield a great preponderance of the trans-isomer, even under solvent and structural conditions which should favor formation of the cis-isomer.

However in certain cases, significant amounts of the cis-isomer is also formed. Kinstle (10) made use of this reaction in the synthesis of unsaturated esters of the type:

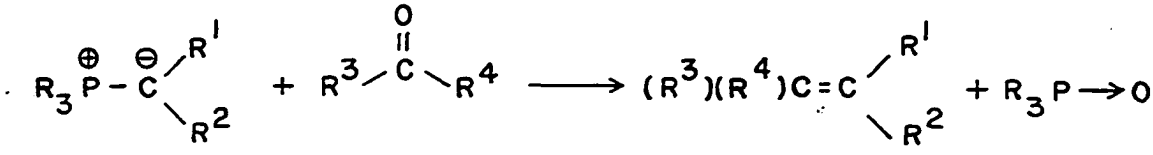


In his study, the cis-isomer was formed in larger amounts than the more stable trans-isomer.

The fundamental idea of this research is to explore the possibility of controlling the course and stereochemistry of this modification of the Wittig reaction through structural alterations in the phosphonate anion and the carbonyl compound. Our long range goal is to obtain an understanding of the nature of the factors controlling the course of this reaction and then to bring it to bear on specific synthesis reactions.

HISTORICAL

The Wittig reaction, in which carbonyl compounds are treated with alkylidene phosphoranes, has become one of the most universal methods for the synthesis of unsaturated compounds. The synthesis has been applied with outstanding success in many fields, e.g., carotenioids, polyenes, vitamins D, etc.



Lately carbanions prepared by the action of bases of phosphonates have also found use as olefinating agents. On the basis of the data available to date, it appears that the stereochemistry and mechanism of these two reactions are, in a gross sense, very similar. And in view of this interesting parallel between the reaction of phosphonium and phosphonate carbanions with carbonyl compounds, a brief review of the studies made on the stereochemistry and mechanism of the Wittig reaction will be made followed by a history of the development of the phosphonate modification of the Wittig reaction.

Wittig Reaction

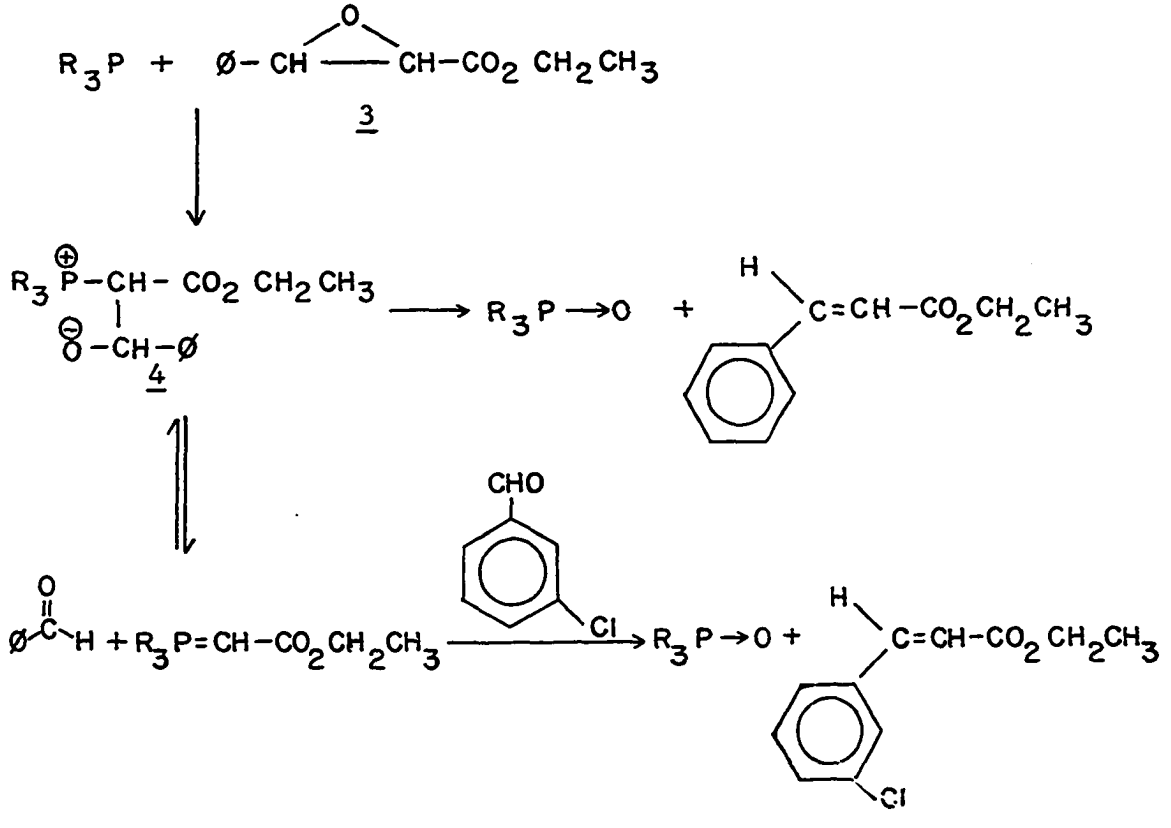
Phosphonium ylids have been broadly classified into "stabilized" and "nonstabilized" ylids. Differentiation between these two types of ylids is not clear-cut although the term "nonstabilized ylid", in general, refers to those ylids which are nonisolable while "stabilized ylid" refers to those which are isolable and contains a group through

which the negative charge at carbon may be delocalized.

Mechanism

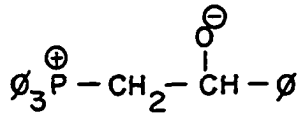
Stabilized ylids: A report by Speziale and Bissing (11) contains the result of an extensive study of the Wittig reaction involving stabilized ylids. Speziale and Bissing provided evidence for the reversibility of betaine formation. They treated cis- and trans-ethyl phenylglycidate (3) with tributyl- and triphenyl-phosphine in refluxing ethanol in the presence of m-chlorobenzaldehyde and obtained a mixture of ethyl cinnamate and ethyl m-chlorocinnamate. The presumed intermediate (4) can eliminate phosphine oxide to form ethyl cinnamate or dissociate to

Scheme 1



benzaldehyde and ylid which is then free to react with m-chlorobenzaldehyde (Scheme 1). They found that the reaction of carbomethoxymethylenetriphenylphosphorane with a series of aromatic aldehydes was cleanly second order - first order in each of ylid and aldehyde. They established that the rate of disappearance of the ylid was the same as the rate of olefin formation. They also noted that the reaction rate is increased by increasing solvent polarity, i.e., the rate of the reaction is about 5-6 times faster in chloroform than in benzene and about a thousand times faster in methanol than in benzene. These observations are consistent with a mechanism involving a reversible formation of a polar betaine in the slow step of the reaction followed by a fast decomposition to olefin and phosphine oxide. Additional support for this mechanism is obtained from the facts that the ρ value is found to be +2.7 which is comparable to the ρ value of reactions known to involve nucleophilic addition to a carbonyl group; and substitution in the ylid of tributyl for triphenyl increases the rate of reaction while substitution of α-halogen in the ylid decreases the reaction rate.

Nonstabilized ylids: The question of reversibility of formation of betaines derived from nonstabilized ylids is somewhat ambiguous. Earlier, it was reported by Wittig, et al. (12) that heating 5 in the presence of benzophenone gave triphenyl phosphine oxide and styrene and only "trace amounts" of 1,1-diphenylethylene. From this observation, Wittig concluded



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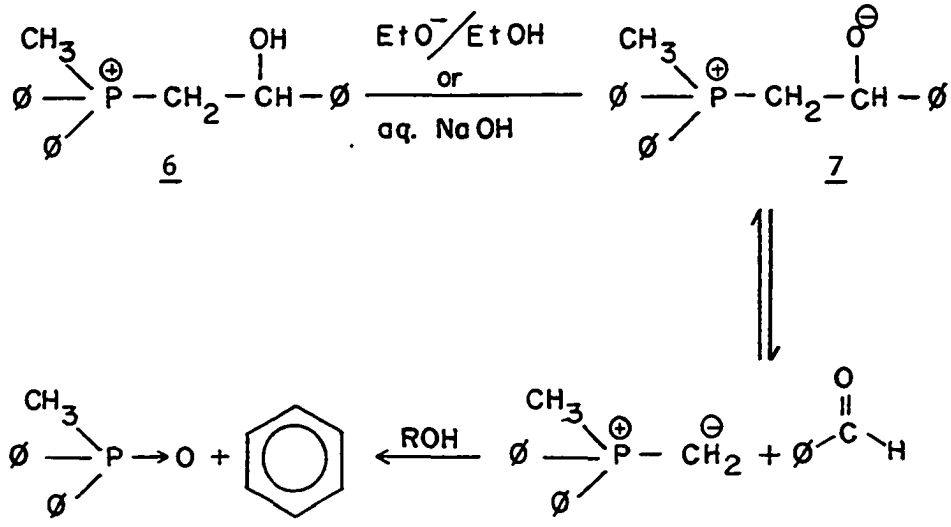
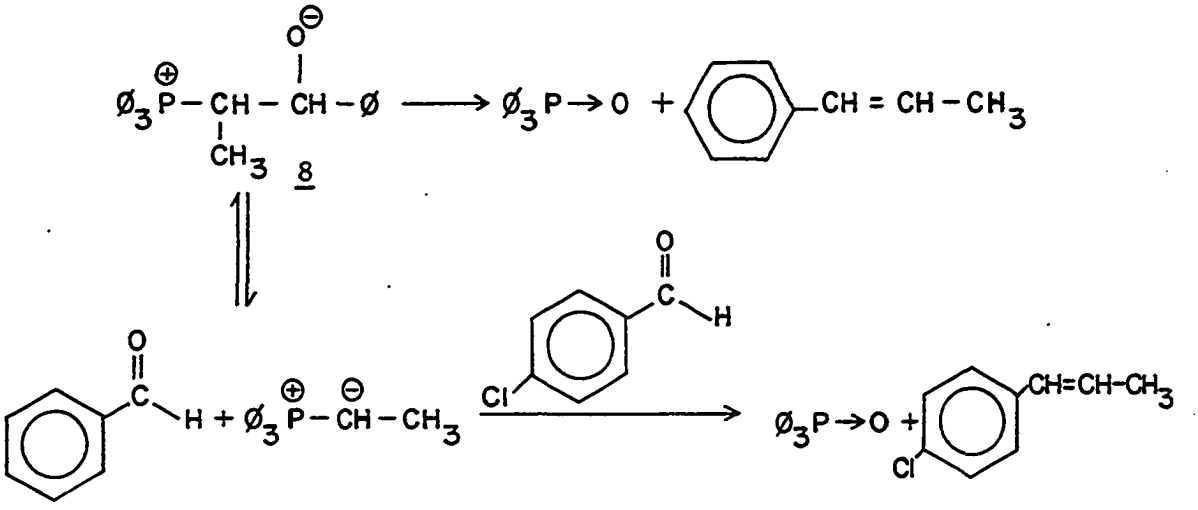
that betaine formation was irreversible. Recently, Trippett (13, 14) reported generating betaine 7 by treatment of (2-phenyl-2-hydroxy) ethyldiphenylmethylphosphonium iodide (6) with either sodium ethoxide in ethanol or aqueous sodium hydroxide (Scheme 2). In both instances

Scheme 2



only dimethylphenylphosphine oxide and benzaldehyde could be isolated, perhaps indicating that the betaine reverted to ylid and aldehyde. The ylid is then hydrolyzed by the alcohol. However, Schlosser (7) found that betaine formation is irreversible in the reaction of triphenylphosphonium alkylid and primary aliphatic aldehydes. Schlosser and Christmann (15, 16) have shown that betaine formation is partially reversible in the reaction of ethylidenetriphenylphosphorane with α, β-unsaturated- and aromatic-aldehydes. When they added ρ-chlorobenzaldehyde to a suspension in benzene or a solution in ether- t-butanol of the betaine (8), ρ-chloro-β-methylstyrene was formed in addition to β-methylstyrene (Scheme 3). Fliszar, et al. (17) were able to isolate betaine 5 and they followed its

Scheme 3

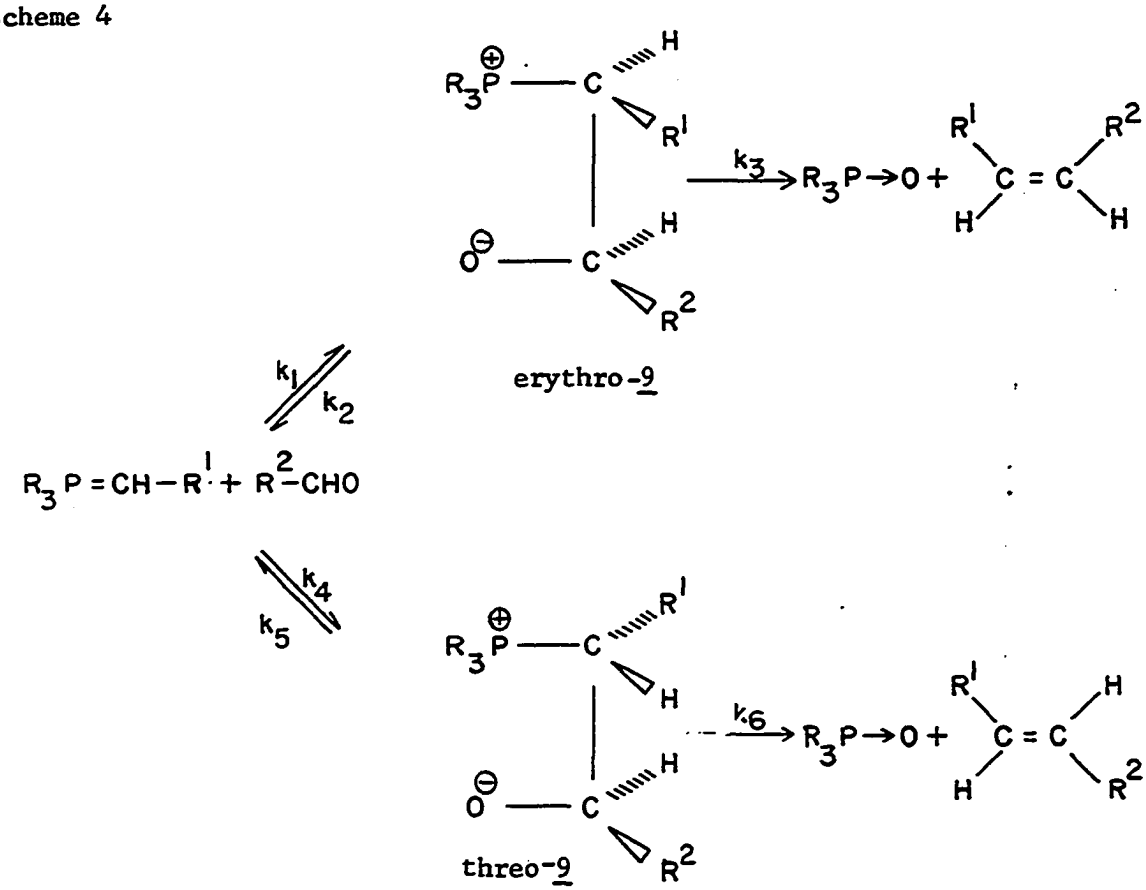


reversal to benzaldehyde and ylid by monitoring the benzaldehyde concentration by IR. They observed that at low temperatures the betaine reverted to ylid and benzaldehyde and that heating to higher temperatures was needed to obtain the olefin and phosphine oxide. They then concluded that in this case, betaine decomposition was the slow step of the reaction. However, Bergelson, et al. (18, 19) have interpreted their results to indicate that the rate-determining step is betaine formation, even in the case of nonstabilized ylids.

Stereochemistry

One of the main virtues of the Wittig reaction is its structural specificity in the sense that the double bond created by the reaction appears exclusively at the site of the former carbonyl function. Despite this structural specificity, the Wittig synthesis can lead to the formation of cis- and trans-olefins (Scheme 4). In discussing the factors affecting the stereochemistry of the reaction, it is convenient again to deal separately with the extreme cases of "stabilized" and "nonstabilized" ylids.

Scheme 4



Stabilized ylids: Using the steady state approximation for the formation of the erythro- and threo-betaines (9), one can write equations 1 and 2 for the formation of the cis- and trans-olefins, respectively.

$$\frac{d(cis)}{dt} = \frac{k_1 k_3 (ylid)(aldehyde)}{k_2 + k_3} \qquad \text{Equation 1}$$

$$\frac{d(trans)}{dt} = \frac{k_4 k_6 (ylid)(aldehyde)}{k_5 + k_6} \qquad \text{Equation 2}$$

If we assume that d(cis)/d(trans) = (cis)/(trans), then

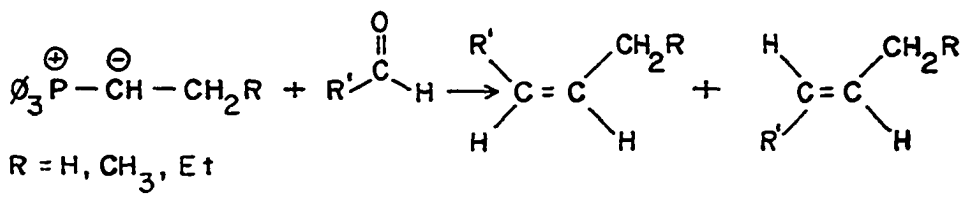
$$(cis)/(trans) = k_1 k_3 \ (k_5 + k_6)/k_4 k_6 \ (k_2 + k_3) \qquad \text{Equation 3}$$

The results obtained by Speziale and Bissing (11) make it possible to interrelate the various rate constants. They found that the reaction of carbethoxymethylenetriphenylphosphorane with benzaldehyde gives the ethyl cinnamates in a trans/cis ratio of 84:16. Generation of erythro-9 (R = phenyl, R' = CO_2Et, R^2 = phenyl) by heating ethyl trans-phenylglycidate with triphenyl phosphine, in the presence of a three molar excess of m-chlorobenzaldehyde gave a mixture of ethyl m-chlorocinnamates and ethyl cinnamates in a ratio of 33.5/66.5. If it is assumed that the ylid formed by the dissociation of the intermediate erythro-9 is immediately trapped by the more electrophilic m-chlorobenzaldehyde, then the ratio of m-chlorocinnamates to cinnamates could be taken as a measure of k_2/k_3. This result therefore indicates that $k_2/k_3 = 0.5$, i.e., the rate of decomposition of the erythro-betaine is twice as fast as its dissociation. The analogous experiment with ethyl cis-phenylglycidate gave a k_5/k_6 of 0.15, i.e., the rate of decomposition of the threo-betaine is 6.7 times the rate of its dissociation. If we substitute these experimental values into Equation 3, it can easily be shown that the threo-betaine is formed four times faster than the erythro-betaine. If one assumes that the rate of dissociation of the erythro- and threo-betaines are the same (i.e., $k_2 = k_5$), then, it can be shown that betaine decomposition is faster for the threo-betaine than for erythro-betaine ($k_6 = 3.3k_3$). On the other hand, if one assumes that the rate of decomposition of the erythro- and threo-betaines are the same (i.e., $k_3 = k_6$), then it would follow that the rate of betaine dissociation is faster for the erythro-betaine than the threo-betaine ($k_2 = 3.3k_5$). From these calculations, one can conclude that in the case of stabilized ylids,

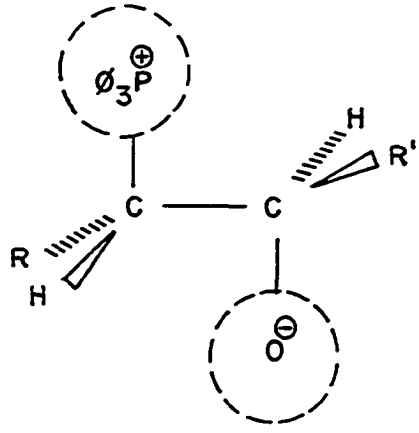
the ratios of the rate constants involved are in the direction that favors the dominance of the trans-olefin and the major factor controlling the stereochemistry of the reaction is the relative rate of betaine formation.

Nonstabilized ylids: The situation regarding the stereochemistry of the Wittig reaction with nonstabilized ylids is not as clear as for stabilized ylids. While stabilized ylids react with aldehydes to give almost exclusively trans-olefins, it has become apparent that nonstabilized ylids often give predominantly the thermodynamically less stable cis-olefins (4, 20-23).

Immediately after mixing triphenylphosphonium-ethylid and n-propylid with benzaldehyde at 0°C, Schlosser (7) found a ratio erythro/threo betaines of 90:10 and 96:4, respectively. If betaine formation is irreversible, the cis/trans ratio strictly reflects the erythro/threo ratio of the intermediate betaines. Even in the case of partial reversibility, the cis/trans ratio of olefins still allows a fair estimate on the distribution of betaine diastereoisomers. It has been found that the cis/trans ratios for the reaction of nonstabilized ylids with aliphatic and aromatic aldehydes indicate a great preference for the formation of cis-olefins. Homologous unbranched triphenylphosphonium alkylids actually yield an average cis/trans ratio of 95:5 (7).



The predominant formation of the erythro-betaines and cis-olefins when the reaction is run in polar solvents has been explained by Bergelson and Shemyakin (20) in terms of solvation of the phosphorus and oxygen of the betaine. For the solvated betaine, the most stable conformation is that with the solvated groups situated trans with respect to each other. In such a conformation the erythro-betaine is more stable than the threo-betaine. So that under these conditions, the erythro-betaine becomes the



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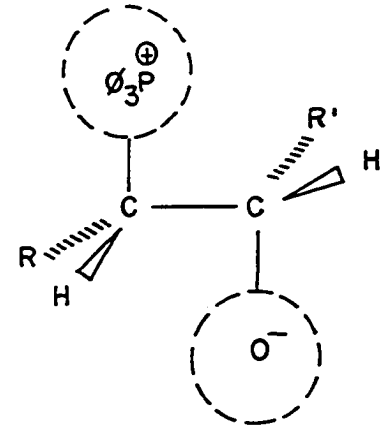
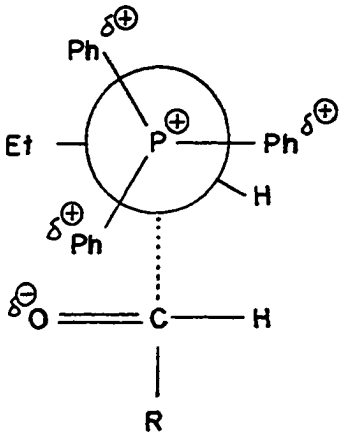


threo

energetically preferred isomer, the threo-isomer being destabilized by steric repulsion of the skewed R and R' substituents. However, no convincing explanation has yet been given for the preferred formation of the less stable erythro-betaines and cis-olefins in the reaction of non-stabilized ylids with aldehydes in nonpolar media. Bergelson, et al. (19, 22) have attributed the preferred formation of the erythro-betaine to attraction of the carbonyl oxygen to one of the electron-deficient phenyl groups attached to the phosphorus in the ylid. In the transition state leading to the erythro-betaine, 10, these groups are much closer than in the transition state leading to the threo-betaine, 11.



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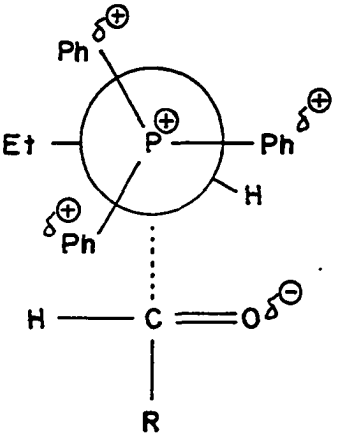

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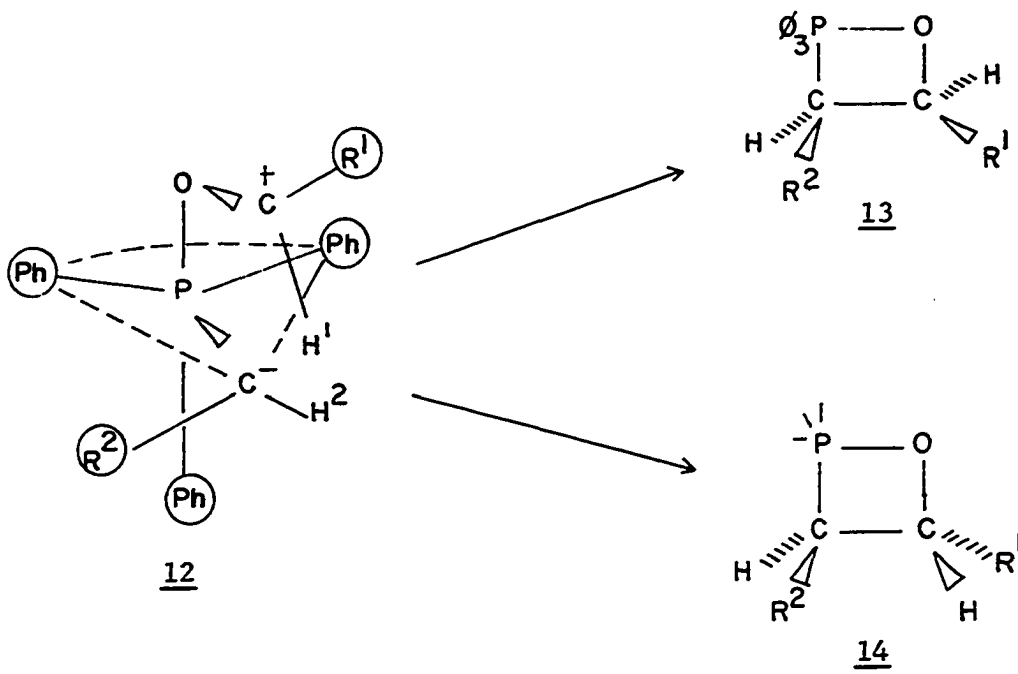
Quite another approach has been discussed by Schneider (24) who argues on the basis of an assumed initial attack of the carbonyl oxygen atom on the ylid phosphorus atom. He considered a model using a trigonal-bipyramidal phosphorus with oxygen complexed at an apical position and with the ylid carbon at an equatorial position (12). The bulky aldehyde alkyl group is directed upwards, away from the equatorial substituents around phosphorus and the hydrogen is directed downwards into the least crowded trisection of the equatorial plane. Counterclockwise rotation about the C^{+}-O bond and subsequent bond formation between C^{+} and C^{-} leads to the formation of the immediate precursor to the cis-olefin (13). The alternate (clockwise) mode of rotation about the C^{+}-O bond to give the precursor to the trans-olefin (14) results in serious interaction of R' with the closest equatorial phenyl group.

Several arguments have been raised against this proposal. If this proposal were correct, the rate of reaction ought to be increased when an aldehyde carrying a more nucleophilic oxygen was used. However it has



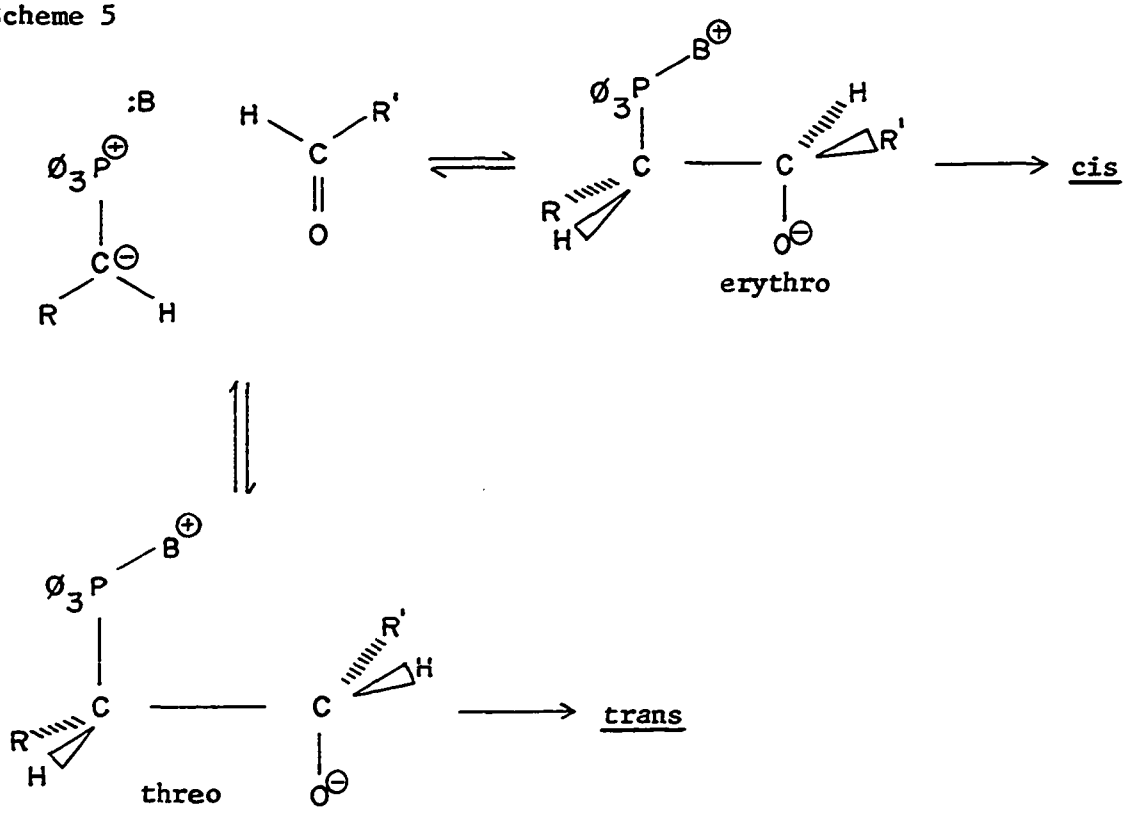
12 13 14

been found by Speziale and Bissing (11) that the carbonyl compounds with the more nucleophilic oxygen are the least reactive, i.e., p-nitrobenzaldehyde is much more reactive than p-dimethylaminobenzaldehyde or p-anisaldehyde. In addition, the linear Hammett plot with a ρ value of +2.7 is convincing evidence that the carbonyl group of the benzaldehydes must be undergoing nucleophilic attack on carbon.

Bergelson, et al. (22, 25) have reported on the effect of solvent and of additives on the cis/trans ratio of isomers. They studied, in particular, the formation of 1-phenyl-1-butene from benzylidenetriphenylphosphorane and propionaldehyde and from propylidenetriphenylphosphorane and benzaldehyde. In both cases, the proportion of cis-olefin produced increased with increasing polarity of solvent (i.e., benzene < ether < THF ~ ethanol ~ DMF) and increases markedly on addition of nucleophilic Lewis bases to the reaction mixture. Reactions carried out in DMF containing

lithium iodide gave almost pure cis-olefins. It was suggested that the Lewis base interacts with the positive charge on the ylid phosphorus thereby reducing the relative importance of dipole interaction. In this case, the mechanism may be represented as in Scheme 5. The steric

Scheme 5



repulsion between R and R' is minimal in the erythro-betaine and so the cis-olefin is preferentially formed.

However, House, et al. (26) obtained results which were substantially different from the results of the Russian workers. Their results indicated that there was some enhancement of the proportion of cis-isomer in the presence of inorganic salts but the effect of the halides was attributed only to the influence of the Lewis acid (i.e., coordination of the cation

with oxygen). And in no case were they able to obtain the very high proportion of cis-olefin reported by Bergelson and co-workers (27).

In 1967, Bergelson, et al. (18) made another study on the variation of isomer ratio in the Wittig reaction with solvent and various additives. They made a comparative study of the following four reactions (Equations 4 - 7):

$$CH_3CH_2CHO + \emptyset_3P = CH\ CH_2CH_3 \longrightarrow CH_3CH_2\text{-}CH = CH\text{-}CH_2CH_3 + \emptyset_3P \rightarrow O \quad \text{Equation 4}$$

$$\emptyset\text{ - }CHO + \emptyset_3P = CH\ CH_2CH_3 \longrightarrow \emptyset CHO = CH\text{-}CH_2CH_3 + \emptyset_3P \rightarrow O \quad \text{Equation 5}$$

$$CH_3CH_2CHO + \emptyset_3P = CH\text{-}\emptyset \longrightarrow CH_3CH_2CH = CH\text{-}\emptyset + \emptyset_3P \rightarrow O \quad \text{Equation 6}$$

$$\emptyset\text{ - }CHO + \emptyset_3P = CH\text{-}\emptyset \longrightarrow \emptyset CHO = CH\text{-}\emptyset + \emptyset_3P \rightarrow O \quad \text{Equation 7}$$

The data they obtained in the presence of inorganic halides were not in agreement with House's conclusion. House and co-workers (26) have contended that the effect of the halides is due only to the influence of the Lewis acid and is independent of the nature of the Lewis base. They based their conclusion on the observation that the anion does not affect the stereochemistry of Equation 6 when run in DMF. However, Bergelson, et al., have found that in this solvent, the steric course of the reaction is also independent of the cation. When the reactions were carried out in nonpolar solvents, the stereochemical effect of lithium halide was found to definitely depend on the nature of the halogen anion and also on the nature of the ylid. For the first two reactions (Equations 4 and 5), the presence of LiI increases the % trans-olefin formed whereas for the next two

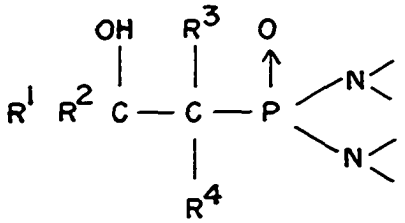
reactions (Equations 6 and 7) the same salt causes an increase in the % cis-olefin. It was suggested that in the case of the semi-stabilized ylid (Equations 6 and 7) the salt coordinates with the intermediate betaine and such coordination promotes the formation of the erythro-betaine. In the case of the nonstabilized ylid (Equations 4 and 5), the coordination of the LiI with the betaine so retards the decomposition of the betaine into the olefins that this stage becomes the rate determining step. Consequently, the stereochemistry of the reaction comes now under thermodynamic control with resultant increase in the trans-isomer.

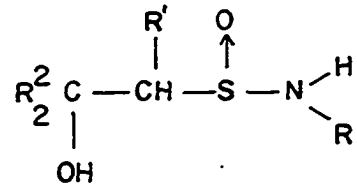
Phosphonate Modification of the Wittig Reaction

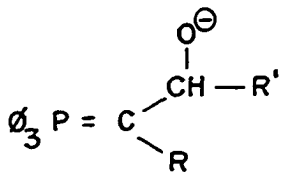
Although the Wittig reaction has found wide application in practical organic synthesis, it has some rather important limitations. For example, stabilized ylids in many cases do not react with ketones under the usual reaction conditions or only reacts under severe conditions, i.e., by heating the components for many hours at 100 - 170^{o} in sealed tubes, or high boiling solvents. In this connection, development and modification of the Wittig reaction is of considerable interest.

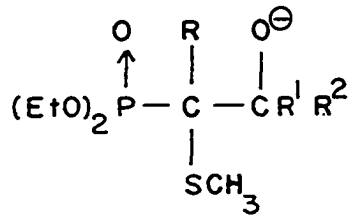
There have been several modifications of the Wittig reaction. Among these modifications are the thermal decomposition of β-hydroxyphosphonamides (15) (28-30), of β-hydroxysulfinamides (16) (31-33), of β-oxidophosphonium ylids (17) (34-37), and of (1-methylthio) alkylphosphonate esters (18) (38).

A modification of the Wittig reaction which we will be mainly concerned with involves the reaction of phosphonate carbanions with

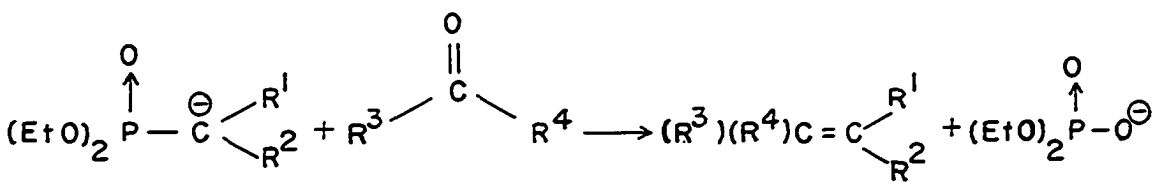
15 

 16

17 

 18

carbonyl compounds to form olefins. The phosphonate anions are, in most cases, more readily accessible less expensive, and more reactive than the



1a. $R' = CO_2Et$ $R^2 = H$

1b. $R' = CO_2Et$ $R^2 = CH_3$

1c. $R' = CO_2Et$ $R^2 = Et$

1d. $R' = CO_2Et$ $R^2 = Br$

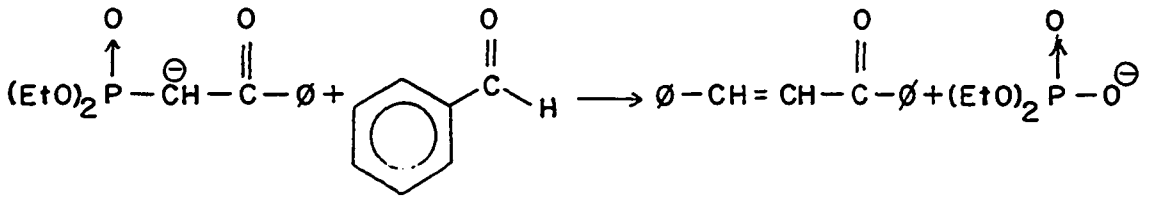
1e. $R' = CO_2Et$ $R^2 = Cl$

1f. $R' = CoI$ $R^2 = H$

1g. $R' = CoI$ $R^2 = CH_3$

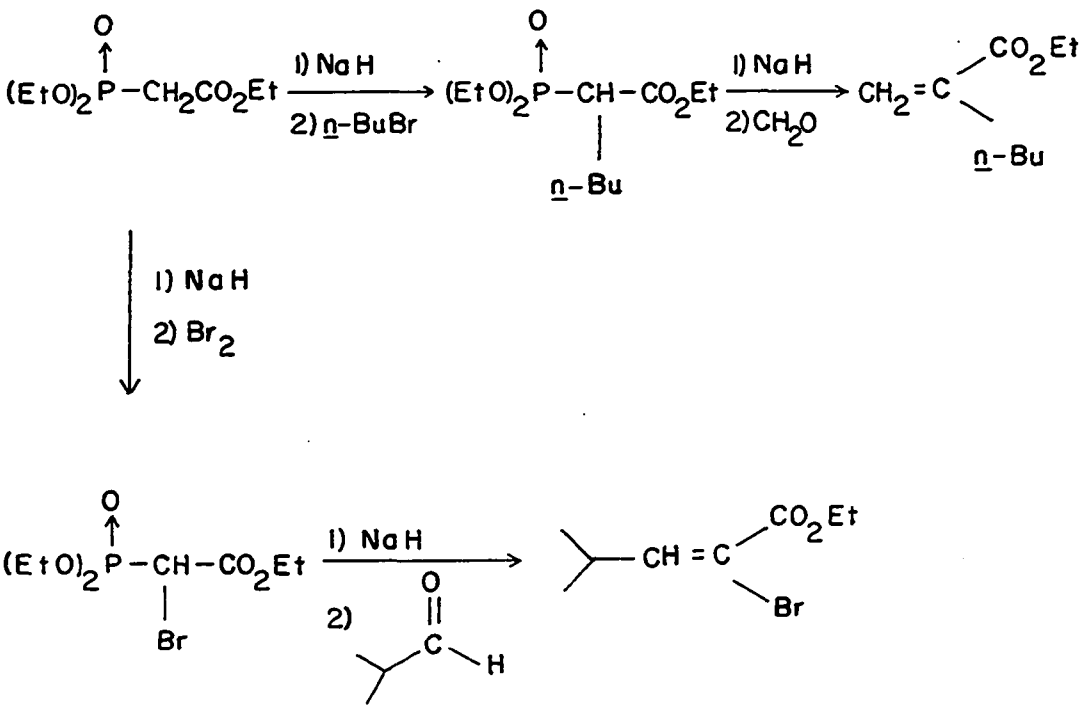
corresponding phosphonium ylids. For example, Trippett and Walker (39) indicated that the carbanion of triethyl α-phosphonoacetate (1a) would react with most ketones whereas carbethoxymethylenetriphenylphosphorane would not. Also, whereas the reaction of phenacylidenetriphenylphosphorane with benzaldehyde has been carried out by refluxing the reagents in THF

for thirty hours, the analogous reaction using diethyl phenacylphosphonate anion was exothermic at room temperature and gave comparable yields of olefin after immediate work-up.



In 1961, Wadsworth and Emmons (8) carried out a broad study of the use of phosphonate carbanions in olefin synthesis. Using a slurry of sodium hydride in DME to generate the carbanion from a variety of alkyl diethyl phosphonates, they were able to effect reaction with both aldehydes and ketones under mild conditions to obtain high yields of olefins. They also showed that alkylation and halogenation of the phosphonate could be carried out easily and the phosphonate so obtained could be used, without isolation,

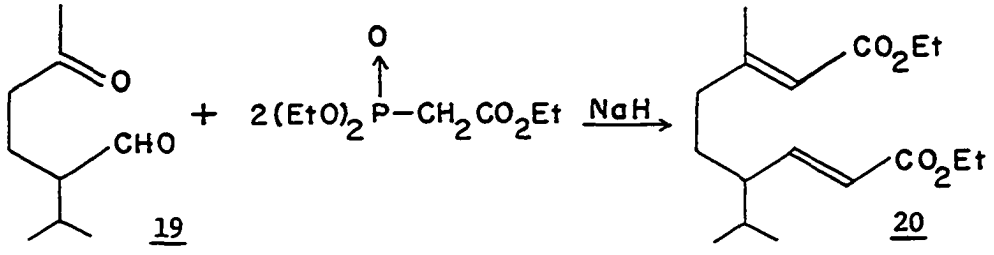
Scheme 6



in olefin synthesis (Scheme 6).

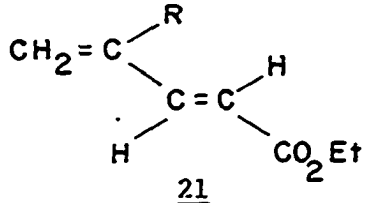
In early works (8, 40-42) on the phosphonate modification of the Wittig reaction initiated the use of this reaction in the preparation of a wide variety of compounds.

M. Brown (43) observed that condensation of the keto-aldehyde 19 with two equivalents of triethyl α-phosphonoacetate afforded the bis-unsaturated diester 20.



19 20

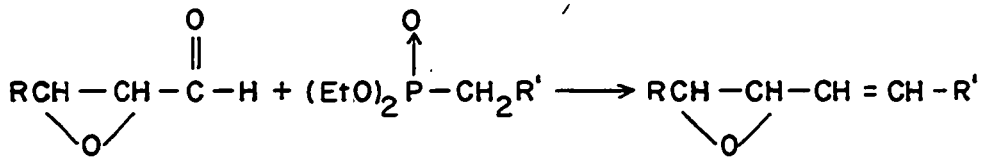
4-Alkyl-2,4-pentadienoates (21) were prepared by this method in 50-65% yield using 2-alkylacrolein and triethyl α-phosphonoacetate (44).



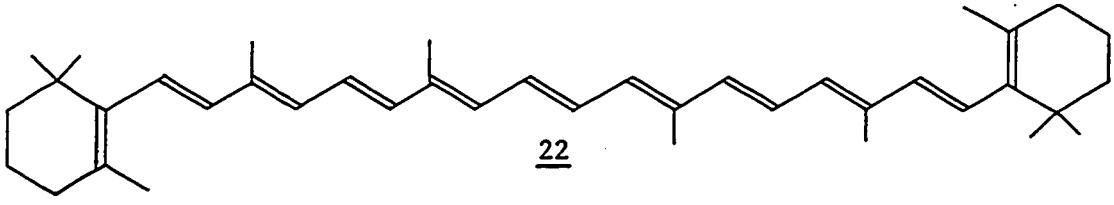
21

The configurational isomers were examined by nmr and from the observed coupling constants (15-16 cps) only the trans-esters were formed with no trace of the cis-esters.

The phosphonate modification of the Wittig reaction was also used to prepare functionally substituted α, β-unsaturated epoxides. Kozyrkin, et al. (45) found that phosphonate carbanions react smoothly with 2,3-epoxy aldehydes to form the desired products.

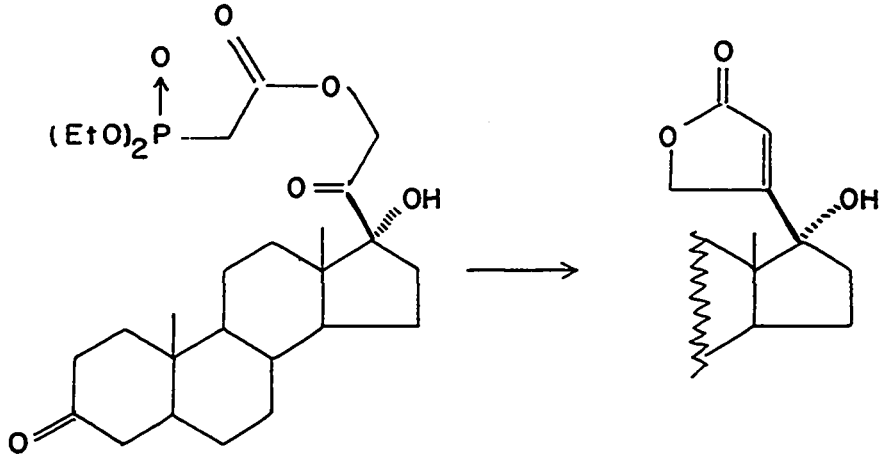


It has also been used to prepare acetylenes, dienes, trienes, and polyenes (46-55). β-carotene (22), a very important and most widely distributed plant pigment could be prepared by this modification. Pommer (56) had shown that this method is superior compared with the Wittig reaction in terms of fewer steps and availability of starting materials.



22

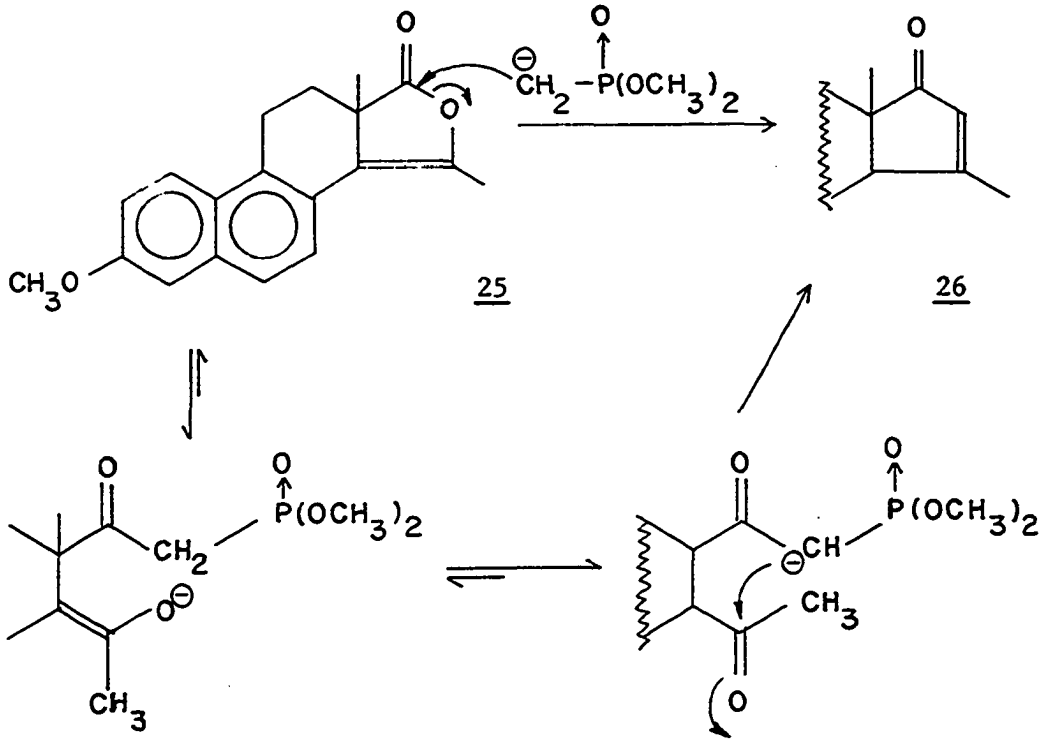
Lehman and Wiechert (57) reported the first example of an intramolecular phosphonate condensation. 23 in the presence of potassium carbonate in refluxing t-butanol gave the cardenolide 24.



23 24

The phosphonate approach has also provided a new and useful methodology for the synthesis of steroids. Henrick, et al. (58) utilized the carbanion of dimethoxymethylphosphonate to convert the enol lactone 25 to the enone 26. The production of 26 has been explained in terms of the mechanism shown in Scheme 7.

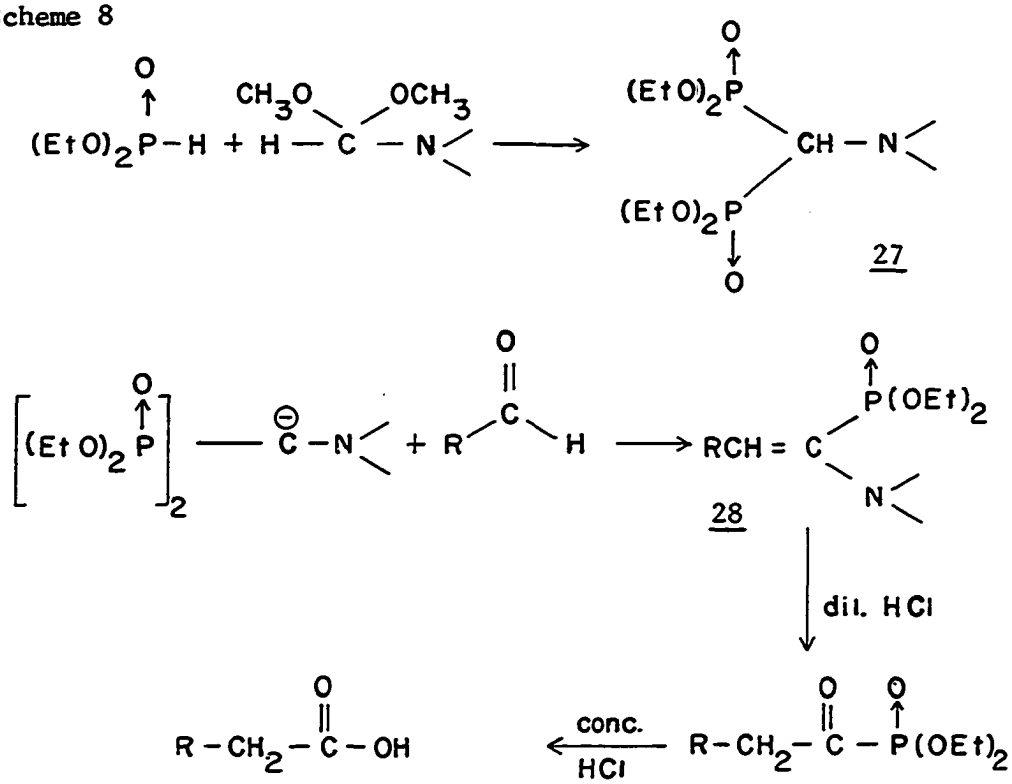
Scheme 7



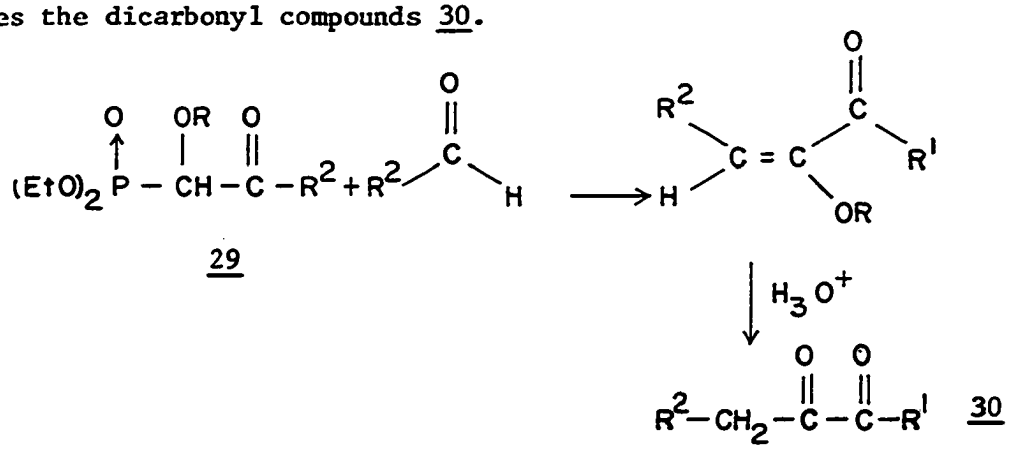
A rather interesting application of the phosphonate reaction was reported by Gross and Cortisella (59). They prepared tetraethyl dimethylaminomethylene phosphonate (27) by reacting diethyl phosphite with dimethylformamide acetal. Reaction of 27 with various aldehydes followed by treatment with dilute HCl gives the acyl phosphonate (28). Acidic hydrolysis of 28 gives the corresponding acid. This sequence of reactions enables one to synthesize carboxylic acids from aldehydes containing one less carbon atom (Scheme 8).

In the same vein, Grell and Macleidt (60) prepared phosphonates of the type 29. Reaction of the carbanions of these phosphonates with

Scheme 8

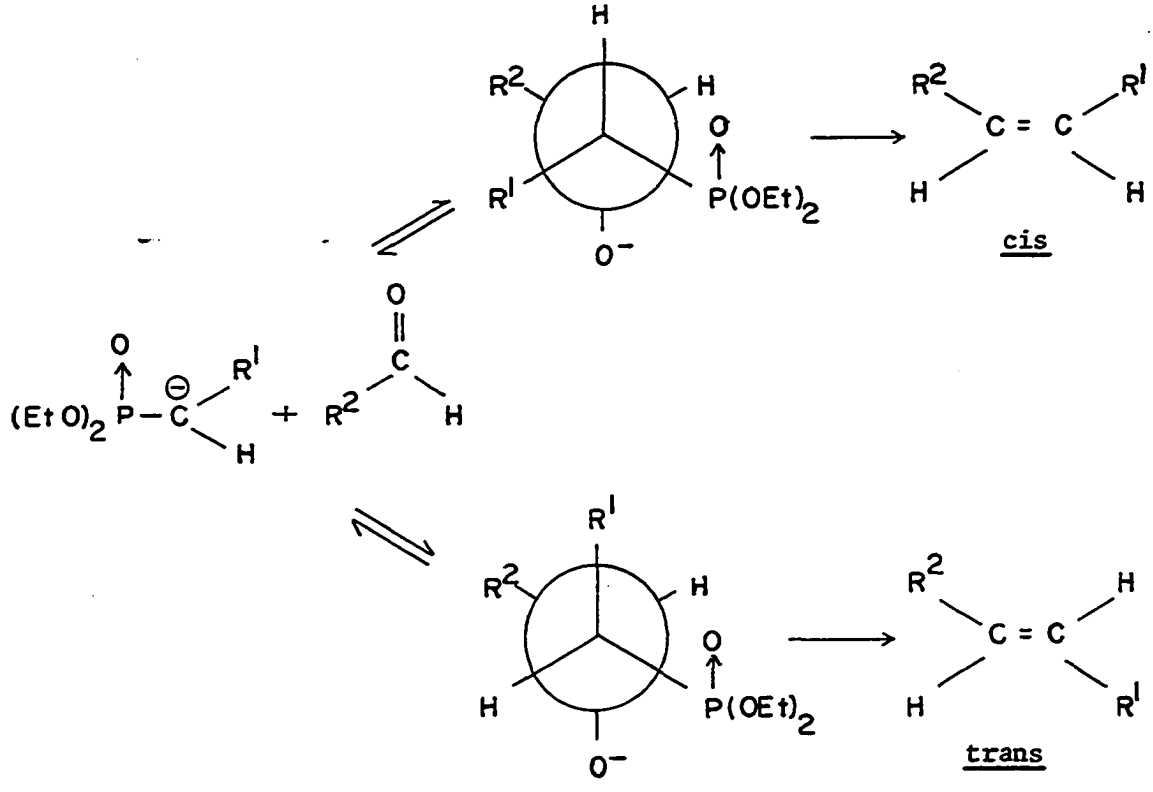


aldehydes results in the formation of enol ethers which upon hydrolysis gives the dicarbonyl compounds 30.



There has been very little work done on the mechanism of the phosphonate modification of the Wittig reaction. It has been assumed that the reaction occurs via the mechanism indicated in Scheme 9.

Scheme 9

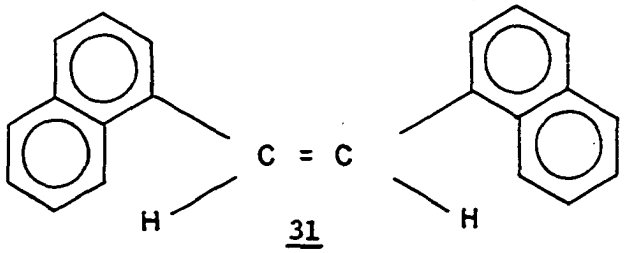


The stereochemistry of the olefin formation has not been clarified adequately. In most of the cases studied so far, the trans-olefin is formed predominantly.

Yanovskaya and Kucherov (61) observed that the reaction of triethyl α-phosphonoacetate with aldehydes is stereospecific and yields only the trans-isomers.

Factors which affect the steric nature of the products from the Wittig reaction does not seem to affect the stereochemistry of the phosphonate reaction. Wadsworth, et al. (9) observed that the use of sterically and electronically different starting materials has produced only minor changes in the stereospecific nature of the reaction. In the many cases that they studied in only one case was a significant amount of cis-isomer formed

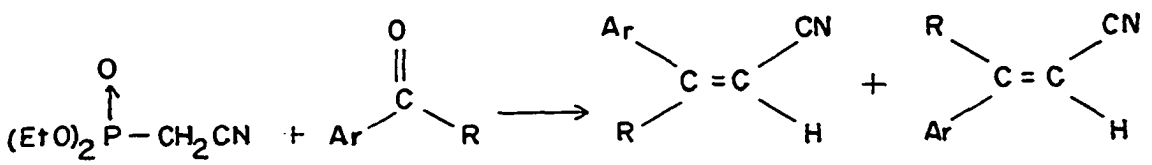
(6.4% cis-1,2-(1,1'-dinaphthyl) ethylene (31) in a 1:10 cis-trans mixture).



31

It has also been shown by Bergelson and Shemyakin (62-64) that altering the reaction media and the presence of Lewis-base additives are ineffective in changing the tendency of the reaction to produce trans-olefins. For example, they found that when the solvent used in the reaction between diethylbenzylphosphonate with benzaldehyde was changed from DMF to cyclohexane, the % cis-olefin only changed from 2% to 6%.

Recently Jones and Maisey (65) have studied the stereochemistry of the reaction between diethyl α-phosphonoacetonitrile (1f) and a series of alkyl phenyl ketones. They have shown that the amounts of cis-isomer



1f cis trans

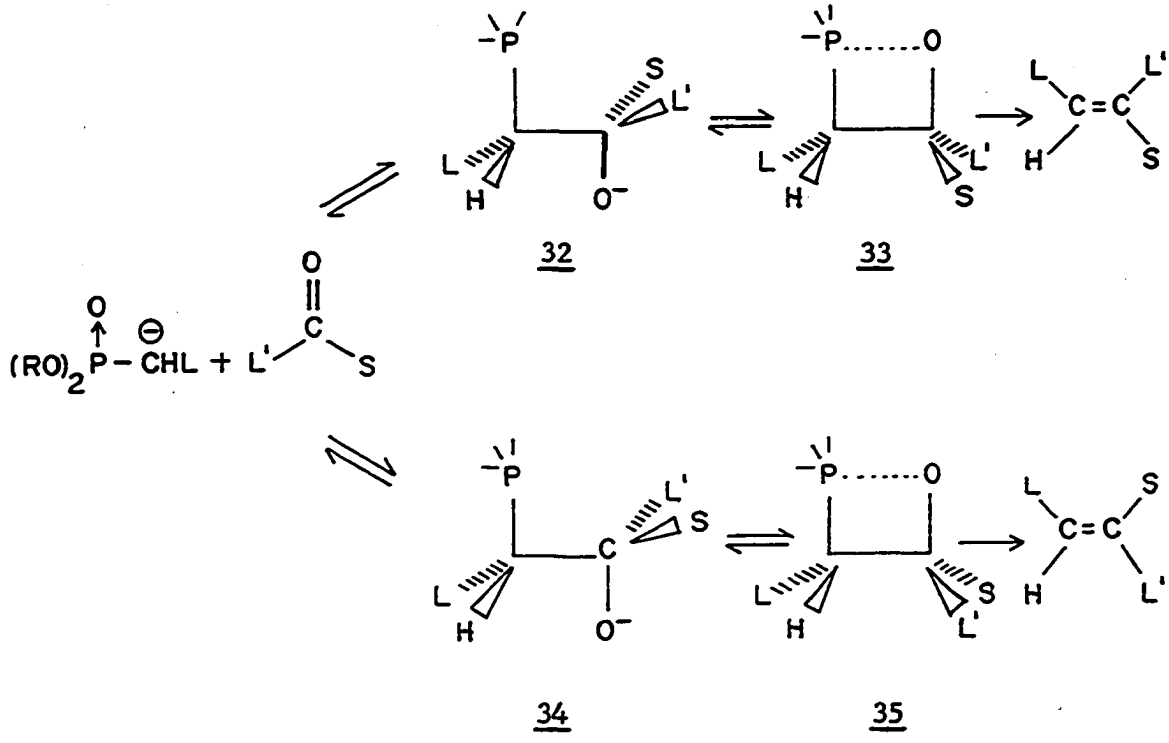
formed were dependent on the structure of the aryl ketone used, particularly its steric bulk.

RESULTS AND DISCUSSION

The condensation of phosphonate carbanions with carbonyl compounds has been reported to invariably yield a great preponderance of trans-olefin.

Attempts have been made to increase the proportion of cis-olefin by means of structural and environmental variation. From the reaction path proposed by Wadsworth and Emmons (8) (Scheme 10) several schemes were devised which might increase the amount of cis-products.

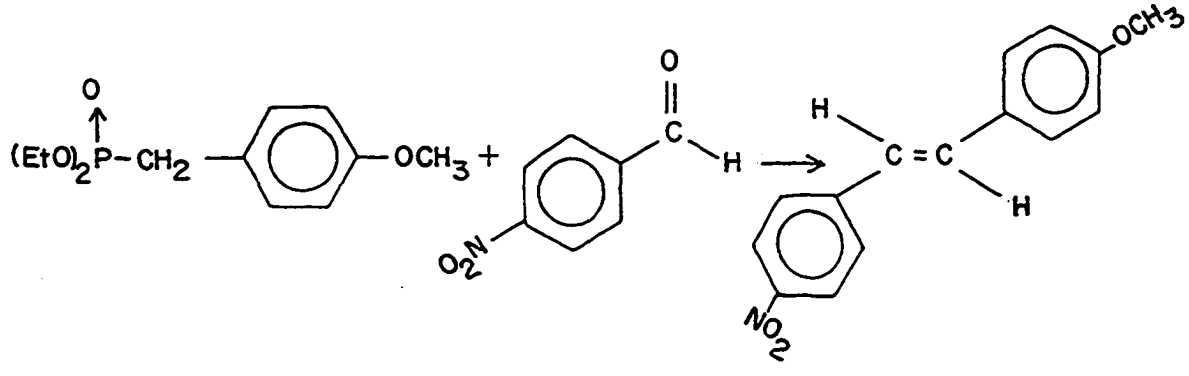
Scheme 10



L and L' = large groups; S = small group

One scheme attempted by Wadsworth and co-workers (9) was to use starting materials with large bulky groups. They were hoping that with these large groups, 32 would be preferentially formed due to steric factors and more of the cis-olefin would be formed. But upon using 1-naphthaldehyde and dimethyl 1-naphthylmethylphosphonate they only obtained 7-9% of the cis-olefin.

It was also thought that by the use of a reactive phosphonate carbanion and an electrophilic carbonyl compound, kinetic control of stereochemistry may be achieved. However, with p-nitrobenzaldehyde and diethyl p-methoxybenzylphosphonate, only trans-4-methoxy-4'-nitrostilbene was obtained.

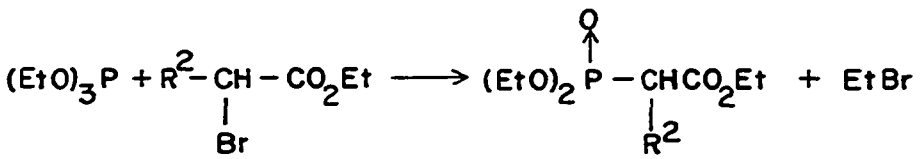


In fact, the methods which were used successfully in the "normal" Wittig reaction to increase the amount of cis-products were found to be ineffective in the phosphonate modification of the Wittig reaction.

It was noted that at this time attempts have been focused mainly on the variation of substituents on the carbonyl compound and all the stereochemical studies on the phosphonate modification of the Wittig

reaction had employed phosphonate esters with only a single α-substituent.

It was of interest then to investigate whether the introduction of an additional α-substituent in the phosphonate ester would affect the stereochemical course of the reaction. The phosphonate esters were prepared by the Michaelis-Arbusov reaction (66) wherein the appropriate α-bromoester is refluxed with triethyl phosphite to yield the phosphonate esters.



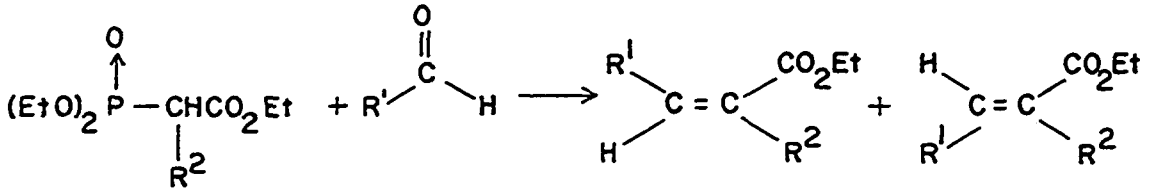
1b. $R^2 = CH_3-$

1c. $R^2 = CH_3CH_2-$

We first examined the reaction of triethyl α-phosphono-acetate (1a) and -propionate (1b) with a series of aliphatic aldehydes and our results are summarized in Table 1 (67).

Our synthetic method involved the slow addition of a slight excess of the aldehyde to a DME solution of the phosphonate carbanion at 15°. The mixture was stirred for three hours at room temperature, then diluted with water and extracted with ether to yield the mixture of esters.

Table 1. Reaction of triethyl α-phosphono-acetate (1a) and -propionate (1b) with aliphatic aldehydes:



cis 36 trans

Compound	R^2	R'	Position of vinyl proton in cis-isomer (ppm)	Position of vinyl proton in trans-isomer (ppm)	% cis[a]
36a	H	i-propyl	-	6.84	none detectable
36b	H	t-butyl	-	6.86	none detectable
36c	CH_3	CH_3	-	6.74	none detectable
36d	CH_3	C_2H_5	5.85	6.65	16
36e	CH_3	i-propyl	5.62	6.46	62-73[b]
36f	CH_3	i-butyl	5.58	6.45	67
36g	CH_3	t-butyl	5.40	6.64	50[b]

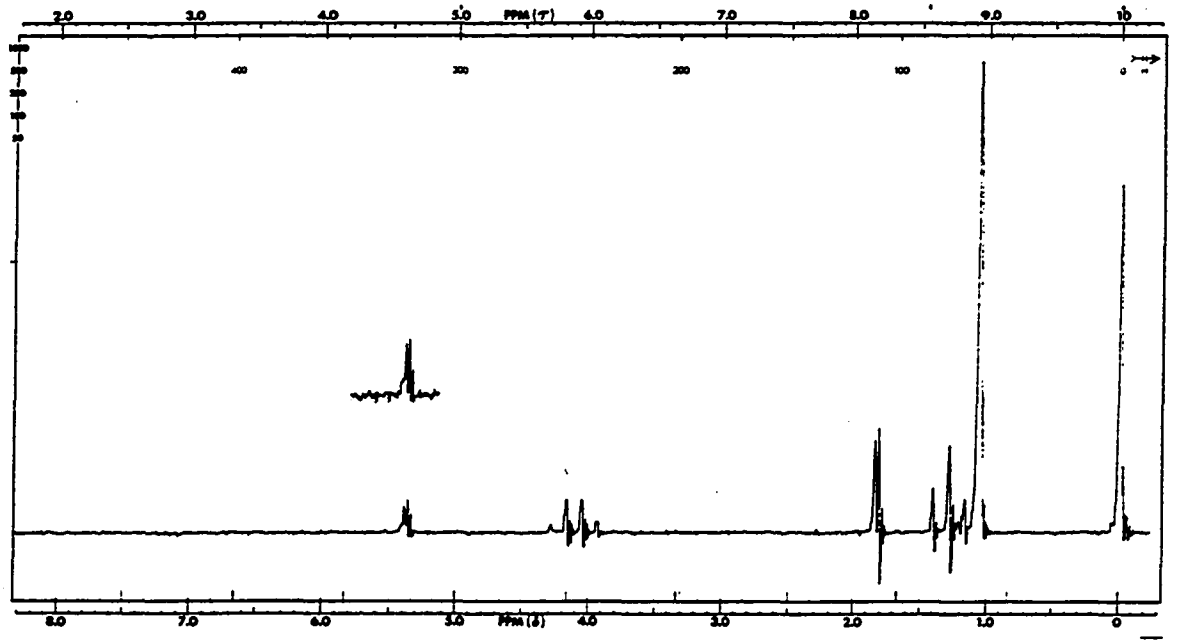
[a]We have demonstrated that no cis ⇌ trans equilibration occurs under the reaction conditions or even in the presence of a large excess of hot phosphonate anion solution. Relatively rapid isomerization of cis ⟶ trans occurs using sodium hydride in refluxing DME.

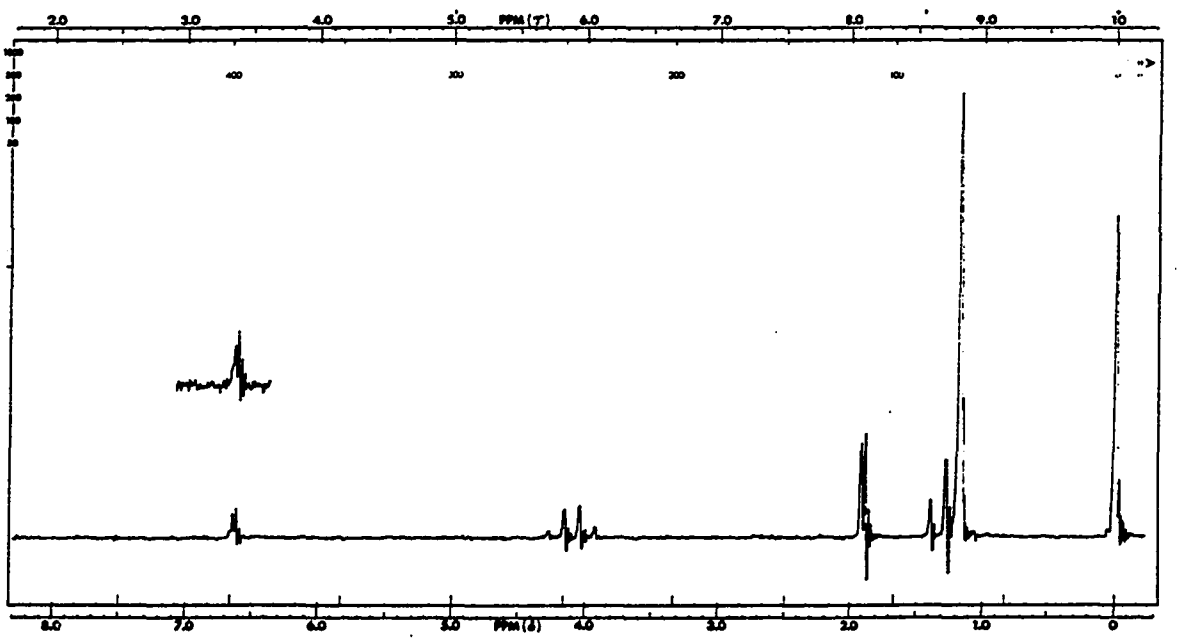
[b]The % cis-isomer was unchanged when dimethylformamide replaced 1,2-dimethoxyethane.

Our structural assignments were based on the chemical shift of the β-vinyl proton. Due to the anisotropic effect of the carbethoxy group

Figure 1. The nmr spectrum of ethyl cis-2,4,4-trimethyl-2-pentenoate (36g)

Figure 2. The nmr spectrum of ethyl trans-2,4,4-trimethyl-2-pentenoate (36g)


2.0
3.0
4.0
5.0
PPM(τ)
6.0
7.0
8.0
9.0
10
400
300
200
100
0
8.0
7.0
6.0
5.0
PPM(δ)
4.0
3.0
2.0
1.0
0

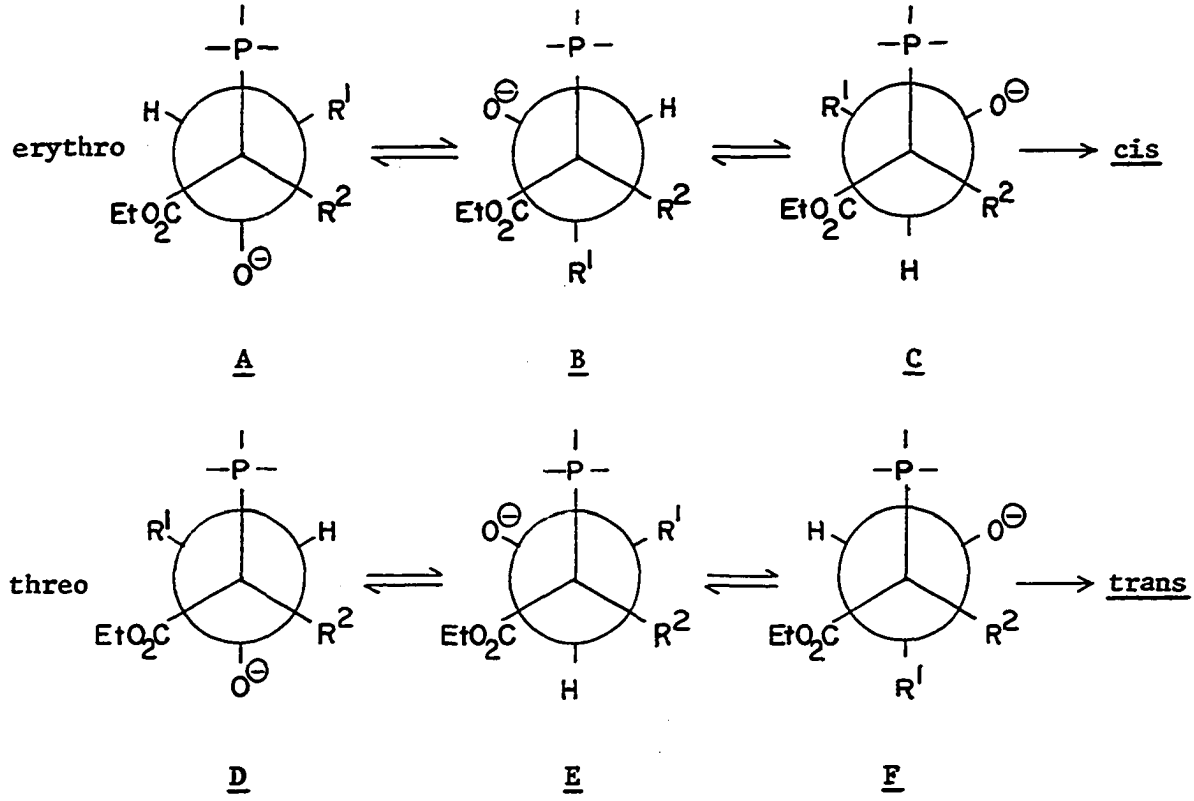

2.0
3.0
4.0
5.0
PPM(τ)
6.0
7.0
8.0
9.0
10
400
300
200
100
0
8.0
7.0
6.0
5.0
PPM(δ)
4.0
3.0
2.0
1.0
0

(68), a vinyl proton cis to it (i.e., in the trans-isomer) would appear at lower field than a vinyl proton trans to it (i.e., in the cis-isomer). These observations are in agreement with those of other workers (69a,b, 70, 71, 72). For example, McGreer, et al. (72a,b) found that in methyl cis-2-methyl-2-pentenoate the β-vinyl proton appears at 5.84 δ from TMS while in the trans-isomer, the β-vinyl proton appears at 6.52 δ from TMS. This point is further illustrated in Figure 1 and Figure 2. It should also be noted that the γ-methyl groups of the cis-isomer appear upfield compared with the γ-methyl groups of the trans-isomer. These observations are in accord with those of Hayashi, et al. (73) in their nmr studies of alkylidene cyanoacetic esters.

We found that when R^2 = H, only the trans-ester is formed, even with pivaldehyde as the carbonyl compound. However, with R^2 = CH_3, the amount of cis-isomer increases as R' gets larger, then decreases again when R' is t-butyl.

These results can be explained by the following mechanism. The phosphonate anion reacts with the carbonyl compound in the orientation suggested by rotamers A and D in Scheme 11. These betaines, presumably formed in a fast equilibrium step are freely rotating around the new C-C bond when R^2 = H and the more stable trans-isomer is formed exclusively. When R^2 = CH_3, and R^1 = CH_3 or C_2H_5, much the same reasoning explains the preferred formation of the trans-isomer. But for R^2 = CH_3, R^1 = i-propyl or i-butyl, the rotation becomes hindered, and since the erythro-isomer A should be formed much faster than the threo-isomer D due to the unfavorable steric repulsion between the i-propyl or i-butyl and carbethoxy groups in D,

Scheme 11

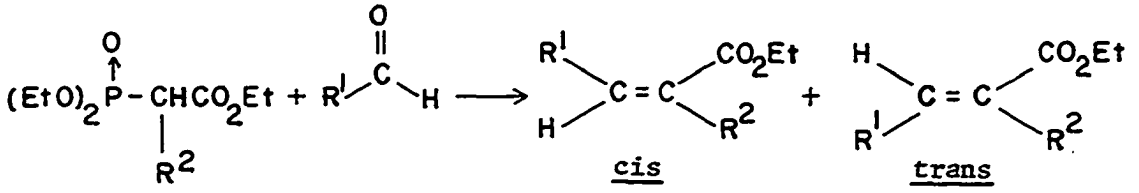


the cis-isomer becomes the major product. When $R^2 = CH_3$, R' = t-butyl or larger, although the formation of rotamer A is probably still favored, models suggest that rotation about the new C-C bond toward the transition state configuration is severely hindered due the t-butyl-phosphorus group interactions. Space-filling models further suggest that rotation of the t-butyl group past the phosphorus group in rotamer D is easier than any rotation in A, thus increasing the amount of trans-isomer. An alternative explanation for the increase in trans-isomer with R' = t-butyl is that the strained rotamer D is not formed first, i.e., the usual orientation for reactants is not followed due to steric interference, and that a less strained rotamer as E or a skewed rotamer more nearly like the

transition state structure is formed first.

From the above arguments one would predict that similar results would be obtained when triethyl α-phosphono-α-haloacetates (R^2 = Br,Cl) are used and when $R^2 = C_2H_5$, one would expect an increased amount of cis-products. These predictions are borne out by our results which are shown in Table 2.

Table 2. Reaction of triethyl α-phosphono -butyrate (1c) and -α-haloacetates (1d,e) with aliphatic aldehydes:



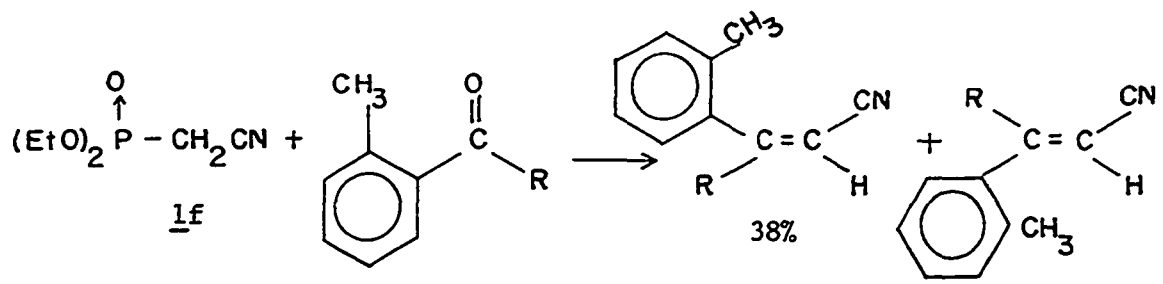
1c: R_2^2 = Et
1d: R_2^2 = Br
1e: R^2 = Cl

36

Compound	R^2	R'	Position of vinyl proton in cis-isomer (ppm)	Position of vinyl proton in trans-isomer (ppm)	% cis
36h	C_2H_5	CH_3	5.91	6.75	18
36i	C_2H_5	Et	5.8	6.68	41
36j	C_2H_5	i-propyl	5.52	6.42	84[a]
36k	C_2H_5	t-butyl	5.35	6.52	55
36l	Br	CH_3	6.74	7.34	19
36m	Br	Et	6.55	7.15	25
36n	Br	i-propyl	6.39	6.95	58
36o	Br	i-butyl	6.38	7.05	54
36p	Br	t-butyl	6.18	7.4	36
36q	Cl	i-propyl	6.17	6.84	65
36r	Cl	i-butyl	6.15	6.83	52

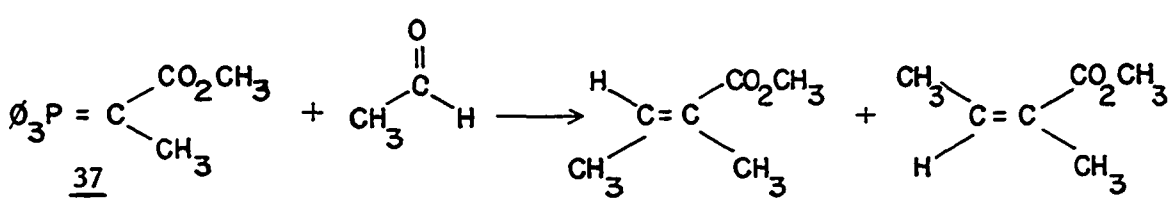
[a]The % cis-isomer was unchanged when dimethylformamide replaced 1,2-dimethoxyethane.

Previously, phosphonate anion condensations which have yielded significant amounts of cis-olefin have used ketones as the carbonyl compound (54, 65). For example, Jones and Maisey (65) reported that in the reaction of diethyl α-phosphonoacetonitrile (1f) with 2-methylacetophenone and with 2-methylphenyl n-butyl ketone, they obtained, in both instances, 38% of the cis-olefin.



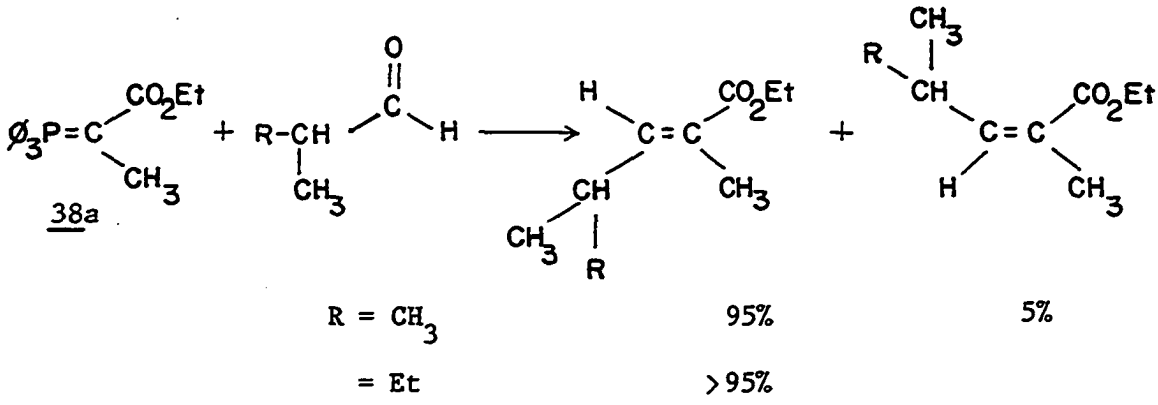
The results summarized in Tables 1 and 2 are the first examples of significant formation of cis-esters (i.e. up to 84% cis) using aldehydes as the carbonyl compounds.

It has been reported by House and Rasmusson (74) that the reaction of α-methylcarbomethoxymethylenetriphenylphosphorane (37) with acetaldehyde gave predominantly the trans-isomer. It was interesting then to examine



the stereochemistry of the reaction using α-methylcarbethoxymethylenetriphenylphosphorane (38a) and a bulky aldehyde as 2-methylpropanal and 2-methylbutanal. In both cases, we obtained mostly the trans-isomer. There was such a small amount of cis-isomer formed that it could be detected

by NMR only with difficulty. This result is interesting in that in the



R = CH_3	95%	5%
= Et	>95%	

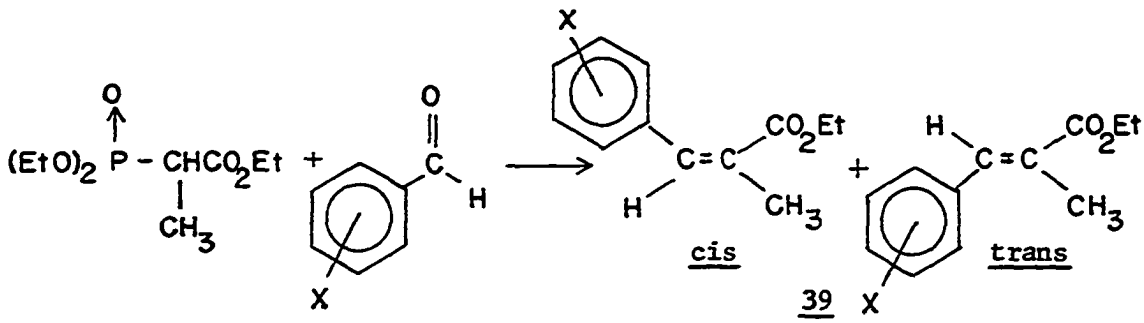
"normal" Wittig reaction, the stereochemical course of the reaction does not seem to be affected by the presence of bulky groups in the carbonyl compound and by the additional α-substituent, whereas with the corresponding phosphonate ester condensation, predominant formation of the cis-isomer is observed with such substitutions (see Tables 1 and 2).

The vastly different behavior of the Wittig reaction and the phosphonate reactions might be indicative of a difference in reaction mechanism or a difference in the rate ratios of the individual steps in the reaction. With the data in hand, we are not able to decide between these two possibilities.

At this point, we looked at the reaction of triethyl α-phosphonopropionate with a series of benzaldehydes and acetophenones and examined the effects of substituents on the benzene ring on the stereochemistry of the reaction. Our results are tabulated in Tables 3 and 4.

The isomeric composition of the crude olefin mixture was determined by analysis of its nmr spectrum in each case. Our structural assignments were based on the following considerations: a) the β-Me of the trans-

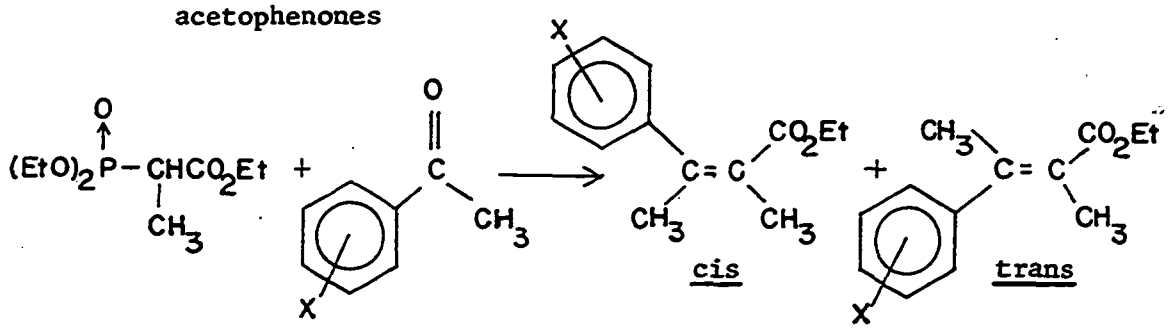
Table 3. Reaction of triethyl α-phosphonopropionate with a series of benzaldehydes



Compound	X	% cis
39a	H	none detectable
39b	m-OMe	none detectable
39c	p-OMe	none detectable
39d	o-Cl	none detectable
39e	2,6-diCl	2.5
39f	2,3,4,5,6-penta F	10

series (i.e., cis to the carbethoxy group) is deshielded with respect to the β-Me of the cis-series; b) the α-Me of the trans-series (i.e., cis to the phenyl group) are shielded with respect to the α-Me of the cis-series Our data are in agreement with the results obtained by Kampmeier and Fantazier (75) in their study of ethyl α,β-dimethyl cinnamates. Similar results were also reported by other workers (70, 71, 76, 77). Examination of models also show that the ethoxyl protons are located, at least part of the time, directly over the phenyl ring in the cis-isomer and are in

Table 4. Reaction of triethyl α-phosphonopropionate with a series of acetophenones

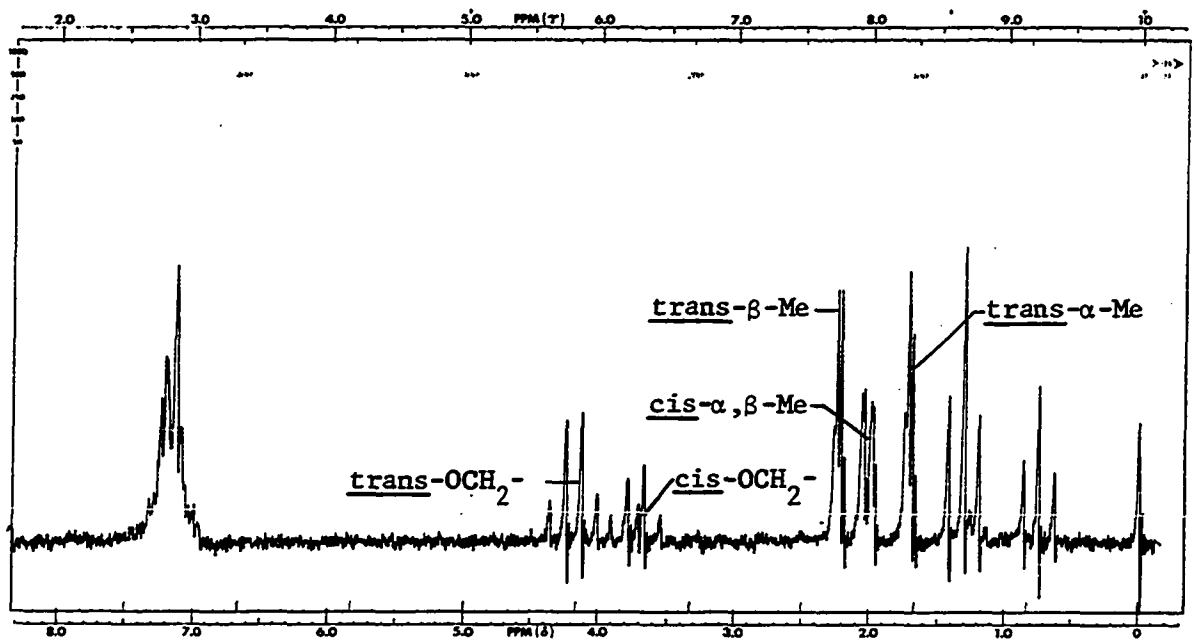


40

Compound		X	α-Me (ppm)	β-Me	% cis
40a	cis	H	2.0 (or 2.06)	2.06 (or 2.0)	36
	trans	H	1.71	2.25	
40b	cis	m-OMe	1.98 (or 2.05)	2.05 (or 1.98)	35
	trans	m-OMe	1.75	2.25	
40c	cis	p-OMe	~2.0	~2.0	39
	trans	p-OMe	1.78	2.25	
40d	cis	p-NO_2	2.02 (or 2.12)	2.12 (or 2.02)	45
	trans	p-NO_2	1.74	2.28	
40e	cis	p-Cl	1.98	2.03	42
	trans	p-Cl	1.7	2.2	
40f	cis	2,5-diCl	2.01	2.01	53
	trans	2,5-diCl	1.62	2.2	

the shielding cone of the phenyl ring. We would expect therefore, that in the cis-isomers, the ethoxyl protons should resonate at higher fields than those in the trans-isomers. This is indeed what we observe. The above

Figure 3. NMR spectrum of a mixture of ethyl cis- and trans-α,β-dimethylcinnamates (40a)


2.0
3.0
4.0
5.0
PPM(τ)
6.0
7.0
8.0
9.0
10
trans-β-Me
trans-α-Me
cis-α,β-Me
trans-OCH2-
cis-OCH2-
8.0
7.0
6.0
5.0
PPM(δ)
4.0
3.0
2.0
1.0
0

points are illustrated in Figure 3.

Examination of Table 3 shows that the reaction of triethyl α-phosphonopropionate with benzaldehyde derivatives yields predominantly or exclusively trans-products. One notes that the same phosphonate ester reacts with acetophenone derivatives to yield significant amounts of cis-products.

For comparative purposes, we also looked at the reaction:

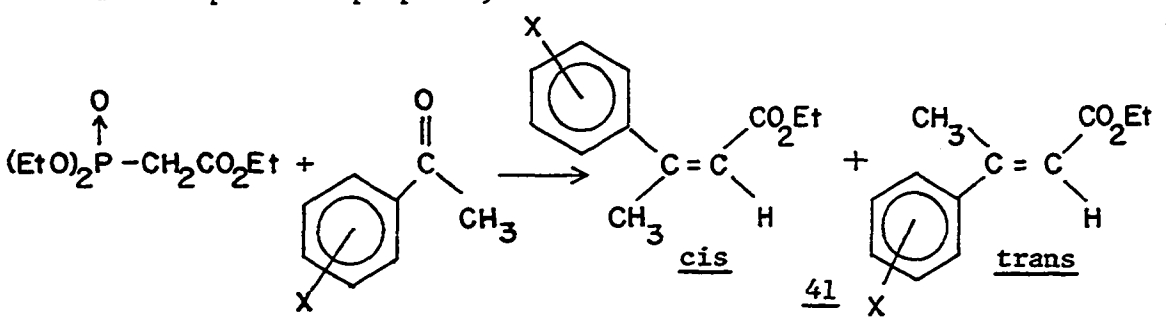


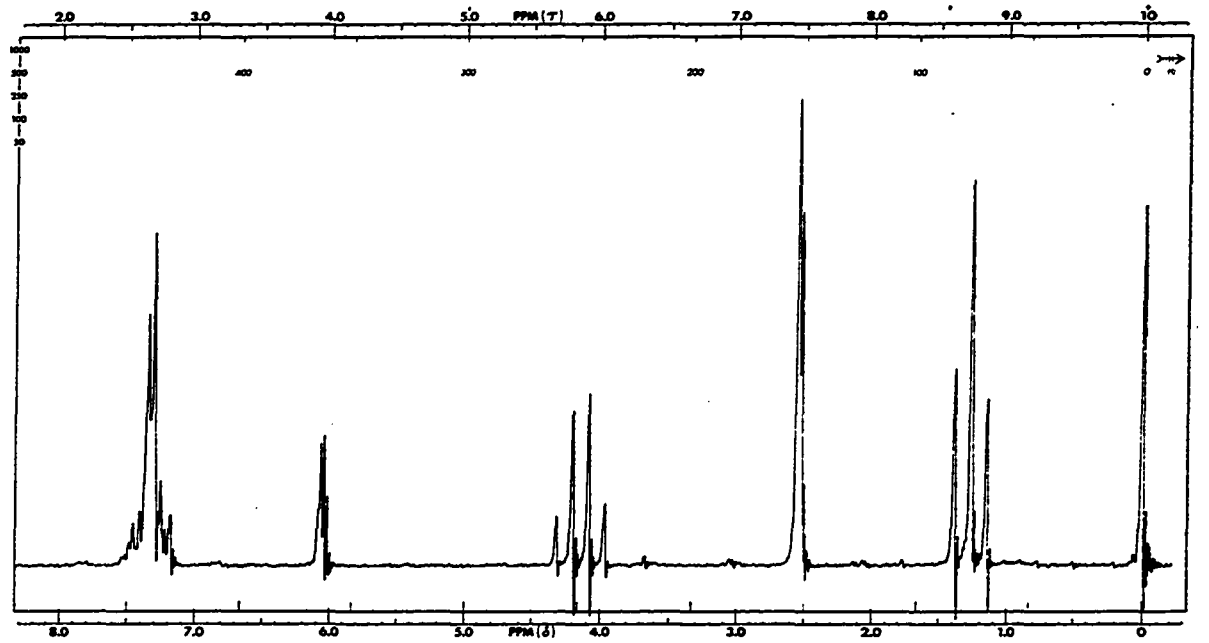
Table 5. Reaction of triethyl α-phosphonoacetate with acetophenone and with 2,5-dichloracetophenone

Compound		X	α-H	β-CH_3	-OCH_2CH_3	% cis
41a	cis	H	5.8	2.15	3.9, 1.03	19
	trans	H	6.06	2.53	4.14, 1.28	
41b	cis	2,5-diCl	5.92	2.12	4.06, 1.08	24
	trans	2,5-diCl	5.76	2.44	4.16, 1.29	

We observed that in these cases there was less cis-ester formed compared with the reaction of triethyl α-phosphonopropionate with the same ketones (see Table 4). An interesting feature of the nmr data in Table 5 is that in 41a, the α-proton in the trans-ester is deshielded with respect to the

Figure 4. NMR spectrum of ethyl cis-β-methylcinnamate (41a)

Figure 5. NMR spectrum of ethyl trans-β-methylcinnamate (41a)


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

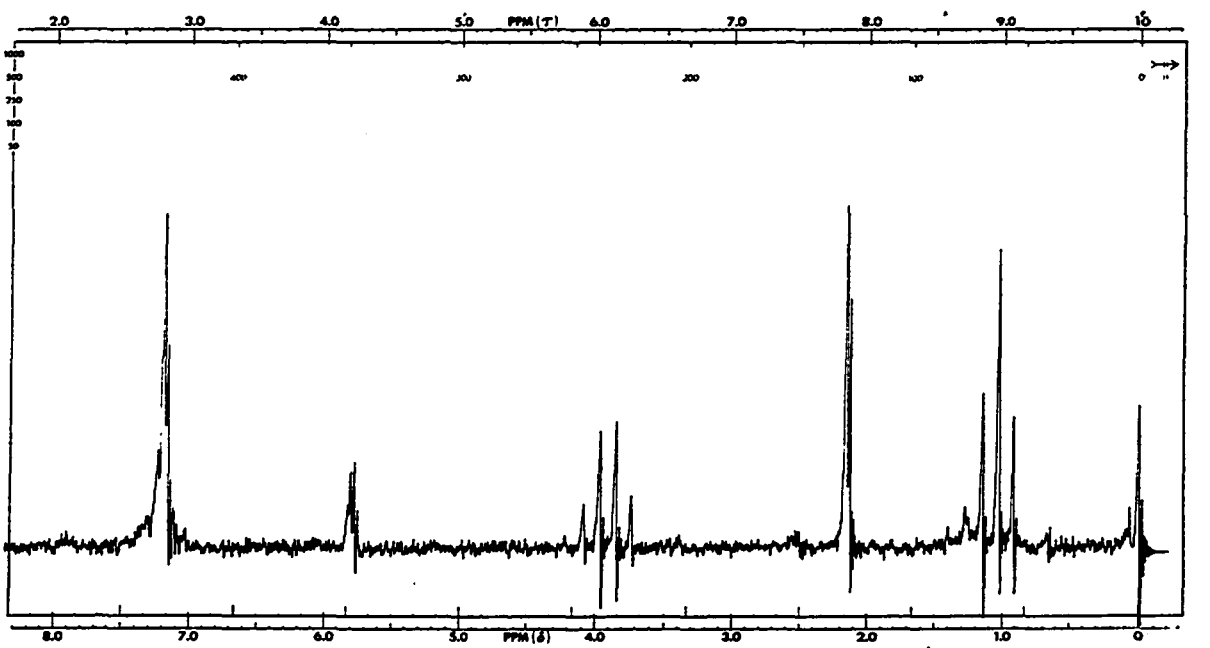
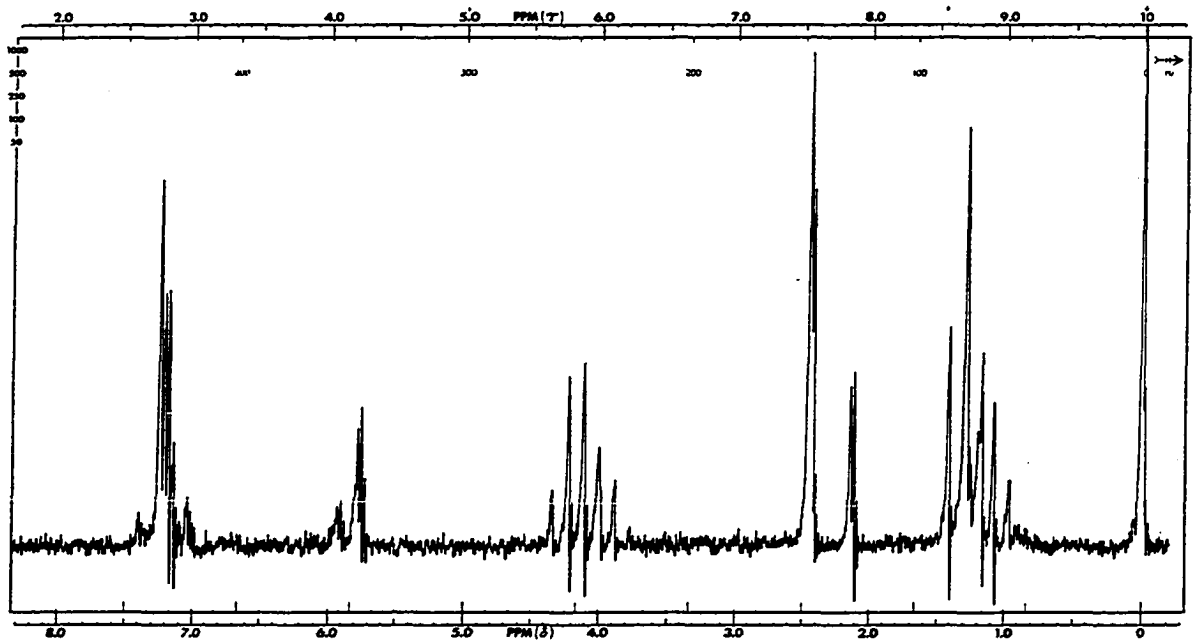

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

Figure 6. NMR spectrum of ethyl cis- and trans-2,5-dichloro-ß-methyl-cinnamates (41b)


2.0
3.0
4.0
5.0
PPM(τ)
6.0
7.0
8.0
9.0
10
8.0
7.0
6.0
5.0
PPM(δ)
4.0
3.0
2.0
1.0
0

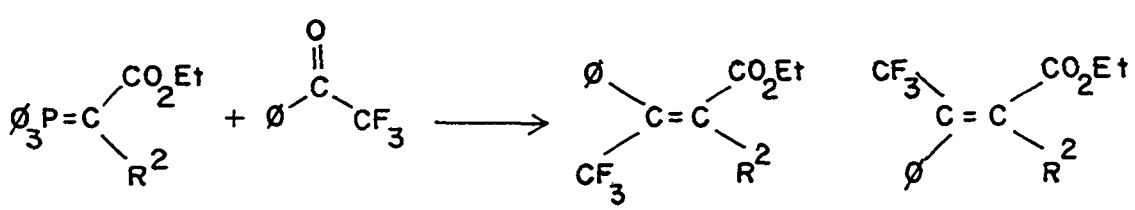
cis-isomer. However in 41b, the reverse relationship is observed, i.e., the α-proton in the trans-isomer is upfield from the α-proton in the cis-isomer. This indicates that in 41a, the phenyl ring is in the plane of the molecule in the trans-isomer causing the usual deshielding of the α-proton, whereas in 41b, the phenyl ring is twisted out of the plane of the molecule placing the α-proton in the shielding cone of the phenyl ring. See Figures 4, 5, and 6. Wiley and van der Plas (78) have previously reported that the α-proton and β-methyl group in cis-β-methylcinnamic acid resonated at 2.13 and 6.11 δ, respectively. Ide and Kishida (79) found that in ethyl trans-β- methylcinnamate, the α-proton and β-methyl group resonated at 2.46 and 6.07 δ, respectively. These results are in accord with our observations.

In the cases that we have examined, we find that the presence of ortho-substituents increases the amount of cis-olefin formed. In terms of our proposed mechanism (Scheme 11), the introduction of the ortho-substituents would sterically hinder the formation of rotamer D, thereby decreasing the relative amount of the trans-products. Also, with ortho-substitution, the conjugative stabilization of the incipient double bonds in the transition state is decreased. Such stabilization is usually greater in the transition state leading to the trans-olefin and so the % trans-olefin would be decreased. These findings are in accord with the results obtained by Jones and Maisey (65). They found that the reaction of diethyl α-phosphonoacetonitrile (1f) with a series of alkylphenyl ketones yields predominantly trans-products whenever the alkyl group is unbranched and the phenyl group is unsubstituted in the ortho-position. However when

there was substitution in the ortho-position of the phenyl group and when the alkyl groups became bulkier, the reaction yielded a substantial amount of cis-products.

A recent report by I. Shahak, et al. (80) concluded that α-substituted phosphonate carbanions only undergo condensation with aldehydes but not with ketones. However we find these reactions to be clean and good yield reactions.

It was observed by Dull, et al. (81) that one predominant product is formed in the reaction of trifluoromethyl ketones with resonance stabilized phosphoranes. These workers, however, did not attempt to establish the configuration of the predominant isomer. Since these isomers are of potential interest in the mechanistic studies of the phosphonate modification of the Wittig reaction, we examined the reaction of α-carbethoxymethylene- and α-carbethoxymethylene-ethylidene-triphenylphosphorane with 1,1,1-trifluoroacetophenone. We found that the reactions yielded the cis-isomer predominantly although a significant

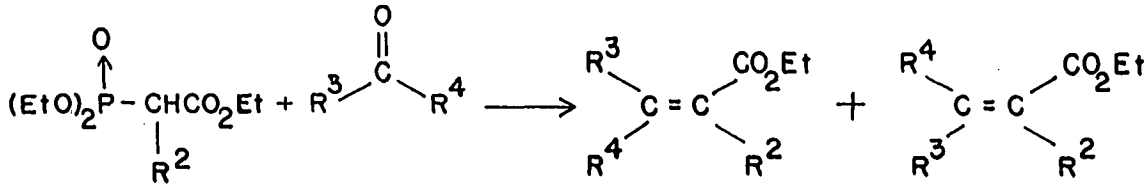


		cis	trans
38a	$R = CH_3$	86%	14
38b	$R = H$	63%	37

amount of the trans-isomer was formed when $R = CH_3$.

We also investigated the stereochemistry of the reaction of several fluoro-containing carbonyl compounds with triethyl α-phosphono-acetate (1a) and -propionate (1b). Our results are summarized in Table 6. The results in Table 6 clearly indicate that the presence of fluorine atoms in the carbonyl component has a profound effect on the stereochemistry of the reaction, i.e., more cis-products are formed. It is noted that in the reaction involving triethyl α-phosphonopropionate (1b), when 1,1,1-trifluoroacetophenone is used in place of acetophenone, the amount of cis-isomer increases from 36% to 70%. The increase in % cis-isomer is even greater in the reaction involving triethyl α-phosphonoacetate (1a), i.e., from 19% to 84%. This large increase in the amount of cis-isomer cannot be due only to steric differences between a trifluoromethyl group and a methyl group. Comparison of the van der Waal's radii (r_H = 1.2A°; r_F = 1.4A°) and the covalent radii (r_{CH} = 1.09A°; r_{CF} = 1.37A°) shows that there is no substantial difference in the steric bulk of these two groups. In addition to the steric effect, the increased electrophilicity of the carbonyl group in trifluoroacetophenone may have contributed to the increased percentage of cis-products. Because of the very electrophilic and reactive carbonyl function in trifluoroacetophenone, the reversibility of the initial step of the reaction (betaine formation) could be reduced or prevented, causing kinetic control of the stereochemistry of the reaction. In such a situation, since rotamer A would be preferentially formed over rotamer D for steric reasons (see Scheme 11), it would be expected that more cis-products would be formed.

Table 6. Reaction of fluorinated carbonyl compounds with triethyl α-phosphono-acetate and -propionate:



cis trans

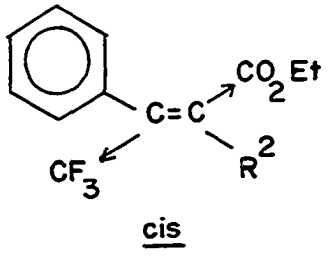
42

Compound		R^2	R^3	R^4	α-CH_3 (or α-H)	β-CH_3	-OCH_2CH_3	% cis
42a	cis	H	phenyl	CF_3	6.53	-	3.94, 0.98	84
	trans	H	phenyl	CF_3	6.24	-	4.25, 1.3	
42b	cis	CH_3	phenyl	CF_3	1.8	-	3.8, 0.75	70
	trans	CH_3	phenyl	CF_3	1.8	-	4.25, 1.3	
42c	cis	CH_3	p-F phenyl	CH_3	1.9	2.03	3.78, 0.85	38
	trans	CH_3	p-F phenyl	CH_3	1.7	2.20	4.19, 1.32	
42d	cis	CH_3	2,5-diF phenyl	CH_3	2.04	2.04	3.86, 0.9	48
	trans	CH_3	2,5-diF phenyl	CH_3	1.72	2.21	4.21, 1.3	
42e	cis	CH_3	2,4-diF phenyl	CH_3	2.0	2.0	3.85, 0.9	58
	trans	CH_3	2,4-diF phenyl	CH_3	1.7	2.2	4.2, 1.31	
42f	cis	H	CF_3	CH_3	6.02	2.0	4.2, 1.3	10
	trans	H	CF_3	CH_3	6.28	2.23	4.2, 1.3	
42g	cis	CH_3	CF_3	CH_3	1.87	1.95	4.16, 1.3	
	trans	CH_3	CF_3	CH_3	1.95	2.05	4.2, 1.3	

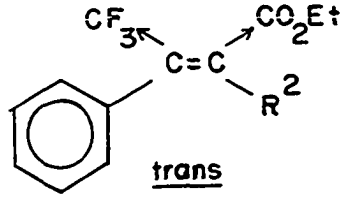
The very electrophilic and reactive nature of trifluoroacetophenone was demonstrated by running a competition reaction involving a single phosphonate ester, triethyl α-phosphonopropionate (1b), and two ketones, acetophenone and 1,1,1-trifluoroacetophenone. We found that upon addition of the phosphonate carbanion to a 4-fold molar excess mixture of the two ketones, only products from 1,1,1-trifluoroacetophenone could be detected. 1,1,1-trifluoroacetophenone was, in fact, so much more reactive that even when the competition reaction was carried out by adding the ketone mixture to the phosphonate carbanion, only the products resulting from 1,1,1-trifluoroacetophenone could be detected.

The effect of the electrophilic nature of the carbonyl compound on the stereochemistry of the reaction can also be noted from the increased amount of cis-isomer as R' goes from pF to 2,5-diF to 2,4-diF (Table 6).

Another factor which may have contributed to the rise in % cis-isomer in these cases, is the unfavorable dipole-dipole interaction which is present in the trans-isomer and the favorable alignment of the dipoles in the cis-isomer.



cis

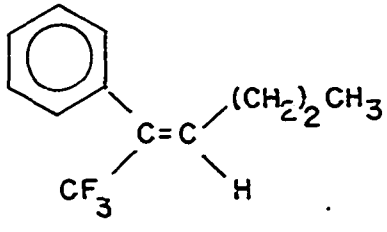


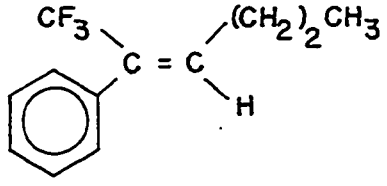
trans

Our structural assignments were made mainly on the basis of the proton nmr spectra of these compounds. Again, we observed that the α-hydrogen or α-methyl group of the trans-isomers resonated at higher

field than the corresponding protons in the cis-isomers. We also noted that the ethoxyl protons of the cis-isomers again appeared at higher field compared with those of the trans-isomers. In addition we noted that $J_{CF_3,H}$ (cis) > $J_{CF_3,H}$(trans) and J_{CF_3,CH_3} (cis) > J_{CF_3,CH_3} (trans). For ethyl cis- -trifluoromethylcinnamate (42a), $J_{CF_3,H}$(cis) $\simeq$ 1.3 cps which is characteristic of cis-coupling of the trifluoromethyl group and a vinyl proton, while for the trans-isomer, $J_{CF_3,H}$(trans) $\simeq$ 0 (Figures 7 and 8).

Previous workers have reported $J_{CF_3,H}$(cis) of 1.2 - 2 cps and $J_{CF_3,H}$ (trans) of ~ 0 cps for coupling of a trifluoromethyl group and a vinyl proton (82, 83, 84). For instance, Burton, et al. (84) observed a $J_{CF_3,H}$ (cis) of 1.4 - 1.5 cps and a $J_{CF_3,H}$(trans) of ~0.7 cps in 43 and 44, respectively.



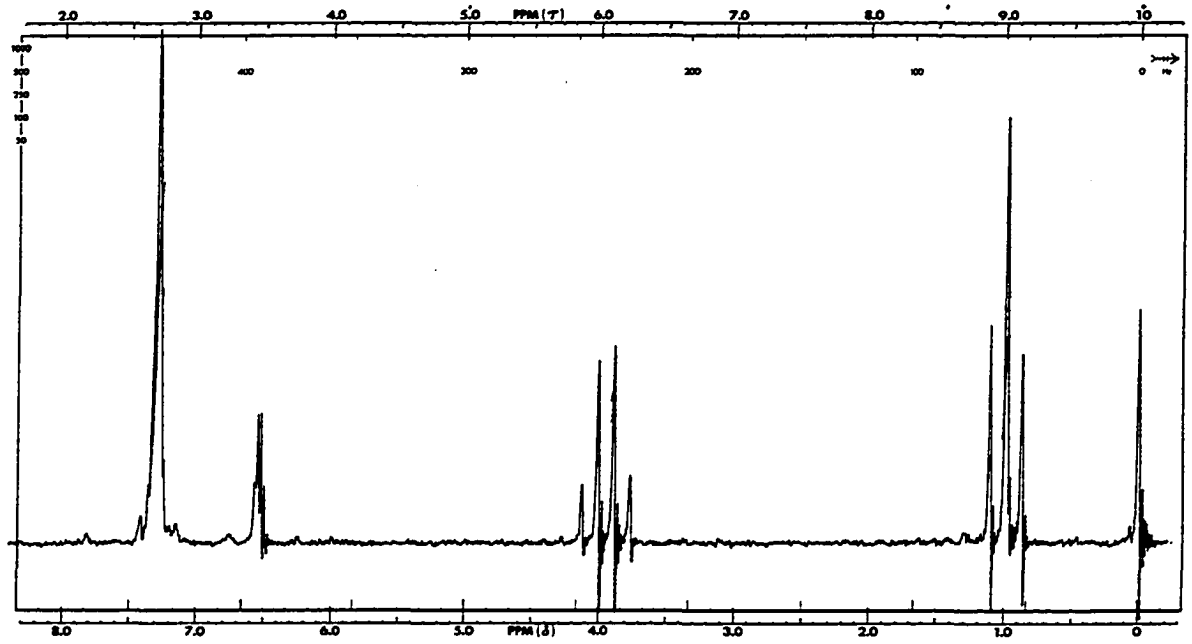


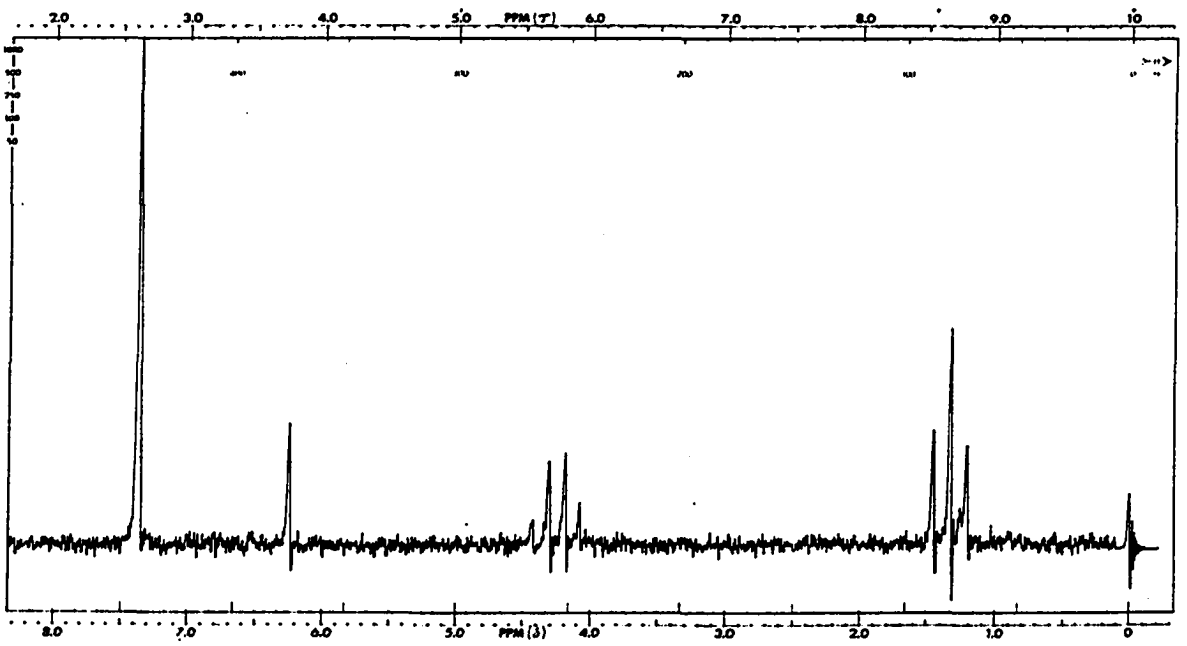
For ethyl α-methyl-β-trifluoromethylcinnamate (42b) we found a J_{CF_3,CH_3}(cis) of 2.6 cps and a J_{CF_3,CH_3} (trans) of ~2.2 cps.

An interesting sidelight to the nmr spectra of some of these compounds is the fact that they seem to closely follow the "additivity rule" devised by Pascual, et al. (85, 86, 87). This rule states that "if one assumes the additivity of substituent effects on the chemical shift of olefinic protons, one can write the following expression for the chemical shift (δ) of any olefinic proton:

Figure 7. NMR spectrum of ethyl cis-β-trifluoromethylcinnamate (42a)

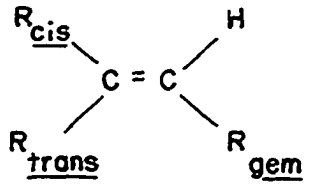
Figure 8. NMR spectrum of ethyl trans-β-trifluoromethylcinnamate (42a)


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

$$\delta = 5.25 + \sum_i Z_i$$

where Z_i are the respective shielding increments for substituents (R) in the gem, cis, and trans relationship to the proton.



A comparison between the observed and calculated chemical shifts of protons is made in Table 7.

Table 7. Calculated chemical shifts of vinyl protons and comparison with the observed chemical shifts

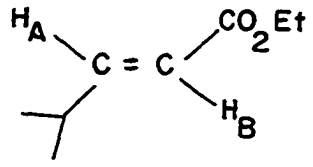
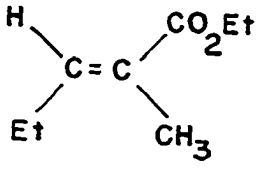
Structure	Calculated chemical shifts
	H_i: 5.25 .45 (gem alkyl) 1.18 (cis CO_2R) 6.88 ($\Delta = 0.04\delta$)
	H_B: 5.25 .80 (gem CO_2R) -.22 (cis alkyl) 5.83 ($\Delta = 0.15\delta$)
	H : 5.25 .45 (gem alkyl) 1.18 (cis CO_2R) -.28 (trans alkyl) 6.60 ($\Delta = -0.05\delta$)

Table 7. (Continued)

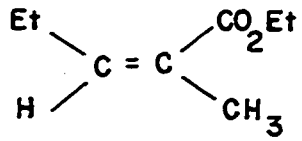
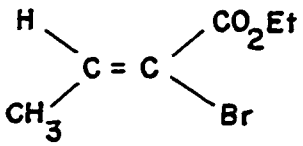
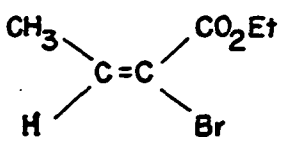
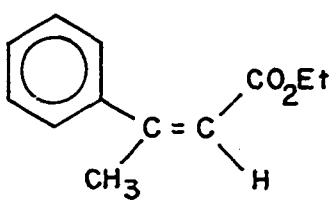
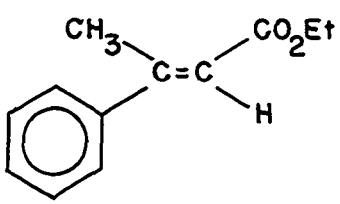
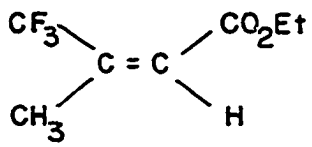
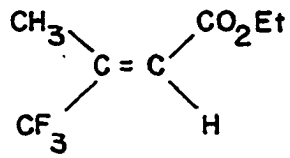
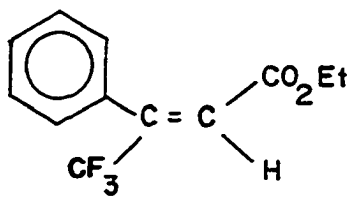
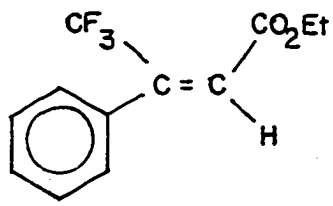
Structure	Calculated chemical shifts
	H: 5.25 .45 (gem alkyl) -.22 (cis alkyl) .55 (trans CO_2R) 6.03 (Δ = 0.18δ)
	H: 5.25 .45 (gem alkyl) 1.18 (cis-CO_2R) .55 (trans Br) 7.43 (Δ = 0.09δ)
	H: 5.25 .45 (gem alkyl) .45 (cis Br) .55 (trans CO_2R) 6.70 (Δ = -0.04δ)
	H: 5.25 .80 (gem CO_2R) -.22 (cis alkyl) -.07 (trans aromatic) 5.76 (Δ = 0.04δ)
	H: 5.25 .80 (gem CO_2R) .36 (cis aromatic) -.28 (trans alkyl) 6.13 (Δ = 0.07δ)

Table 7. (Continued)

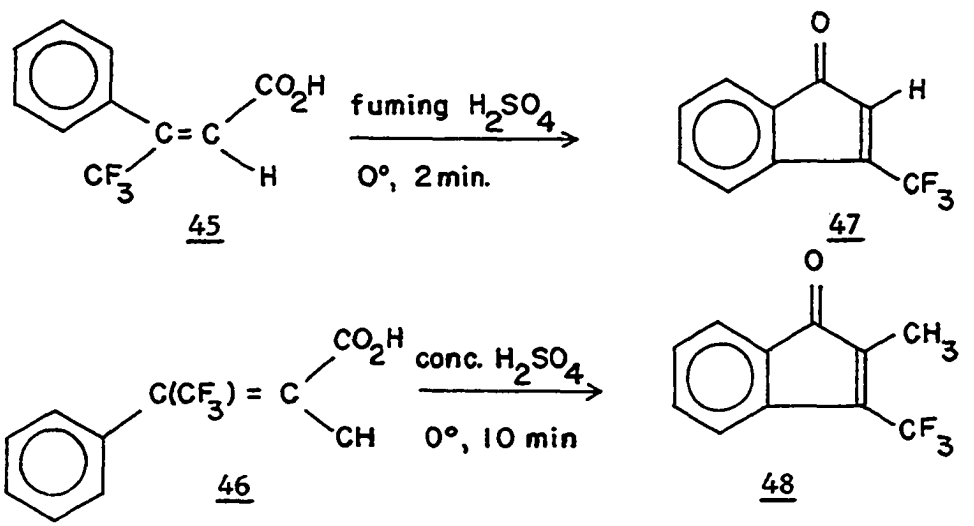
Structure	Calculated chemical shifts
	H: 5.25 .80 (gem CO_2R) -.22 (cis alkyl) .32 (trans CF_3) 6.15 (Δ = 0.13δ)
	H: 5.25 .80 (gem CO_2R) .61 (cis CF_3) -.28 (trans alkyl) 6.38 (Δ = 0.10δ)
	H: 5.25 .80 (gem CO_2R) .61 (cis CF_3) -.07 (trans arom) 6.59 (Δ = 0.06δ)
	H: 5.25 .80 (gem CO_2R) .36 (cis arom) .32 (trans CF_3) 6.73 (Δ = 0.49δ)

We found that, in most cases, the additivity rule not only predicted the relative positions of the protons in geometrical pairs but also

predicted quite closely the chemical shifts of these protons. For the cases shown in Table 7, in only the last pair of isomers was the rule incorrect in predicting the relative positions of the protons, i.e., if predicted that the α-proton of the cis-isomer would be at a higher field relative to the trans-isomer. This discrepancy may be due to the fact that the rule failed to take into account the fact that the phenyl ring is twisted out of the plane of the molecule a reversal in the relative chemical shifts of these protons.

Further evidence which confirms our structural assignments was provided by the fact that the acids corresponding to cis-42a and cis-42b, 45 and 46 respectively, readily underwent cyclization in sulfuric acid to 3-trifluoromethyl-1-indenone (47) and 2-methyl-3-trifluoromethyl-1-indenone (48), respectively (Scheme 12). The resulting indenones showed the correct molecular ion in the mass spectrometer and were identified from the nmr spectra.

Scheme 12

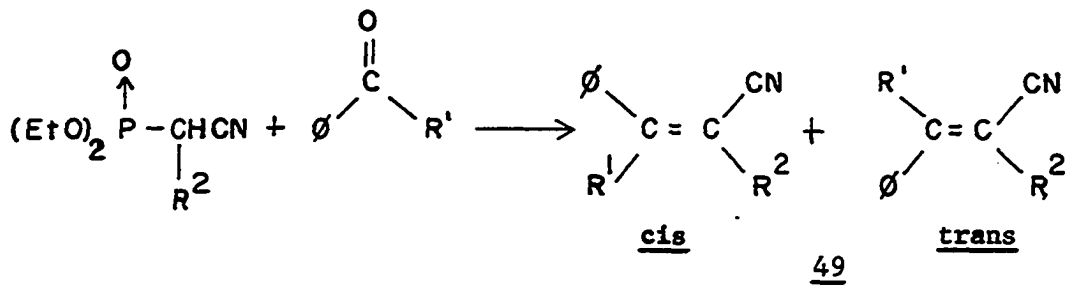


The cyclization experiment was carried out using the procedure employed by Kampmeier and Fantazier (75) on α,β-dimethylcinnamic acids. When a mixture of cis- and trans- 46 was treated with concentrated sulfuric acid at 0°, the reaction mixture immediately turned yellow. After 10 minutes elapsed, the mixture was poured into ice and extracted with ether. The ether extract was then washed with $NaHCO_3$ to remove the unreacted acid and concentrated to yield 48. The $NaHCO_3$ extract contained mostly the trans acid-46. It was noted by Kampmeier and Fantazier (75) that under these conditions virtually all (99%) of ethyl trans-α,β-dimethylcinnamic acids could be recovered unchanged.

We observed that 46 underwent cyclization much more readily than 45. Only a very slight amount of cyclization occurred when 45 was stirred in concentrated sulfuric acid at 40° for 20 minutes whereas 46 cyclized almost completely when it was stirred in concentrated sulfuric acid at 0° in 10 minutes. However, 45 cyclized readily in fuming sulfuric acid at 0°. Presumably this difference in the rate of cyclization of these two compounds is due to a steric effect exerted by the α-methyl group in 46. The α-methyl group pushes the carboxyl function closer to the benzene ring causing the cyclization to occur more readily.

It became of interest to investigate the stereochemistry of the reaction using diethyl α-phosphonopropionitrile. We wanted to investigate the effect of the trifluoromethyl group on the stereochemistry of the reaction and compare the results with those in Table 6. These results are summarized in Table 8.

Table 8. Reaction of diethyl α-phosphono -acetonitrile and -propionitrile with aromatic ketones



cis trans

49

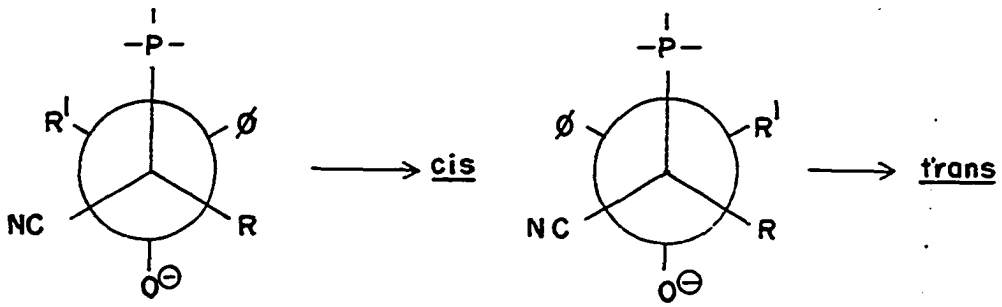
Compound		R	R'	α-CH_3 (or H)	% cis
49a	cis	H	CF_3	6.07	70
	trans	H	CF_3	5.89	
49b	cis	CH_3	CH_3	2.0, 2.10[a]	24
	trans	CH_3	CH_3	1.78, 2.29[a]	
49c	cis	CH_3	CF_3	2.29	55
	trans	CH_3	CF_3	1.94	

[a]Chemical shift of the β-CH_3.

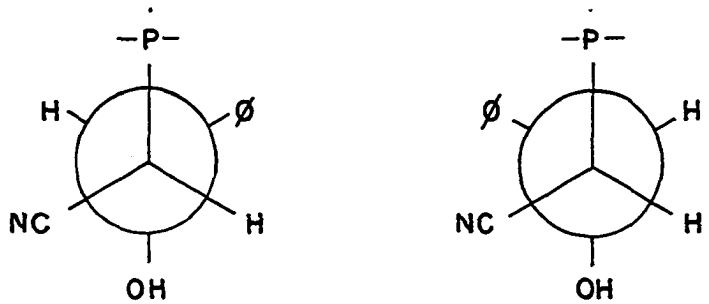
We observe that a significant amount of cis-isomer is formed whenever trifluoroacetophenone is used although comparison with results in Table 6 show that the amount of cis-products formed is less than the amount formed when using phosphono esters. This decrease in % cis-isomer may be accounted for by considering that when R^2 = H, although the erythro-betaine is still formed preferentially, the energy difference between the initially formed betaines is less for the cases involving phosphononitriles than the phosphonoesters. However when R^2 = CH_3, from steric considerations, the

threo-betaine is now formed preferentially although its decomposition to products may be hindered by the developing steric interaction between the phenyl group and the methyl group (Scheme 13).

Scheme 13

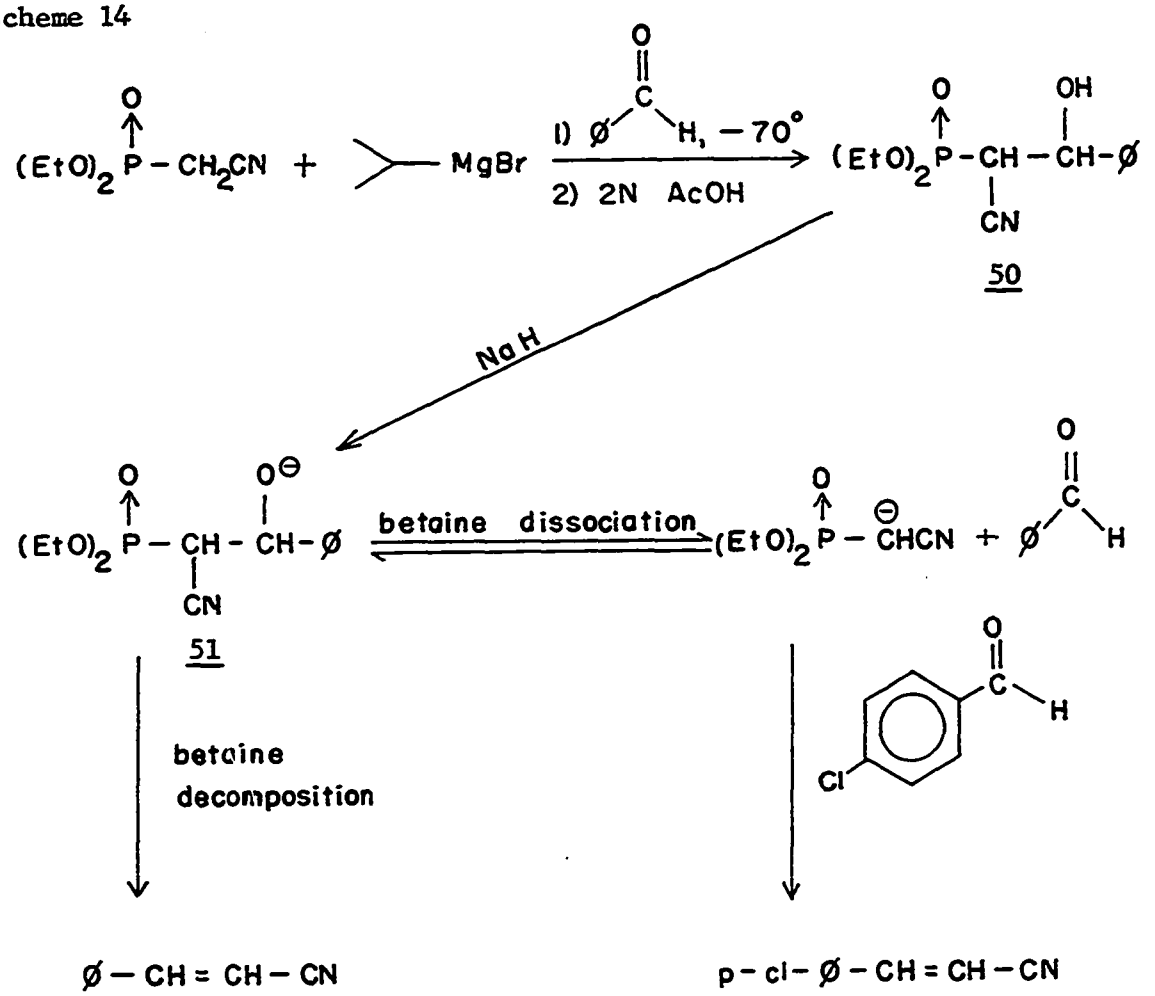


Very recently Lefebvre and Seyden-Penne (88) reported the isolation of erythro- and threo- diethyl 1-cyano-2-hydroxy-2-phenyl-phosphonate (50). Benzaldehyde was allowed to react with the carbanion formed by treatment of diethyl α-phosphonoacetonitrile with isopropylmagnesium bromide in



tetrahydrofuran at -70°. Quenching the reaction with 2N acetic acid yielded a mixture of erythro and threo-50. They observed that treatment of erythro or threo-50 with sodium hydride in the presence of a 2-fold molar excess of p-chlorobenzaldehyde resulted in the formation of a mixture of p-chlorocinnamonitrile and cinnamonitrile (Scheme 14).

Scheme 14



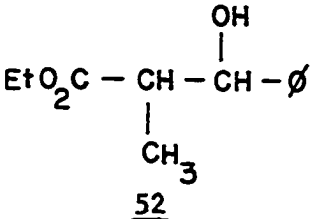
The work of Lefebvre and Seyden-Penne (88) establishes that the initial step (betaine formation) is indeed reversible. However, these workers did not attempt to trap the carbanion, resulting from the dissociation of 51, with a more reactive aldehyde like m-chlorobenzaldehyde. With such a reactive aldehyde one may be able to obtain a quantitative value for the ratio of rate of betaine dissociation/rate of betaine decomposition by simply obtaining the ratio of m-chlorocinnamonitrile/cinnamonitrile, with the assumption that the phosphonate carbanion formed from the dissociation of 51 is immediately trapped by m-chlorobenzaldehyde.

In view of this we prepared 50 using the procedure employed by Lefebvre and Seyden-Penne (88). We obtained white crystals which were recrystallized in an ether-pentane mixture. The nmr spectrum of the recrystallized material was in agreement with 50. However we suspected from the nmr spectrum that only one isomer was formed. The sharp melting point, 104-6°, of the recrystallized material substantiated our suspicion. The observed melting point for this material agrees well with the material obtained by Lefebvre and Seyden-Penne which they assigned to be the erythro-isomer of 50 (reported m.p. 108°). No trace of the lower melting isomer (reported m.p. 66°) could be detected.

We then treated the material we obtained with sodium hydride in the presence of a 3-fold molar excess of m-chlorobenzaldehyde. The ratio of m-chlorocinnamonitrile/cinnamonitrile was determined by vpc (8' Apiezon L, 190°) and was found to be 92/8. This indicates that the rate of betaine dissociation in this case is about 11.5 times faster than its decomposition.

There has been growing interest on the use of nmr shift reagents and recently attention has been focused on the use of lanthanide complexes as shift reagents (89-95). These complexes are Lewis acids and they form complexes with a wide variety of organic Lewis bases, including alcohols, esters, ketones, ethers, epoxides, sulfoxides and many others. These reagents causes shifts, either downfield or upfield, of proton nmr resonances and makes the analysis of an nmr spectrum simpler, i.e. much more "first-order" in nature. Indeed, these reagents greatly enhance the power and versatility of nmr spectroscopy.

Of the many functional groups that have been studied with these reagents, there has yet been no study made involving the >P=O group. It was of interest, therefore, to determine whether europium complexes would spread out and simply the nmr spectrum of 50. The normal ^1H nmr spectrum of 50 (in $CDCl_3$) is shown in Figure 9. On addition of ~5 mg of the europium complex, to the solution, a rather unexpected and interesting phenomenon occurred (Figure 10). Compound 50 completely reverted to benzaldehyde and diethyl α-phosphonoacetonitrile in the presence of catalytic amounts of $Eu(DPM)_3$. To the best of our knowledge, there has been no report of a dissociation of this type catalyzed by a europium chelate. This catalytic dissociation may be unique to this type of phosphorus compounds because when ethyl β-hydroxy-β-phenyl-α-methyl-propionate (52) was treated with $Eu(DPM)_3$, nothing happened except that there was broadening of the nmr peaks. This dissociation also takes place



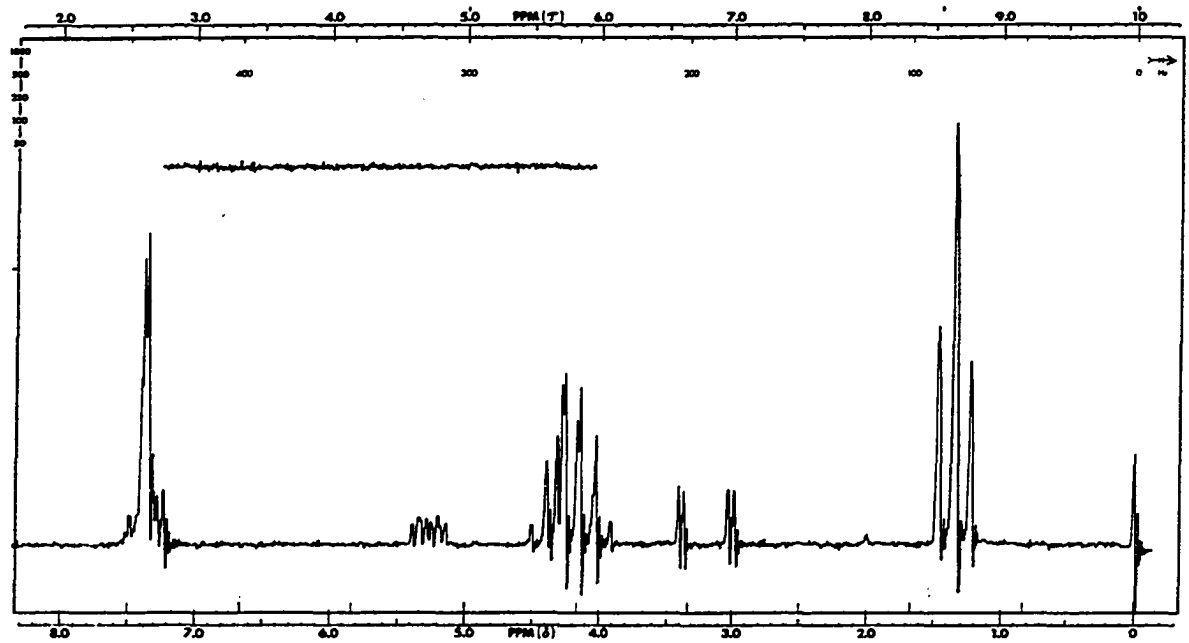
52

when benzene-d_6 is used as the solvent. An interesting feature of the nmr spectrum of 50 when run in benzene-d_6 is the fact that in this solvent we observe an aromatic solvent-induced shift (68). We noted a "spreading-out" of the spectrum and we could distinguish two types of ethoxyl groups in 50 (Figure 11).

We found that this dissociation is independent of the ligands attached to europium. We observed that tris (dipavalomethanato) europium III

Figure 9. NMR spectra of diethyl 1-cyano-2-hydroxy-2-phenyl-phosphonate (50) in $CDCl_3$

Figure 10. NMR spectra of 50 after treatment with ~5 mg of Eu $(DPM)_3$


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
400
300
200
100
0
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

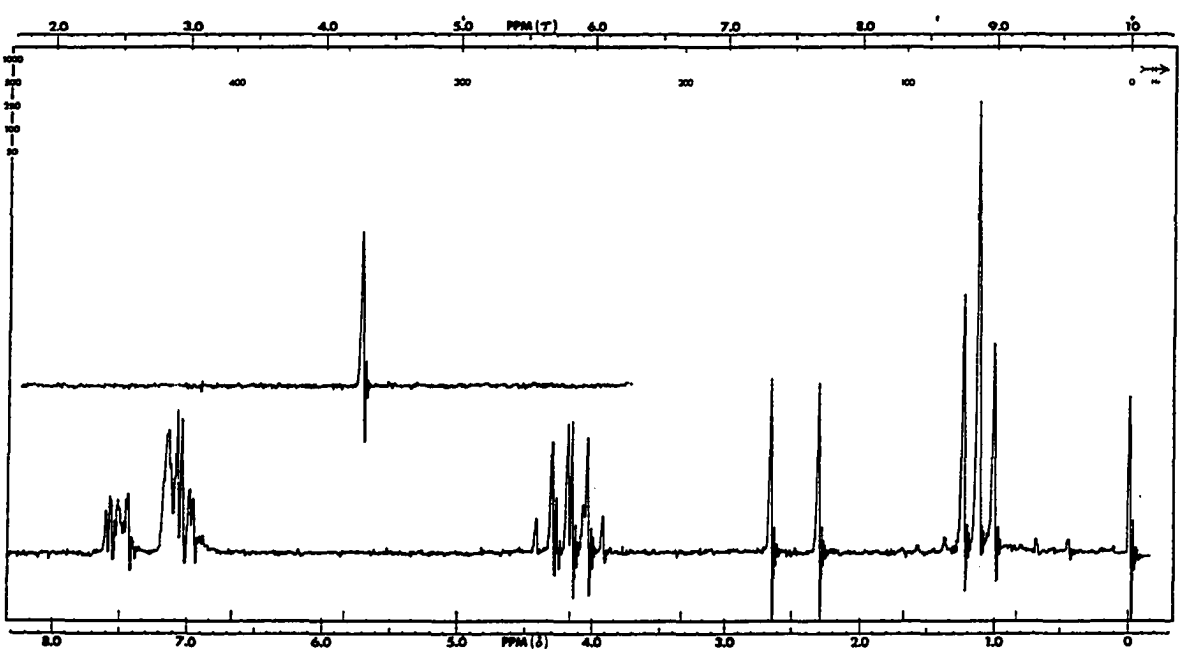
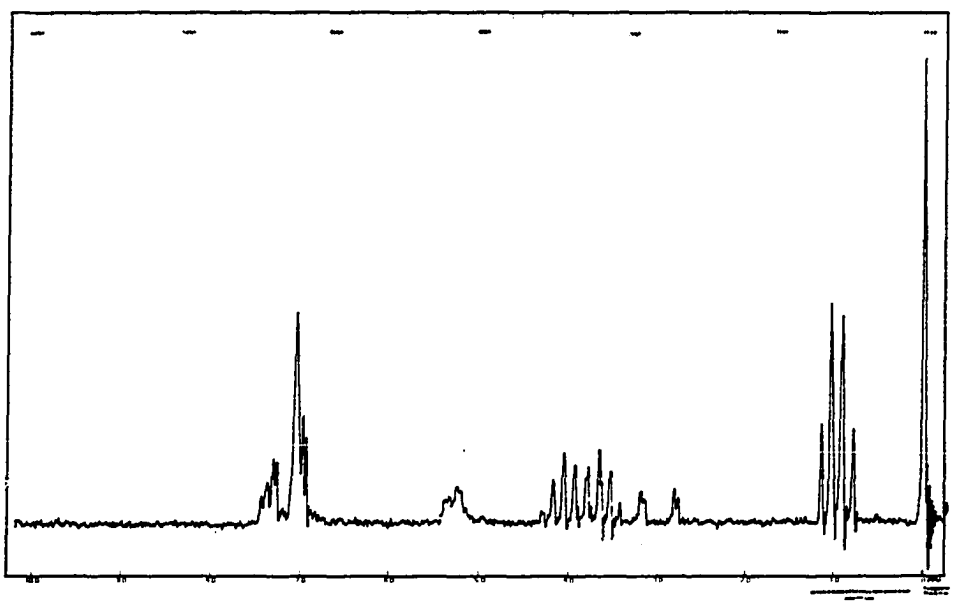
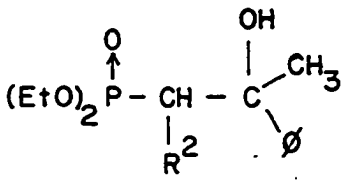

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
400
300
200
100
0
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

Figure 11. NMR spectrum of diethyl 1-cyano-2-hydroxy-2-phenylphosphonate (50) in benzene-d_6



$[Eu(DPM)_3]$ and europium nitrate, $[Eu(NO_3)_3]$, also effected the dissociation of 50. Although $Eu(NO_3)_3$ was only very slightly soluble in benzene-d_6 or deuterochloroform, partial dissociation of 50 to benzaldehyde and diethyl α-phosphonoacetonitrile could be detected by nmr.

We also attempted to prepare 53a and 53b by reacting the appropriate carbanion with acetophenone at low temperatures (-5° to -70°) and quenching the reaction with 2N acetic acid. We failed in these attempts in that the intermediate betaines proceeded on to the expected olefins even



53a: $R^2 = CO_2Et$

53b: $R^2 = CN$

at these temperatures. Despite these failures, we think it is interesting to note that even at these low temperatures, the cis/trans ratio did not differ very much from the cis/trans ratio obtained when the same reactions were carried out at higher temperatures (Table 9).

These results indicate that this reaction is a stereoselective reaction and that the observed cis/trans ratio is not the result of equilibration of the olefinic mixture as originally reported by Wadsworth and Emmons (8).

In summary then, we have found that the phosphonate modification of the Wittig reaction, in most cases, yields predominantly trans-olefins. However the introduction of an additional α-substituent in the phosphonate

Table 9. Reaction of triethyl α-phosphono-acetate (1a) and -acetonitrile (1f) with acetophenone at low temperatures

Phosphonate	Reaction temperature	% cis
1a	- 5°	17[a]
1f	-50°	12[b]
1f	-70°	13[b]

[a]At room temperature, % cis = 19% (Table 5).

[b]Jones and Maisey (65) observed 11% cis-olefin when the same reaction was run at 50°.

ester and the use of bulky, reactive, and/or electrophilic aldehydes and ketones result in a marked increase in the amount of cis-olefins formed. In some of the cases we have investigated, the cis-olefin became the predominant product. There is clearly a need for experimental investigation into the kinetics of this reaction.

EXPERIMENTAL

Instruments and Methods

The 60 MH_z nuclear magnetic resonance (nmr) spectra were obtained using a Varian Associates Model A-60 and Hitachi Perkin-Elmer Model R-20B spectrometers. Unless otherwise noted, all nmr spectra were obtained as solutions in carbon tetrachloride (CCl_4) with tetramethylsilane (tms) as the internal standard. The chemical shift values are reported in parts per million (ppm), δ units, relative to the internal standard.

Infrared (ir) spectra were obtained on a Beckman Model IR-12 spectrometer.

High resolution mass spectrometric measurements were made on an A.E.I. MS 902 double focusing instrument using the peak-matching technique.

Microanalytical data were obtained from Chemalytics, Inc., Tempe, Arizona.

Although absolute yields of the resulting α,β-unsaturated esters were not determined, these reactions generally give good yields of the esters (65-95%). The reaction goes smoothly and cleanly especially when sterically unhindered, electrophilic carbonyl compounds are used.

Ethyl 4-methyl-2-pentenoate (36*a*)

To a suspension of 1.44 g (0.03 moles) of sodium hydride (50% dispersion in oil) in 30 ml of 1,2-dimethoxyethane (freshly distilled from sodium hydride) was slowly added, with stirring, 6.72 g (0.03 moles) of triethyl α-phosphonoacetate (1*a*, obtained from Aldrich Chemical Co.). The reaction mixture was occasionally cooled in an ice-bath during the

addition to prevent excessive hydrogen bubbling. After the addition was complete, it was stirred at 15° for 1.5 hours, then warmed to 35° for 15 minutes and cooled to 15°. To the stirred solution was added dropwise 2.88 g (0.04 moles) of isobutyraldehyde. A gelatinous precipitate separated during the addition. The reaction mixture was stirred for 3 hours at room temperature after the addition of the aldehyde. About 75 mls of water was then added and the resulting homogenous solution was extracted with ether. The ether extracts were washed with two portions of water and dried over anhydrous magnesium sulfate. Under reduced pressure the ether was distilled off leaving a residue which, by nmr and vpc (8', 10% Carbowax 20M, 110°), contained only ethyl trans-4-methyl-2-pentenoate. The nmr spectrum of a purified sample of 36a (8', 10% Carbowax, 110°) exhibited resonances at 1.08 δ (terminal CH_3's, d, J = 6.7 cps), 1.23 δ ($-OCH_2\underline{CH_3}$, t, J = 7 cps), 2.4 δ (γ-H, m), 4.1 δ ($-O\underline{CH_2}CH_3$, q, J = 7 cps), 5.68 δ (α-H, doublet of doublets, $J_{\alpha,\beta}$(trans) = 15.7 cps, $J_{\alpha,\gamma}$(cis) = 1.5 cps), and at 6.84 δ (β-H, doublet of doublets, $J_{\beta,\alpha}$(trans) = 15.7 cps, $J_{\beta,\gamma}$ = 6.7 cps). Jorgenson and Leung (96) reported resonances at 5.72 δ and 6.88 δ for the α- and β-protons of 36a. IR (film): 1730 cm^{-1} (c = o), 1660 cm^{-1} (c = c).

Ethyl 4,4-dimethyl-2-pentenoate (36b)

This compound was prepared in the manner described above for the preparation of ethyl 4-methyl-2-pentenoate (36a) using 0.48 g (0.01 moles) of 50% NaH, 2.24 g (0.01 moles) or triethyl α-phosphonoacetate (1a) and 1.72 g (0.02 moles) or pivaldehyde. Only ethyl trans-4,4-dimethyl-2-pentenoate could be detected by nmr and vpc (8', 10% Carbowax 20M, 110°).

The nmr spectrum of a purified sample of 36b (8', 10% Carbowax 20M, 110°) exhibited resonances at 105 δ (terminal CH_3's, s), 1.23 δ ($-OCH_2\underline{CH_3}$, t, J = 7 cps), 4.1 δ ($-O\underline{CH_2}CH_3$, q, J = 7 cps), 5.68 δ (α-H, d, $J_{\alpha\beta}$(trans) = 16 cps), and at 6.86 δ (β-H, d, $J_{\beta\alpha}$(trans) = 16 cps). IR (film): 1727 cm^{-1} (c = o), 1655 cm^{-1} (c = c); Anal. Calcd. for $C_9H_{16}O_2$:156.115; Found: 156.116.

Triethyl α-phosphonopropionate (1b)

This compound was prepared by the method described by Michaelis-Arbusov (66). In a 500 ml, three-necked, round-bottom flask equipped with a mechanical stirrer, a gas dispersion tube, and a condenser which was connected to a dry ice-isopropanol trap, a mixture of 90.5 g (0.5 moles) of ethyl α-bromopropionate and 166 g (1.0 mole) of triethyl phosphite was heated to reflux at 140-145° for 7 hours. Nitrogen gas was bubbled through the reaction mixture to carry over the ethyl bromide, as it was formed, into the dry ice-isopropanol trap. Distillation of the resulting solution at reduced pressure using a bantam-size Vigreaux column gave 98.8 g (83%) of triethyl α-phosphonopropionate (1b), b.p. 86-92°/0.5 mm [lit. (97) 102-103°/2 mm].

Ethyl 2-methyl-2-butenoate (36c)

Using the procedure described for the preparation of 36a, this compound was prepared using 1.92 g (0.04 moles) of 50% NaH, 9.52 g (0.04 moles) of triethyl α-phosphonopropionate (1b), and 2.2 g (0.05 moles) of acetaldehyde. Only ethyl trans-2-methyl-2-butenoate could be detected by nmr and by vpc (8', 10% Carbowax, 20M, 110°). The nmr spectrum of a purified sample of 36c (8', 10% Carbowax 20M, 110°) exhibited resonances at 1.27δ

($-OCH_2\underline{CH_3}$, t, J = 7 cps), 1.78 δ (α- and β-CH_3's, m), 4.12 δ($-O\underline{CH_2}CH_3$, q, J = 7 cps), and at 6.74 (β-H, m). Our assignment is in agreement with the results of Fraser (98) in his nmr study of methyl tiglate and methyl angelate. He reported resonances at 1.75 δ, 1.8 δ, and 6.72 δ for the β-methyl, α-methyl, and β-proton, respectively. IR (film): 1715 cm^{-1} (c = o), 1655 cm^{-1} (c = c).

Ethyl 2-methyl-2-pentenoates (36d)

Using the procedure described for the preparation of 36a, this compound was prepared using 1.92 g (0.04 moles) of 50% NaH, 9.52 g (0.04 moles) of 1b and 2.90 g (0.05 moles) of propionaldehyde. The nmr spectrum of the crude ester mixture exhibited triplet of quartets at 5.85 δ and 6.65 δ, corresponding to the β-proton of the cis- and trans-isomer, respectively. Integration of these peaks showed a cis/trans ratio of 16:84. Vpc analysis (8', 10% Carbowax 20M, 100°) of the same mixture showed a cis/trans ratio of 18:82. Pure samples of ethyl cis- and trans-36d were collected by preparative vpc (8', 10% Carbowax 20M, 100°). Only a small amount of the cis-isomer could be collected; ir (film): 1715 cm^{-1} (c=o), 1650 cm^{-1} (c=c). The nmr spectrum of the trans-isomer exhibited resonances at 1.06 δ (CH_3, t, J = 7 cps), 1.28 δ ($-OCH_2\underline{CH_3}$, t, J = 7 cps), 1.79 δ (α-CH_3, m), 2.18 δ ($-CH_2-$, m), 4.11 δ ($-O\underline{CH_2}$ H_3, q, J = 7 cps) and at 6.61 δ (β-H, triplet of quartets, $J_{\beta\alpha}$ = 7.2 cps, J_{H,CH_3} (trans) = 1.5 cps). IR (film): 1710 cm^{-1} (c=o), 1650 cm^{-1} (c=c). These results are in agreement with results obtained by McGreer, et al. (72a, b) in their study of the methyl ester corresponding to 36d.

Ethyl 2,4-dimethyl-2-pentenoates (36e)

Using the procedure described for the preparation of 36a, this compound was prepared using 1.92 g (0.04 moles) of 50% NaH, 9.52 g (0.04 moles) of 1b, and 3.6 g (0.05 moles) of 2-methylpropionaldehyde. The nmr spectrum of the crude ester mixture exhibited a pair of doublet of quartets at 5.62 δ and 6.46 δ corresponding to the β-proton of the cis- and trans-ester, respectively. Integration of these peaks showed a cis/trans ratio of 70:30. Vpc analysis (8', 10% Carbowax 20M, 110°) of the same mixture indicated a cis/trans ratio of 72:28.

The above reaction was repeated using dimethylformamide as solvent. A mixture of 75:25 cis/trans ester was obtained. Pure samples of cis- and trans-36e were collected by preparative vpc (8', 10% Carbowax 20M, 110°).

cis-36e exhibited resonances at 0.97δ (terminal CH_3's, d, J = 6.5 cps), 1.27δ ($-CH_2\underline{CH_3}$, t, J = 7 cps), 1.82δ (α-CH_3, d, J = 1.5 cps), 3.25δ (methine, m), 4.1δ ($-O\underline{CH_2}CH_3$, q, J = 7 cps), and at 5.62δ (β-H, doublet of quartets, $J_{\beta\gamma} \cong 9.6$ cps, J_{H,CH_3} (cis) = 1.5 cps).

trans-36e exhibited resonances at 1.0δ (terminal CH_3's, d, J = 6.5 cps), 1.23δ ($-OCH_2\underline{CH_3}$, t, J = 7 cps), 1.8δ (α-CH_3, d, J = 1.5 cps), 2.63δ (methine, m), 4.12δ ($-O\underline{CH_2}CH_3$, q, J = 7 cps) and at 6.46 δ (β-H, doublet of quartets, $J_{\beta\gamma}$ = 9.6 cps, J_{H,CH_3} (trans) = 1.5 cps).

These results are in accord with the results obtained by Jorgenson and Leung (96) who prepared cis- and trans-36e using the same method. They observed that the cis- and trans-esters were formed in the ratio of 3:1. The β-proton of cis-36e appeared at 5.62δ, while the β-proton of trans-36e appeared at 6.42δ.

To establish that these compounds were stable under the reaction conditions, the following experiments were carried out:

a) 2.38 g (0.01 moles) of 1b was added to a slurry of 0.48 g (0.01 mole) of 50% NaH in 10 mls of 1,2-dimethoxyethane at room temperature. To the resulting solution was added 1.98 g (0.013 moles) of a mixture of cis- and trans-36e (67:33). After 11 hours, a 4 ml aliquot portion was worked up in the usual manner. The nmr spectrum of the crude product from this portion showed a cis/trans ratio of 68:32. Trans-36e (0.5 g, 0.0032 moles) was then added to the reaction mixture. Three hours after the addition, another 4 ml aliquot portion showed a cis/trans ratio of 55:45 (assuming no equilibration, a cis/trans of 54:46 was expected). Then 0.48 g (0.01 moles) of 50% NaH was added and the ratio of isomers remained the same after stirring for an additional 5 hours at room temperature.

b) 36e was prepared in the usual manner using 0.96 g (0.02 moles) of 50% NaH, 4.76 g (0.02 moles) of 1b and 1.8 g (0.025 moles) of 2-methyl-propionaldehyde. Twenty hours after the addition of the aldehyde, a 10 ml aliquot portion was drawn out and worked up as usual. This portion contained cis- and trans-36e in a ratio of 63:37. To the reaction mixture was then added 1.0 g of a mixture enriched in the cis-isomer (82% cis) at room temperature. After 24 hours, another 10 ml aliquot was drawn out and worked up. This portion contained 70% cis and 30% trans. Assuming a quantitative yield and no isomerization, the theoretical cis/trans ratio is 69:31.

Ethyl 2,4-dimethyl-2-hexenoates (36f)

Using the procedure described for the preparation of 36a, this compound was prepared using 1.44 g (0.03 moles) of 50% NaH, 7.14 g (0.03

moles) of 1b and 3.44 g (0.04 moles) of 2-methylbutyraldehyde. From the nmr spectrum and vpc analysis (8', 10% Carbowax 20M, 110°) of the reaction mixture, the cis/trans ratio was 67:33. Pure samples of cis- and trans-36f were collected by preparative vpc (8', 10% Carbowax 20M, 110°).

cis-36f exhibited resonances at 0.92 δ (5H, m), 1.3 δ (6H, t, J = 7 cps), 1.86 δ (3H, d, J = 1.8 cps), 3.0 δ (1H, m), 4.13 δ (2H, q, J = 7 cps), and at 5.58 δ (1H, broad doublet, J = 9.2 cps). IR (film): 1720 cm^{-1}(c=o), 1650 cm^{-1} (c=c); Anal. Calcd. for $C_{10}H_{18}O_2$:170.130; Found: 170.129.

trans-36f exhibited resonances at 1.0 δ (5H, m), 1.3 δ (6H, t, J = 7 cps), 1.8 δ (3H, d, J = 1.8 cps), 2.38 δ (1H, m), 4.13 δ (2H, q, J = 7 cps), and at 6.45 δ (1H, broad doublet, J = 9.2 cps). IR (film): 1720 cm^{-1} (c=o), 1655 cm^{-1} (c=c).

Ethyl 2,4,4-trimethyl-2-pentenoates (36g)

Using the procedure described for the preparation of 36a, this compound was prepared using 1.92 g (0.04 moles) of 50% NaH, 9.52 g (0.04 moles) of 1b and 4.3 g (0.05 moles) of pivaldehyde. By nmr and by vpc (8', 10% Carbonwax 20M, 110°), this reaction yielded a 50:50 mixture of cis- and trans-36g. When the same reaction was run in dimethylformamide it yielded a cis/trans ratio of 47:53. Pure samples of cis- and trans-36g were collected by preparative vpc (8', 10% Carbowax 20M, 110°).

cis-36g exhibited resonances at 1.07 δ (9H, s), 1.29 δ (3H, t, J = 7 cps), 1.72 δ (3H, d, J = 1.5 cps), 4.12 (2H, q, J = 7 cps), and at 5.39 δ (1H, q, J = 1.5 cps). See Figure 1. IR (film): 1730 cm^{-1} (c=o), 1655 cm^{-1} (c=c); Anal. Calcd. for $C_{10}H_{18}O_2$: 170.130; Found: 170.131.

trans-36g exhibited resonances at 1.19 δ (9H, singlet superimposed on triplet), 1.29 δ (3H, t, J = 7 cps), 1.89 δ (3H, d, J = 1.5 cps), 4.1δ (2H, q, J = 7 cps), and at 6.64δ (1H, q, J = 1.5 cps). See Figure 2. IR (film): 1720 cm^{-1} (c=o), 1645 cm^{-1} (c=c).

Triethyl α-phosphonobutyrate (1c)

Using the procedure described for the preparation of 1b, this compound was prepared using 40.7 g (0.2 moles) of ethyl α-bromobutyrate and 66.4 g (0.4 moles) of triethyl phosphite. The reaction yielded 40.32 g (80% of triethyl α-phosphonobutyrate, b.p. 85-87°/0.05 mm [lit. (99) b.p. 101-103°/0.2 mm].

Ethyl 2-ethyl-2-butenoates (36h)

Using the procedure described for the preparation of 36a, this compound was prepared using 0.96 g (0.02 moles) of 50% NaH, 5.04 g (0.02 moles) of 1c, and 1.32 g (0.03 moles) of acetaldehyde. The nmr spectrum of the resulting ester mixture exhibited a pair of quartets in the 5-7 δ region in addition to the other expected peaks: 5.91 δ (cis β-H, quartet of triplets, $J_{\beta\gamma}$ = 7.5 cps, J_{H,CH_2} (cis) = 1.5 cps) and 6.75 δ (trans β-H, q, $J_{\beta\gamma}$ = 7 cps). Integration of these peaks gave a cis/trans ratio of 18:82. The mass spectrum of this mixture showed a parent ion at m/e 142. Anal. Calcd. for $C_8H_{14}O_2$:142.099; Found: 142.101.

Ethyl 2-ethyl-2-pentenoate (36i)

Using the procedure described for the preparation of 36a, this compound was prepared using 1.44 g (0.03 moles) of 50% NaH, 7.56 g (0.03 moles) of 1c, and 2.32 g (0.04 moles) of propionaldehyde. The nmr spectrum of the

resulting ester mixture exhibited a pair of triplets in the 5-7 δ region in addition to the other expected peaks: 5.8 δ (cis β-H, triplet of triplets, J_{H,CH_2} (vic) = 7.2 cps, J_{H,CH_2} (cis) = 1.5 cps), and 6.68 δ (trans β-H, t, J_{H,CH_2} (vic) = 7.2 cps). Integration of these peaks showed that the mixture contained cis- and trans-36i in the ratio of 41:59. The mass spectrum of this mixture showed a parent ion at m/e 156. Anal. Calcd. for $C_9H_{16}O_2$: 156.115; Found: 156.115.

Ethyl 2-ethyl-4-methyl-2-pentenoates (36j)

Using the procedure described for the preparation of 36a, this compound was prepared using 1.92 g (0.04 moles) of 50% NaH, 10.08 g (0.04 moles) of 1c and 3.60 g (0.05 moles) of 2-methylpropionaldehyde. The nmr spectrum of the resulting ester mixture exhibited a pair of doublets in the 5-7 δ region in addition to the other expected peaks: 5.52 δ (cis β-H, doublet of triplets, $J_{H,CH}$(vic) = 9.5 cps, J_{H,CH_2} (cis) = 1.5 cps), and 6.42 δ (trans β-H, doublet, $J_{H,CH}$(vic) = 9.5 cps). Integration of these peaks and vpc analysis (8', LAC 446, 150°) of the mixture showed that it contained cis- and trans-36j in the ratio of 84:16. The mass spectrum of the mixture exhibited a parent ion at m/e 170. Anal. Calcd. for $C_{10}H_{18}O_2$:170.1305; Found: 170.131.

Ethyl 2-ethyl-4,4-dimethyl-2-pentenoates (36k)

Using the procedure described for the preparation of 36a, this compound was prepared using 1.92 g (0.04 moles) of 50% NaH, 10.08 g (0.04 moles) of 1c and 4.3 g (0.05 moles) of pivaldehyde. By nmr and vpc analysis (8', LAC 446, 150°) the ester mixture was shown to contain cis- and trans-36k in the ratio of 55:45. Samples of cis- and trans-36k were collected by preparative

vpc (8', LAC 446, 150°).

cis-36k exhibited resonances at 1.05 δ (terminal CH_3's, singlet superimposed on triplet), 1.27 δ ($-OCH_2\underline{C}H_3$, t, J = 7 cps), 2.16 δ (methylene, m), 4.12 δ ($-O\underline{C}H_2CH_3$, q, J = 7 cps) and at 5.35 δ (β-H, t, J_{H,CH_2} (cis) = 1.5 cps). Anal. Calcd. for $C_{11}H_{20}O_2$:184.146; Found: 184.146.

trans-36k exhibited resonances at 1.0 δ (terminal CH_3, t, J = 7 cps), 1.19 δ (terminal CH_3's, singlet superimposed on triplet), 1.27 δ ($-OCH_2\underline{C}H_3$, t, J = 7 cps), 2.30 δ (methylene, m), 4.12 δ ($-O\underline{C}H_2CH_3$, q, J = 7 cps), and at 6.52 δ (β-H, s). Anal. Calcd, for $C_{11}H_{20}O_2$:184.146; Found: 184.145.

Ethyl 2-bromo-2-butenoates (361)

These compounds were prepared using the method described by Wadsworth and Emmons (8). Triethyl α-phosphonoacetate (4.48 g, 0.02 moles) was added dropwise at 20° to a slurry of 50% NaH (0.96 g, 0.02 moles) in 30 mls of dry 1,2-dimethoxyethane. The solution was stirred for about one hour. Bromine (3.2 g, 0.02 moles) was added dropwise to the solution. Occasional cooling with ice water was necessary as the reaction with bromine was exothermic and the color was discharged immediately. After the addition of bromine, a yellowish slurry resulted. The reaction mixture was warmed at 40° for about five minutes and then cooled to 10°. 50% NaH (0.96 g, 0.02 moles) was then added all at once and rapid gas evolution took place. After stirring for one hour at room temperature, acetaldehyde (1.32 g, 0.03 moles) was added dropwise. Near the end of the addition, a gummy precipitate formed. Stirring was continued for three hours and the mixture was diluted with 150 mls of water. The aqueous solution was extracted with ether. The

ether extracts were dried over anhydrous magnesium sulfate and concentrated. From the nmr and vpc analysis (8', 10% Carbowax 20M, 110°) it was shown that the mixture contained cis- and trans-36l in the ratio of 19:81. A purified sample (8', 10% Carbowax 20M, 110°) of cis- and trans-36l exhibited resonances at 1.28 δ ($-OCH_2\underline{CH_3}$, t, J = 7 cps), 1.92 δ (trans-β-CH_3, d, J = 7 cps), 2.0 δ (cis-β-CH_3, d, J = 7 cps), 4.22 δ ($-O\underline{CH_2}CH_3$, q, J = 7 cps), 6.74 δ (cis-β-H, q, J = 7 cps), and at 7.34 δ (trans-β-H, q, J = 7 cps). IR (film): 1720 cm^{-1} (c=o), 1630 cm^{-1} (c=c); Anal. Calcd. for $C_6H_9BrO_2$: 191.978; C, 37.33; H, 4.70; Found: 191.979; C, 37.68; H, 4.95.

Ethyl 2-bromo-2-pentenoates (36m)

Using the procedure described for the preparation of 36l, this compound was prepared using 4.48 g (0.02 moles) of 1a, 0.96 g (0.02 moles) of 50% NaH, 3.2 g (0.02 moles) of bromine, 0.96 g (0.02 moles) of 50% NaH, and 1.74 g (0.03 moles) of propionaldehyde. Nmr and vpc (8', LAC 446, 100°) analyses of the resulting ester mixture indicated a cis/trans ratio of 25:75. A purified sample (8' LAC 446, 100°) of cis- and trans-36m exhibited resonances at 1.12 δ (CH_3-, t, J = 7 cps), 1.32 δ ($-OCH_2\underline{CH_3}$, t, J = 7 cps), 2.35 δ (methylene, m), 4.21 δ ($-O\underline{CH_2}CH_3$, q, J = 7 cps), 6.55 δ (cis-β-H, t, J = 7 cps) and at 7.15 δ (trans-β-H, t, J = 7.2 cps). Anal. Calcd. for $C_7H_{11}BrO_2$:205.994; C, 40.60; H, 5.35; Found: 205.993; C, 40.88; H, 5.58.

Ethyl 2-bromo-4-methyl-2-pentenoates (36n)

Using the procedure described for the preparation of 36l, this compound was prepared using 2.24 g (0.01 moles) of 1a, 0.48 g (0.01 moles) of 50% NaH, 1.6 g (0.01 moles) of bromine, 0.48 g (0.01 moles) of 50% NaH,

and 1.08 g (0.015 moles) of 2-methylpropionaldehyde. The nmr spectrum of the resulting ester mixture exhibited a pair of doublets in the 6-8 δ region in addition to the other expected peaks: 6.39 δ (cis-β-H, d, J = 10 cps) and 6.95 δ (trans-β-H, d, J = 9.5 cps). Integration of these peaks and vpc analysis (8' 10% Carbowax 20M, 125°) showed a cis/trans ratio of 58:42. Pure trans-36n exhibited resonances at 1.1 δ (terminal CH_3's, d, J = 7 cps), 1.33 δ ($-OCH_2\underline{C}H_3$, 5, J = 7 cps), 2.83 δ (methine, m), 4.2 δ ($-O\underline{C}H_2CH_3$, q, J = 7 cps) and at 6.95 δ (β-H, d, J = 10 cps). IR (film): 1730 cm^{-1} (c=o), 1625 cm^{-1} (c=c); Anal. Calcd. for $C_8H_{13}BrO_2$:220.010, Found: 220.008.

Ethyl 2-bromo-4-methyl-2-hexenoates (36o)

Using the procedure described for the preparation of 36l, this compound was prepared using 4.48 g (0.02 moles) of 1a, 0.96 g (0.02 moles) of 50% NaH, 3.2 g (0.02 moles) of bromine, 0.96 g (0.02 moles) of 50% NaH, and 2.58 g (0.03 moles) of 2-methylbutyraldehyde. From the nmr spectrum and vpc analysis (8' LAC 446, 100°) of the resulting ester mixture, it was shown that the cis/trans ratio was 53:46. A purified sample (8' LAC 446, 100°) of cis- and trans-36o exhibited resonances at 1.02 δ (5H, m), 1.3 (6H, t, J = 7 cps), 2.2-3.4 δ (1H, m), 4.20 δ (2H, q, J = 7 cps), 6.38 δ (0.5H, d, J = 10 cps) and at 7.05 δ (0.5H, d, J = 9.5 cps). IR (film): 1730 cm^{-1} (c=o), 1630 cm^{-1} (c=c); Anal. Calcd. for $C_9H_{15}BrO_2$: C, 45.97; H, 6.43; Found: C, 45.71; H, 6.38.

Ethyl 2-bromo-4,4-dimethyl-2-pentenoates (36p)

Using the procedure described for the preparation of 36l, this compound was prepared using 4.48 g (0.02 moles) of 1a, 0.96 g (0.02 moles)

of 50% NaH, 3.2 g (0.02 moles) of bromine, 0.96 g (0.02 moles) of 50% NaH, and 2.58 g (0.03 moles) of pivaldehyde. The nmr spectrum of the resulting ester mixture exhibited a pair of singlets in the 6-8 δ region: 6.18 δ (cis-β-H, s) and 7.4 δ (trans-β-H, s). Integration of these peaks and vpc analysis (8' 10% Carbowax 20M, 125°) showed a cis/trans ratio of 36:64. Pure trans-36p exhibited resonances at 1.29 δ (terminal CH_3's, singlet overlapping a triplet), 1.33 δ ($-OCH_2\underline{C}H_3$, t, J = 7 cps), 4.21 δ ($-O\underline{C}H_2CH_3$, q, J = 7 cps), and at 7.4 δ (β-H, s). IR (film): 1730 cm^{-1} (c=o), 1625 cm^{-1} (c=c); Anal. Calcd. for $C_9H_{15}BrO_2$: C, 45.97; H, 6.43; Found: C, 45.82; H, 6.33.

Ethyl 2-chloro-4-methyl-2-pentenoates (36q)

A phosphonate carbanion was formed in the usual manner using 4.48 g (0.02 moles) of 1a and 0.96 g (0.02 moles) of 50% NaH. Chlorine gas was then bubbled through the solution whereupon some sodium chloride precipitated. Bubbling of chlorine gas was continued until the reaction mixture remained yellow. Then 0.96 g (0.02 moles) of 50% NaH was added all at once. Stirring was continued for one hour at room temperature and 2.16 g (0.03 moles) of 2-methylpropionaldehyde was added dropwise. Work up was done in the usual manner. The nmr spectrum of the resulting ester mixture exhibited a pair of doublets in the 6-7 δ region: 6.7 δ (cis-β-H, d, J = 10 cps) and 6.84 δ (trans-β-H, d, J = 9 cps). Grell and Macleidt (100) have previously reported that these protons appear at 6.15 δ and 6.81 δ, respectively. Integration of these peaks indicated a cis/trans ratio of 65:35. The mass spectrum of the mixture exhibited a parent ion at m/e 176. Anal. Calcd. for $C_8H_{13}ClO_2$:176.060; Found: 176.060.

Ethyl 2-chloro-4-methyl-2-hexenoates (36r)

Triethyl α-chloro-α-phosphonoacetate (1e) was prepared using the procedure described above. The same amount of materials were used. After the phosphonate ester was formed, 0.96 g (0.02 moles) of 50% NaH was added all at once. Stirring was continued for one hour at room temperature and 2.57 g (0.03 moles) of 2-methylbutyraldehyde was added dropwise. The crude ester mixture resulting from the usual work up procedure exhibited a pair of doublets in the 6-7 δ region: 6.15 δ (cis-β-H, d, J = 10 cps) and 6.83 δ (trans-β-H, d, J = 9.5 cps). Integration of these peaks showed a cis/trans ratio of 52:48. The mass spectrum of the mixture exhibited a parent ion at m/e 190. Anal. Calcd. for $C_9H_{15}ClO_2$:190.076; Found: 190.076.

α-Carbethoxyethylidenetriphenylphosphorane (38a)

This compound was prepared using the method described by O. Isler, et al. (101). To a solution of 66.6 g (0.254 moles) of triphenylphosphine in 300 mls of benzene was added, dropwise, with stirring, 45.25 g (0.25 moles) of ethyl α-bromopropionate at room temperature. After the addition, the resulting solution was heated to 40-45°. The phosphonium bromide started to crystallize out of solution. Heating at 40-45° was continued overnight. The resulting mixture was concentrated and the residue was extracted with water. To the water extract was added dilute sodium hydroxide until the solution was basic to phenolphthalein. The precipitate that formed was filtered, washed with water, and dried to give 36 g (40%) of crude 38a, m.p. 148-156°. Recrystallization from an ethyl acetate - petroleum ether mixture gave 27 g of pure 38a, m.p. 154-156° [lit. (101) m.p. 156-157°].

Ethyl 2,4-dimethyl-2-pentenoates (36e) using phosphorane method

This compound was prepared according to the procedure described by House and Rasmusson (74). To a solution of 6.6 g (0.02 moles) of 38a in 50 mls of methylene chloride was added dropwise and with stirring, 1.1 g (0.018 moles) of 2-methylpropionaldehyde. The solution was stirred overnight at 35-40°. Then it was concentrated by distillation of about half of the methylene chloride and diluted with 50 mls of petroleum ether. The triphenylphosphine oxide was filtered and washed with petroleum ether. The combined petroleum ether solutions were concentrated to give 95% trans-36e and 5% cis-36e.

Ethyl 2,4-dimethyl-2-hexenoates (36f) using phosphorane method

Using the procedure described above for the preparation 36e, this compound was prepared using 6.6 g (0.02 moles) of 36a and 1.72 g (0.02 moles) of 2-methylbutyraldehyde. The nmr spectrum of the resulting ester mixture indicated an almost exclusive formation (>95%) of trans-36f with trace amounts of cis-36f.

Ethyl α-methylcinnamate (39a)

Using the procedure described for the preparation of 36a, this compound was prepared using 2.4 g (0.05 moles) of 50% NaH, 11.9 g (0.05 moles) of 1b, and 10.5 g (0.10 moles) of benzaldehyde. The presence of a large excess of benzaldehyde interfered with the analysis of the nmr spectrum of the crude product mixture. Vpc analysis (8' 10% Carbowax 20M, 165°) of this mixture showed the presence of only one isomer. A sample of this isomer was collected by preparative vpc (8' 10% Carbowax 20M, 165°).

The nmr spectrum of the purified sample exhibited resonances at 1.3 δ ($-OCH_2\underline{CH}_3$, t, J = 7 cps), 2.05 δ (α-CH_3, d, J = 1.5 cps), 4.2 δ ($-O\underline{CH}_2CH_3$, q, J = 7 cps), 7.25 δ (phenyl, s), and at 7.4 δ (β-H, q, J = 1.5 cps). We have assigned a trans-configuration to this isomer. This assignment is in accord with results obtained by Valente and Wolfhagen (102). They reported that the β-proton of cis-39a appeared at 6.41 δ and the β-proton of the trans-isomer appeared at 7.35 δ. IR (film): 1715 cm^{-1} (c=o), 1635 cm^{-1} (c=c).

Ethyl m-methoxy-α-methylcinnamate (39b)

Using the procedure described for the preparation of 36a, this compound was prepared using 0.96 g (0.02 moles) of 50% NaH, 4.76 g (0.02 moles) of 1b, and 4.5 g (0.03 moles) of m-methoxybenzaldehyde. The nmr spectrum and vpc analysis (8' LAC 446, 175°) of the resulting ester mixture showed the presence of only one isomer. A sample of this isomer was collected by preparative vpc (8' LAC 446, 175°). The nmr spectrum of the purified sample exhibited resonances at 1.31 δ ($-OCH_2\underline{CH}_3$, t, J = 7 cps), 2.07 δ (α-CH_3, d, J = 1.5 cps), 3.75 δ (m-OCH_3, s), 4.2 δ ($-O\underline{CH}_2CH_3$, q, J = 7 cps), 6.92 δ (phenyl, m), and at 7.63 δ (β-H, q, J = 1.5 cps). We have assigned a trans-configuration to this isomer. IR (film): 1715 cm^{-1} (c=o), 1640 cm^{-1} (c=c). Anal. Calcd. for $C_{13}H_{16}O_3$: 220.110; Found: 220.108.

Ethyl p-methoxy-α-methylcinnamate (39c)

Using the procedure described for the preparation of 36a, this compound was prepared using 0.48 g (0.01 moles) of 50% NaH, 2.38 g (0.01 moles) of 1b and 2.72 g (0.02 moles) of p-methoxybenzaldehyde. The nmr

spectrum and vpc analysis (8' LAC 446, 175°) of the resulting ester mixture showed the presence of only one isomer. The nmr spectrum of this mixture exhibited a peak at 2.1 δ (α-CH_3, d, J = 1.5 cps) which is characteristic of the trans-isomer. The mass spectrum of the mixture exhibited a parent ion at m/e 220. Anal. Calcd. for $C_{13}H_{16}O_3$:220.110; Found: 220.109.

Ethyl o-chloro-α-methylcinnamates (39e)

Using the procedure described for the preparation of 36a, this compound was prepared using 0.48 g (0.01 moles) of 50% NaH, 2.38 g (0.01 moles) of 1b, and 2.8 g (0.02 moles) of o-chlorobenzaldehyde. When half of the aldehyde had been added to the phosphonate carbanion, a 5 ml aliquot portion was withdrawn from the reaction mixture and worked up in the usual manner. Another 5 ml aliquot was withdrawn at completion of the addition of the aldehyde to the carbanion. Analyses of the nmr spectra and vpc analyses (8' LAC 446, 175°) of both aliquot portions and the resulting ester mixture after 9 hours of stirring at room temperature each showed that the reaction yielded cis- and trans-39e in the ratio of 11:89. Samples of cis- and trans-39e were collected by preparative vpc (8' LAC 446, 175°).

cis-39e exhibited resonances at 0.95 δ ($-OCH_2\underline{CH_3}$, t, J = 7 cps), 2.1 δ (α-CH_3, d, J = 1.5 cps), 4.0 δ ($-O\underline{CH_2}CH_3$, q, J = 7 cps), 6.8 δ (β-H, q, J = 1.5 cps), and at 7.3 - 7.5 δ (phenyl, m). IR (film): 1720 cm^{-1} (c=o), 1650 cm^{-1} (c=c).

trans-39e exhibited resonances at 1.34 δ ($-OCH_2\underline{C}H_3$, t, J = 7 cps), 1.98 δ (α-CH_3, d, J = 1.6 cps), 4.23 δ ($-O\underline{C}H_2CH_3$, q, J = 7 cps), 7.2 - 7.4 δ (phenyl, m), and at 7.67 δ (β-H, q, J = 1.6 cps). IR (film): 1720 cm^{-1} (c=o), 1645 cm^{-1} (c=c). Anal. Calcd. for $C_{12}H_{13}ClO_2$:224.060; Found: 224.058.

Ethyl o,o'-dichloro-α-methylcinnamates (39f)

Using the procedure described for the preparation of 36a, this compound was prepared using 0.48 g (0.01 moles) of 50% NaH, 2.38 g (0.01 moles) of 1b and 2.62 g (0.015 moles) of 2,6-dichlorobenzaldehyde. Aliquot portions (5 ml) were withdrawn from the reaction mixture during and after the addition of the aldehyde. The nmr spectra and vpc analyses (8' LAC 446, 175°) of these aliquot portions and the resulting product mixture showed that only one isomer was formed with the virtual exclusion of the other. A trace of the other isomer could be detected at 2.1 which is characteristic of the α-methyl group of the cis-isomer. A sample of the major isomer was collected by preparative vpc (8' LAC 446, 175°). The nmr spectrum of the purified sample exhibited resonances at 1.36 δ ($-OCH_2\underline{C}H_3$, t, J = 7 cps), 1.75 δ (α-CH_3, d, J = 1.5 cps), 4.25 δ ($-O\underline{C}H_2CH_3$, q, J = 7 cps), 7.28 δ (phenyl, m), and 7.35 δ (β-H, q, J = 1.5 cps). IR (film): 1725 cm^{-1} (c=o), 1655 cm^{-1} (c=c); Anal. Calcd. for $C_{12}H_{12}Cl_2O_2$: 258.021; Found: 258.018.

Ethyl 2,3,4,5,6-pentafluoro-α-methylcinnamates (39f)

Using the procedure described for the preparation of 36a, this compound was prepared using 0.48 g (0.01 moles) of 50% NaH, 2.38 g (0.01

moles) of 1b and 1.96 g (0.01 moles) of 2,3,4,5,6-pentafluorobenzaldehyde. From the nmr spectrum and vpc analysis (8' LAC 446, 170°) of the resulting mixture, it was shown that the cis/trans ratio was 10:90. A purified sample (8' LAC 446, 170°) of cis- and trans-39f exhibited resonances at 1.2 δ (cis-$OCH_2\underline{CH_3}$, t, J = 7 cps), 1.39 δ (trans-$OCH_2\underline{CH_3}$, t, J = 7 cps), 1.91 δ (trans-α-CH_3, m), 2.2 δ (cis-α-CH_3, m), 4.13 δ (cis-$O\underline{CH_2}CH_3$, q, J = 7 cps), 4.28 δ (trans-$O\underline{CH_2}CH_3$, q, J = 7 cps), 6.54 δ (cis-β-H, m), and at 7.3 δ (trans-β-H, m). IR (film): 1730 cm^{-1} (c=o), 1660 cm^{-1} (c=c). Anal. Calcd. for $C_{12}H_9F_5O_2$:280.052; Found: 280.053.

Ethyl α,β-dimethylcinnamates (40a)

Using the procedure described for the preparation of 36a, this compound was prepared using 0.96 g (0.02 moles) of 50% NaH, 4.76 g (0.02 moles) of 1b and 3.6 g (0.03 moles) of acetophenone. The nmr spectrum and vpc trace (8' LAC 446, 175°) of the resulting ester mixture indicated that cis- and trans-40a were formed in the ratio of 36:64. It was shown that this ratio remained constant during the addition of the aldehyde to the phosphonate carbanion by analysis of 5 ml aliquot portions taken during the addition. This compound was also prepared by adding the phosphonate carbanion to a 5-fold molar excess of acetophenone. Using this method, a cis/trans ratio of 34:66 was obtained. A purified sample (8' LAC 446, 175°) of cis- and trans-40a exhibited resonances at 0.75 δ (cis-$OCH_2\underline{CH_3}$, t, J = 7 cps), 1.3 δ (trans-$OCH_2\underline{CH_3}$, t, J = 7 cps), 1.71 δ (trans-α-CH_3, q, J = 1.7 cps), 2.0 δ (cis-α-CH_3, q, J $\simeq$ 1.2 cps), 2.06 δ (cis-β-CH_3, q, J $\simeq$ 1.2 cps), 2.25 δ (trans-β-CH_3, q, J $\simeq$ 1.7 cps), 3.74 δ (cis-$O\underline{CH_2}CH_3$, q, J = 7 cps), 4.19 δ (trans-$O\underline{CH_2}CH_3$, q, J = 7 cps), and at 7.0 - 7.35 δ (phenyl, m),

Figure 3. IR (film): 1720 cm^{-1} (c=o), 1635 cm^{-1} (c=c).

Ethyl m-methoxy-α,β-dimethylcinnamates (40b)

Using the procedure described for the preparation of 36a, this compound was prepared using 0.96 g (0.02 moles) of 50% NaH, 4.76 g (0.02 moles) of 1b, and 4.5 g (0.03 moles) of m-methoxyacetophenone. The nmr spectrum and vpc trace (8' LAC 446, 175°) of the resulting ester mixture indicated that cis- and trans-40b were formed in the ratio of 35:65. A purified sample (8' LAC 446, 175°) of cis- and trans-40b exhibited resonances at 0.79 δ (cis-$OCH_2\underline{CH}_3$, t, J = 7 cps), 1.27 δ (trans-$OCH_2\underline{CH}_3$, t, J = 7 cps), 1.75 δ (trans-α-CH_3, q, J = 1.7 cps), 1.98 δ (cis-α-CH_3, q, J = 1.2 cps), 2.05 δ (cis-β-CH_3, q, J = 1.2 cps), 2.25 δ (trans-β-CH_3, q, J = 1.7 cps), 3.72 δ (cis-m-OCH_3, s), 3.75 δ (trans-m-OCH_3), 3.8 δ (cis-OCH_2CH_3, q, J = 7 cps), 4.2 δ (trans-OCH_2CH_3, q, J = 7 cps) and at 6.5 - 7.3 δ (phenyl, m). IR (film): 1720 cm^{-1} (c=o), 1640 cm^{-1} (c=c); Anal. Calcd. for $C_{14}H_{18}O_3$:234.125; Found: 234.127.

Ethyl p-methoxy-α,β-dimethylcinnamates (40c)

Using the procedure described for the preparation of 36a, this compound was prepared using 0.48 g (0.01 moles) of 50% NaH, 2.38 g (0.01 moles) of 1b and 2.25 g (0.015 moles) of p-methoxyacetophenone. The nmr spectrum of the resulting product mixture indicated that cis- and trans-esters were formed in the ratio of 39:61. The nmr spectrum of the crude mixture exhibited resonances at 1.78 δ (trans-α-CH_3, q, J = 1.5 cps), 2.0 δ (cis-α- and β-CH_3's, m) and at 2.25 δ (trans-β-CH_3, q, J = 1.5 cps) in addition to the expected peaks.

Ethyl p-nitro-α,β-dimethylcinnamates (40d)

Using the procedure described for the preparation of 36a, this compound was prepared using 1.92 g (0.04 moles) of 50% NaH, 9.52 g (0.04 moles) of 1b and 8.25 g (0.05 moles) of p-nitroacetophenone. The nmr spectrum of the resulting ester mixture indicated a cis/trans ratio of 45:55. The nmr spectrum of the crude mixture exhibited resonances at 1.74 δ (trans-α-CH_3, q, J = 1.5 cps), 2.02 δ (cis-α-CH_3, m), 2.12 δ (cis-β-CH_3, m), and at 2.28 δ (trans-β-CH_3, q, J = 1.5 cps) in addition to the expected peaks.

Ethyl p-chloro-α,β-dimethylcinnamates (40e)

Using the procedure described for the preparation of 36a, this compound was prepared using 0.96 g (0.02 moles) of 50% NaH, 4.76 g (0.02 moles) of 1b, and 4.62 (0.03 moles) of p-chloroacetophenone. From the nmr and vpc analysis (8' 10% Carbowax 20M, 150°), it was shown that the mixture contained cis- and trans-40e in the ratio of 42:58. A purified sample (8' 10% Carbowax 20M, 150°) of cis- and trans-40e exhibited resonances at 0.85 δ (cis-$OCH_2\underline{CH_3}$, t, J = 7 cps), 1.32 δ (trans-$OCH_2\underline{CH_3}$, t, J = 7 cps), 1.7 δ (trans-α-CH_3, q, J = 1.5 cps), 1.98 δ (cis-α-CH_3, m), 2.03δ (cis-β-CH_3, m), 2.2 δ (trans-β-CH_3, q, J = 1.5 cps), 3.8δ (cis-$O\underline{CH_2}CH_3$, q, J = 7 cps), 4.17δ (trans-$O\underline{CH_2}CH_3$, q, J = 7 cps), and at 6.8 - 7.4 δ (phenyl, m). IR (film): 1720 cm^{-1} (c=o), 1640 cm^{-1} (c=c); Anal. Calcd. for $C_{13}H_{15}ClO_2$:238.076; Found: 238.077.

2,5-Dichloroacetophenone

Following the procedure of Kshatriya, et al. (103) 37.6 g (0.3 moles) of finely pulverized aluminum chloride was added to a mixture of 29.2 g (0.2 moles) of p-dichlorobenzene and 23.4 g (0.3 moles) of acetyl chloride. The reaction mixture was stirred at room temperature for 24 hours and then heated at 100° for one hour. The resulting solution was cooled to room temperature, poured into a mixture of 200 g of ice and 100 mls of concentrated hydrochloric acid, and extracted with ether. The combined ether extracts were dried and concentrated. The residue was vacuum distilled to give 20 g (53%) of 2,5-dichloroacetophenone, b.p. 130-135/15 mm [lit. (103) b.p. 245-50°/276]. The nmr spectrum of the distillate exhibited resonances at 2.58 δ (3H, s), 7.3 δ (2H, d) and at 7.49 δ (1H, q).

Ethyl 2,5-dichloro-α,β-dimethylcinnamates (40f)

Using the procedure described for the preparation of 36a, this compound was prepared using 0.48 g (0.01 moles) of 50% NaH, 2.4 g (0.1 moles) of 1b and 2.8 g (0.015 moles) of 2,5-dichloroacetophenone. Vpc analysis (8' LAC 446, 175°) of the crude ester mixture showed that cis- and trans-40f were formed in the ratio of 53:47. A purified sample (8' LAC 446 175°) of cis- and trans-40f exhibited resonances at 0.88 δ (cis-$OCH_2\underline{CH}_3$, t, J = 7 cps), 1.32 δ (trans-$OCH_2\underline{CH}_3$, t, J = 7 cps), 1.62 δ (trans-α-CH_3, q, J = 1.5 cps), 2.01 δ (cis-α- and β-CH_3's, s), 2.2 δ (trans-β-CH_3, q, J = 1.5 cps), 3.83 δ (cis-$O\underline{CH}_2CH_3$, q, J = 7 cps), 4.2 δ (trans-$O\underline{CH}_2CH_3$, q, J = 7 cps), and at 7.15 δ (phenyl, m). Anal. Calcd. for $C_{13}H_{14}Cl_2O_2$:272.037; Found: 272.035.

Ethyl β-methylcinnamates (41a)

Using the procedure described for the preparation of 36a, this compound was prepared using 0.48 g (0.01 moles) of 50% NaH, 2.24 g (0.01 moles) of 1a and 1.8 g (0.015 moles) of acetophenone. The nmr spectrum and the vpc trace (8' LAC 446, 175°) of the resulting ester mixture indicated that cis- and trans-41a were formed in the ratio of 19:81. Pure samples of cis- and trans-41a were collected by preparative vpc (8' LAC 446, 175°).

cis-41a exhibited resonances at 1.03 δ ($-OCH_2\underline{CH_3}$, t, J = 7cps), 2.15 δ (β-CH_3, d, J = 1.5 cps), 3.9 δ ($-O\underline{CH_2}CH_3$, q, J = 7 cps), 5.8 δ (α-H, q, J = 1.5 cps), and at 7.19 δ (phenyl, m). Figure 4. IR(film): 1728 cm^{-1} (c=o), 1630 cm^{-1} (c=c).

trans-41a exhibited resonances at 1.28 δ ($-OCH_2\underline{CH_3}$, t, J = 7 cps), 2.53 δ (β-CH_3, d, J = 1.3 cps), 4.14 δ ($-O\underline{CH_2}CH_3$, q, J = 7 cps), 6.06 δ (α-H, q, J = 1.3 cps), and at 7.34 δ (phenyl, m). Figure 5. IR(film): 1718 cm^{-1} (c=o), 1630 cm^{-1} (c=c). The nmr spectrum of trans-41a agrees very well with the spectrum reported by Ide and Kishida (79). They observed the β-methyl and α-proton at 2.54 δ and 6.07 δ, respectively.

Ethyl 2,5-dichloro-β-methylcinnamates (41b)

Using the procedure described for the preparation of 36a, this compound was prepared using 0.48 g (0.01 moles) of NaH, 2.24 g (0.01 moles) of 1a, and 3.0 g (0.016 moles) of 2,5-dichloroacetophenone. The nmr spectrum and vpc trace (8' LAC 446, 175°) of the resulting ester mixture indicated that cis- and trans-41b were formed in the ratio of 24:76. A

purified samples (8' LAC 446, 175°) of cis- and trans-41b exhibited resonances at 1.08 δ (cis-$OCH_2\underline{CH_3}$, t, J = 7 cps), 1.29 δ (trans-$OCH_2\underline{CH_3}$, t, J = 7 cps), 2.12 δ (cis-β-$\underline{CH_3}$, d, J = 1.5 cps), 2.44 δ (trans-β-$\underline{CH_3}$, d, J = 1.5 cps), 4.06 δ (cis-$O\underline{CH_2}CH_3$, q, J = 7 cps), 4.16 δ (trans-$O\underline{CH_2}CH_3$, q, J = 7 cps), 5.76 (trans-α-H, q, J = 1.5 cps), 5.92 δ (cis-α-H, q, J = 1.5 cps), and at 7.0 - 7.3 δ (phenyl, m). Figure 6. IR (film): 1725 cm^{-1} (c=o), 1650 cm^{-1} (c=c); Anal. Calcd. for $C_{12}H_{12}Cl_2O_2$:258.021; Found: 258.018.

Carbethoxymethylenetriphenylphosphorane (38b)

Using the procedure described for the preparation of 38a, this compound was prepared using 66.6 g (0.254 moles) of triphenylphosphine, and 30.5 g (0.26 moles) of ethyl chloroacetate. The reaction yielded 39 g (45%) of crude carbethoxymethylenetriphenylphosphorane. A 2 g-portion was recrystallized from petroleum ether to give 1.3 g of 38b, m.p. 115-118° [lit. (101) m.p. 116-117°].

Ethyl β-trifluoromethylcinnamates (42a)

This compound was prepared according to the procedure of Dull, et al. (81). In a dry 25 ml flask fitted with a reflux condenser was placed 1.3 g (3.7 m moles) of 38b, 0.64 g (3.7 m moles) of 1,1,1-trifluoroacetophenone and 10 mls of benzene. Upon heating to reflux, solution occurred. Refluxing was then continued for 3 hours. After cooling, benzene was removed under reduced pressure and the residue was mixed with petroleum ether. The resulting mixture was filtered, and the filtrate was dried and concentrated. The nmr spectrum of the crude ester mixture showed the

predominance of one isomer (cis/trans = 86:14).

This compound was also prepared by the method described for the preparation of 36a using 0.48 g (0.01 moles) of 50% NaH, 2.24 g (0.01 moles) of 1a and 2.8 g (0.016 moles) of 1,1,1-trifluoroacetophenone. By analyzing 5 ml aliquot portions drawn off during the addition of the ketone to the phosphonate carbanion, it was shown that the cis/trans ratio remained constant throughout the addition of the ketone. The nmr spectrum and vpc analysis (8' XF-1150 cyanosilicone, 175°) of the resulting ester mixture indicated that cis- and trans-42a were formed in the ratio of 84:16. Pure samples of cis- and trans-42a were collected by preparative vpc (8' XF-1150 cyanosilicone, 175°).

cis-42a exhibited resonances at 0.98 δ ($-OCH_2\underline{CH_3}$, t, J = 7 cps), 3.94 δ ($-O\underline{CH_2}CH_3$, q, J = 7 cps), 6.53 δ (α-H, q, J = 1.5 cps), and at 7.29 δ (phenyl, s). Figure 7. For the corresponding acid, the α-proton appears at 6.43 δ (78). IR (film): 1740 cm^{-1} (c=o), 1655 cm^{-1} (c=c); Anal. Calcd. for $C_{12}H_{11}F_3O_2$: C, 59.02; H, 7.54; Found: C, 59.04; H, 7.54

trans-42a exhibited resonances at 1.3 δ ($-OCH_2\underline{CH_3}$, t, J = 7 cps), 4.25 δ ($-\underline{OCH_2}CH_3$, q, J = 7 cps), 6.24 δ (α-H, s), and at 7.36 δ (phenyl, s). Figure 8. IR (film): 1740 cm^{-1} (c=o), 1650 cm^{-1} (c=c); Anal. Calcd. for $C_{12}H_{11}F_3O_2$:244.071; Found: 244.069.

Ethyl α-methyl-β-trifluoromethylcinnamates (42b)

Using the procedure described by Dull, et al. (81), this compound was prepared using 1.5 g (4.1 m moles) of 38a and 0.71 g (4.1 m moles) of 1,1,1-trifluoroacetophenone. The nmr spectrum of the resulting ester

mixture showed a cis/trans ratio of 63:37.

This compound was also prepared by the method described for the preparation of 36a using 0.96 g (0.02 moles) of 50% NaH, 4.76 g (0.02 moles) of 1b and 5.22 g (0.03 moles) of 1,1,1-trifluoroacetophenone. The nmr spectrum and vpc trace (8' 10% Carbowax 20M, 175°) of the resulting ester mixture showed a cis/trans ratio of 70:30.

When the same reaction was carried out by adding the phosphonate anion solution to the ketone, the resulting cis/trans ratio was 65:35. Pure samples of cis- and trans-42b were collected by preparative vpc (8' 10% Carbowax, 175°).

cis-42b exhibited resonances at 0.75 δ ($-OCH_2\underline{CH_3}$, t, J = 7 cps), 2.2 δ (α-$\underline{CH_3}$, q, J = 2.6 cps), 3.78 δ ($-O\underline{CH_2}CH_3$, q, J = 7 cps) and at 7.23 δ (phenyl, s). IR (film): 1735 cm^{-1} (c=o), 1655 cm^{-1} (c=c); Anal. Calcd. for $C_{13}H_{13}F_3O_2$:258.087; C, 60.46; H, 5.07; Found: 258.086; C, 60.46; H, 5.36.

trans-42b exhibited resonances at 1.3 δ ($-OCH_2\underline{CH_3}$, t, J = 7 cps), 1.82 δ(α-$\underline{CH_3}$, q, J = 2.1 cps), 4.25 δ ($-\underline{OCH_2}CH_3$, q, J = 7 cps), and at 7.3 δ (phenyl, s). IR (film): 1740 cm^{-1} (c=o), 1665 cm^{-1} (c=c); Anal. Calcd. for $C_{13}H_{13}F_3O_2$: C, 60.46; H, 5.07; Found: 60.64; H, 5.03.

Competition experiments involving triethyl α-phosphonopropionate (1b) acetophenone, and 1,1,1-trifluoroacetophenone

a) The phosphonate anion was prepared in the usual manner using 0.96 g (0.02 moles) of 50% NaH and 4.76 g (0.02 moles) of 1b. It was then added to a mixture of 9.6 g (0.08 moles) of acetophenone and 13.92 g (0.08 moles) of 1,1,1-trifluoroacetophenone. Aliquot portions were withdrawn during and

after the addition. These portions were analyzed by vpc (8', 10% Carbowax 20M, 175°) and the vpc traces indicated the presence of ethyl α-methyl-β-trifluoromethylcinnamates (42b). There was no trace of ethyl α,β- dimethyl-cinnamates (40a).

b) The same reaction in a) was carried out except that the mixture of ketones was added to the phosphonate anion solution. Vpc analysis again showed only peaks corresponding to cis- and trans-42b but showed no trace of cis- and trans-40a.

p-Fluoroacetophenone

Following the procedure described by Buu-Hoi, et al. (104), this compound was prepared using 30 g (0.31 moles) of fluorobenzene, 25 g (0.32 moles) of acetyl chloride and 50 g (0.37 moles) of aluminum chloride. The reaction was carried out using 100 ml of dry, freshly distilled carbon disulfide. p-Fluoroacetophenone (30 g, 75%) was collected at 60-62°/2.5 mm [lit. (104) b.p. 196°]. The distillate exhibited resonances at 2.5 δ (3H, s), 7.09 δ (2H, t), and at 7.95 (2H, doublet of doublets).

Ethyl p-fluoro-α, β-dimethylcinnamates (42c)

Using the procedure described for the preparation of 36a, this compound was prepared using 0.96 g (0.02 moles) of 50% NaH, 4.8 g (0.02 moles) of 1b, and 2.8 g (0.02 moles) of p-fluoroacetophenone. The nmr spectrum and vpc trace (8' LAC 446, 100°) of the resulting ester mixture indicated that cis- and trans-42c were formed in the ratio 38:62. A purified sample (8' LAC 446, 100°) of cis- and trans-42c exhibited resonances at 0.85 δ (cis-$OCH_2\underline{CH_3}$, t, J = 7 cps), 1.32 δ (trans-$OCH_2\underline{CH_3}$,

t, J = 7 cps), 1.73 δ (trans-α-CH_3, q, J = 1.3 cps), 1.98 δ (cis-α-CH_3, m), 2.05 δ (cis- -CH_3, m), 2.25 δ (trans-β-CH_3, q, J = 1.3 cps), 3.78 δ (cis-OCH_2CH_3, q, J = 7 cps), 4.19 δ (trans-OCH_2CH_3, q, J = 7 cps), and at 6.8 - 7.2 δ (phenyl, m). IR (film): 1715 cm^{-1} (c=o), 1635 cm^{-1} (c=c).

2,5-Difluoroacetophenone

Employing a modification of the procedure of Bergmann and Berkovic (105), 7.6 g (0.1 moles) of acetyl chloride was slowly added to a mixture of 11.4 g (0.1 moles) of p-difluorobenzene and 19.8 g (0.15 moles) of aluminum chloride. The resulting mixture was stirred at room temperature for 24 hours and then refluxed for 45 minutes. It was then poured into a mixture of ice and concentrated hydrochloric acid. Extraction with ether and distillation gave the desired ketone (6.7 g, 50%), b.p. 70-73/15 mm [lit (105) b.p. 61°/5 mm]. The nmr spectrum of the distillate exhibited resonances at 2.59 δ (3H, d, J = 5 cps) and at 7.0 - 7.6 δ (3H, m).

Ethyl 2,5-difluoro-α,β-dimethylcinnamates (42d)

Using the procedure described for the preparation of 36a, this compound was prepared using 0.96 g (0.02 moles) of 50% NaH, 4.8 g (0.02 moles) of 1b and 3.6 g (0.03 moles) of 2,5-difluoroacetophenone. The nmr spectrum and vpc trace (8' LAC 446, 110°) of the resulting ester mixture showed a cis/trans ratio of 48:52. A purified sample (8' LAC 446, 110°) of cis- and trans-42d exhibited resonances at 0.9 δ (cis-OCH_2CH_3, t, J = 7 cps), 1.3 δ (trans-OCH_2CH_3, t, J = 7 cps), 1.72 (trans-α-CH_3, q, J = 1.5 cps), 2.04 δ (cis-α- and β-CH_3's, m), 2.22 δ (trans-β-CH_3, q, J = 1.5 cps), 3.86 δ (cis-OCH_2CH_3, q, J = 7 cps), 4.21 δ (trans-OCH_2CH_3, q,

J = 7 cps), and at 6.6 - 7.2 δ (phenyl, m). IR (film): 1720 cm^{-1} (c=o), 1635 cm^{-1} (c=c); Anal. Calcd. for $C_{13}H_{14}F_2O_2$:240.096; Found: 240.098.

2,4-Difluoroacetophenone

This compound was prepared in the same manner described for the preparation of p-fluoroacetophenone using 2.5 g (0.02 moles) of m-difluorobenzene, 1.56 g (0.02 moles) of acetyl chloride, and 3.3 g (0.025 moles) of aluminum chloride. o,p-Difluoroacetophenone (1.8 g, 58%) was collected at 70-73°/15 mm [lit (106) b.p. 80-85°/25 mm]. The distillate exhibited resonances at 2.52 δ (3H, d, J = 4.9 cps), 6.9 δ (2H, m), and at 7.87 δ (1H, m).

Ethyl 2,4-difluoro-α,β-dimethylcinnamates (42e)

Using the procedure described for the preparation of 36a, this compound was prepared using 0.48 g (0.01 moles) of 50% NaH, 2.4 g (0.01 moles) of 1b, and 1.8 g (0.015 moles) of 2,4-difluoroacetophenone. The nmr spectrum and vpc trace (8' LAC 446, 110°) of the resulting ester mixture showed a cis/trans ratio of 58:42. A purified sample (8' LAC 446, 110°) of cis- and trans-42e exhibited resonances at 0.9 δ (cis-$OCH_2\underline{CH_3}$, t, J = 7 cps), 1.31 δ (trans-$OCH_2\underline{CH_3}$, t, J = 7 cps), 1.7 δ (trans-α-CH_3, q, J = 1.5 cps), 2.04 δ (cis-α- and β-CH_3's, s), 2.2 δ (trans-β-CH_3, q, J = 1.5 cps), 3.8 δ (cis-$O\underline{CH_2}CH_3$, q, J = 7 cps), 4.2 δ (trans-$O\underline{CH_2}CH_3$, q, J = 7 cps), and at 6.5 - 7.3 δ (phenyl, m). Anal. Calcd. for $C_{13}H_{14}F_2O_2$:240.096; Found: 240,096.

Ethyl β-trifluoromethyl-2-butenoates (42f)

Using the procedure described for the preparation of 36a, this compound was prepared using 0.48 g (0.01 moles) of 50% NaH, 2.24 g (0.01 moles) of 1a, and 1.12 g (0.01 moles) of 1,1,1-trifluoroacetone. Vpc analysis (8' LAC 446, 100°) of the resulting ester mixture showed a cis/trans ratio of 10:90. Pure samples of cis- and trans-42f were collected by preparative vpc (8' LAC 446, 100°).

cis-42f exhibited resonances at 1.3 δ ($-OCH_2\underline{CH_3}$, t, J = 7 cps), 2.0 δ (β-CH_3, d, J = 1.7 cps), 4.2 δ ($-O\underline{CH_2}CH_3$, q, J = 7 cps), and at 6.02 δ (α-H, m).

trans-42f exhibited resonances at 1.29 δ ($-OCH_2\underline{CH_3}$, t, J = 7 cps), 2.23 δ (β-CH_3, d, J = 1.7 cps), 4.19 δ ($-O\underline{CH_2}CH_3$, q, J = 7 cps), and at 6.29 δ (α-H, m).

Ethyl α-methyl-β-trifluoromethylbutenoates (42g)

Using the procedure described for the preparation of 36a, this compound was prepared using 0.48 g (0.01 moles) of 50% NaH, 2.38 g (0.01 moles) of 1b, and 2.24 g (0.02 moles) of 1,1,1-trifluoroacetone. Vpc analysis (8' 10% Carbowax 20M, 140°) of the crude ester mixture showed a cis/trans ratio of 10:90. Pure samples of cis- and trans-42g were collected by preparative vpc (8' 10% Carbowax 20M, 140°).

cis-42g exhibited resonances at 1.3 δ ($-OCH_2\underline{CH_3}$, t, J = 7 cps), overlapping multiplets centered about 1.87 δ (α-CH_3) and 1.95 δ (β-CH_3), and at 4.16 δ ($-O\underline{CH_2}CH_3$, g, J = 7 cps).

trans-42g exhibited resonances at 1.32 δ (-$OCH_2\underline{CH}_3$, t, J = 7 cps), overlapping multiplets centered about 1.95 δ (α-CH_3) and 2.05 δ (β-CH_3), and at 4.22 δ ($O\underline{CH}_2CH_3$, q, J = 7 cps).

β-Trifluoromethylcinnamic acids (45)

A mixture of ethyl cis- and trans- -trifluoromethylcinnamate (42a) was prepared by the reaction of 2.4 g (0.05 moles) of 50% NaH, 11.2 g (0.05 moles) of 1a, and 8.7 g (0.05 moles) of 1,1,1-trifluoroacetophenone. To the resulting ester mixture was then added 4 g of potassium hydroxide dissolved in 20 mls of water and 10 mls of 1,4-dioxane. The resulting mixture was refluxed for 10 hours, cooled, and then extracted with ether. The aqueous layer was acidified with ice cold dilute hydrochloric acid and extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate. Removal of the ether yielded 8.72 (80% overall yield) of the crude acids. Fractional recrystallization from petroleum ether yielded a batch of pure cis-45, m.p. 102 (sub) [lit. (78) m.p. 94]. Another batch of crystals was a mixture of the cis- and trans-isomers.

cis-45 exhibited resonances at 6.51 δ (α-H, q, J = 1.3 cps), 7.27 δ (phenyl, m), and at 11.51 δ ($CO_2\underline{H}$, s). Anal. Calcd. for $C_{10}H_7F_3O_2$: C, 55.57; H, 3.26; Found: C, 55.55; H, 3.07.

The nmr spectrum of the mixture of cis- and trans-acids showed, in addition to the resonances due to cis-45, resonances at 6.25 δ (trans-α-H, s) and at 7.32 δ (phenyl, m).

3-Trifluoro-1-indenone (47)

a) Following the procedure described by Kampmeier and Fantazier (75), 0.235 g (1.09 m moles) of cis-45 was added to 5 ml of concentrated sulfuric acid at 0°. The mixture was stirred for 2 minutes, poured into ice, and extracted with ether. The ether extracts were washed with saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. When the ether was evaporated, there was no detectable amount of product.

b) Procedure a) was repeated except that the reaction was allowed to go for 20 minutes. Again no detectable amount of product was formed.

c) Procedure a) was repeated carrying out the reaction at 40° for 20 minutes. Still no detectable amount of product was formed.

d) The same reaction was carried out in 5 mls of fuming sulfuric acid at 0° for 2 minutes. After washing with saturated sodium bicarbonate solution, the ether extract was concentrated to yield a yellow oil. The nmr spectrum of the oil was compatible with the expected indenone. It exhibited resonances at 6.17 (1H, q, J = 1.9 cps) and at 7.33 (4H, m). The mass spectrum of the oil exhibited a parent ion at m/e 198. Anal. Calcd. for $C_{10}H_5F_3O$:198.029; Found: 198.031. The sodium bicarbonate wash, after acidification and extraction with ether, yielded only trace amounts of the unreacted acid.

e) The reaction in d) was carried out on a mixture of cis- and trans-45 (46:54). After 2 minutes at 0°, the reaction mixture was worked up in the same manner as above. The ether extract yielded the desired indenone. The sodium bicarbonate wash only yielded the trans-acid.

Ethyl α-methyl-β-trifluoromethylcinnamic acids (46)

A mixture of ethyl cis- and trans-42b was prepared using 2.4 g (0.05 moles) of 50% NaH, 14.28 g (0.06 moles) of 1b, and 10.44 g (0.06 moles) of 1,1,1-trifluoroacetophenone. The resulting ester mixture was then hydrolyzed with potassium hydroxide as described in the preparation of 45, to give 8.0 g (70% overall yield) of a yellow oil which solidified slowly on standing. The nmr spectrum of the crude product indicated that the desired cinnamic acids were contaminated with benzoic acid. Recrystallization from petroleum ether failed to separate the cinnamic acids from the benzoic acid. It was felt that the presence of benzoic acid would not interfere with the cyclization experiment that no further attempt was made to get rid of the benzoic acid. The nmr spectrum of the recrystallized sample exhibited peaks (in addition to peaks due to benzoic acid) at 1.8 δ (trans-α-CH_3, q, J = 2.2 cps), 2.23 δ (cis-α-CH_3, q, J = 2.5 cps), and at 7.25 δ (phenyl, m).

2-Methyl-3-trifluoromethyl-1-indenone (48)

This compound was prepared by adding 0.70 g of the cis- and trans-acid mixture (85:15) obtained above to 15 mls of concentrated sulfuric acid at 0°. The reaction mixture was stirred for 10 minutes, poured into ice, and then extracted with ether. The ether extracts were washed with a saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate and concentrated to yield yellow crystals. Recrystallization from ether gave pure 48, m.p. 57-59°. The nmr spectrum of the recrystallized sample exhibited resonances at 2.04 δ (3H, q, J = 2.9 cps), and at 7.1 - 7.7 δ

(4H, m). The mass spectrum of 48 exhibited a parent ion at m/e 212. Anal. Calcd. for $C_{11}H_7F_3O$:212.045; Found: 212.046. The sodium bicarbonate wash yielded benzoic acid, trans-46, and a trace of unreacted cis-46.

β-Trifluorocinnamonitriles (49a)

Using the procedure described for the preparation of 36a, this compound was prepared using 0.96 g (0.02 moles) of 50% NaH, 3.54 g (0.02 moles) of diethyl α-phosphonoacetonitrile (1f), and 4.35 g (0.025 moles) of 1,1,1-trifluoroacetophenone. The nmr spectrum and vpc trace (8' Apiezon L, 175°) of the crude nitrile mixture indicated that the cis- and trans-isomers were formed in a ratio of 70:30. Pure samples of cis- and trans-49a were collected by preparative vpc (8' Apiezon L, 175°).

cis-49a exhibited resonances at 6.07 δ (α-H, q, J = 1.5 cps) and at 7.46 δ (phenyl, s). IR (film): 2235 cm^{-1} (c≡N), 1635 cm^{-1} (c=c); Anal. Calcd. for $C_{10}H_6F_3N$:197.045; Found: 197.046.

trans-49a exhibited resonances at 5.89 δ (α-H, s), and 7.42 δ (phenyl, s). IR (film): 2235 cm^{-1} (c≡N), 1630 cm^{-1} (c=c); Anal. Calcd. for $C_{10}H_6F_3N$: 197.045; Found: 197.046.

α-Methyl-β-trifluoromethylcinnamonitriles (49b)

To a suspension of 0.96 g (0.02 moles) of 50 NaH in 30 mls of 1,2-dimethoxyethane was slowly added, with stirring, 3.54 g (0.02 moles) of diethyl α-phosphonoacetonitrile (1f). After the addition, the solution was stirred for one hour. Methyl iodide (2.84 g, 0.02 moles) was added at room temperature and stirred for one hour at the same temperature. The resulting slurry was cooled to 10° and 0.96 g (0.02 moles) of 50% NaH was added all at once. The solution was allowed to come slowly to room temperature during

which time rapid exolution of gas took place. It was stirred for one hour at 40-45° and cooled to room temperature. 1,1,1-Trifluoroacetophenone (4.35 g, 0.025 moles) was then added slowly. The solution was stirred for 3 hours and taken up cautiously in a large excess of water. The aqueous layer was extracted with ether and the ether extracts were dried over anhydrous magnesium sulfate. Under reduced pressure, the ether was distilled off leaving a residue which, by nmr and vpc (8' Apiezon L, 200°), contained cis- and trans-49b in a ratio of 55:45. Pure samples of cis- and trans-49b were collected by preparative vpc (8' Apiezon L. 200°).

cis-49b exhibited resonances at 2.29 δ (3H, q, J = 2.6 cps), and at 7.37 δ (5H, m). IR (film): 2237 cm^{-1} (c≡N), 1635 cm^{-1} (c=c).

trans-49b exhibited resonances at 1.94 δ (3H, q, J = 2.1 cps), and at 7.3 δ (5H, m). IR (film): 2230 cm^{-1} (c≡N), 1640 cm^{-1} (c=c); Anal. Calcd. for $C_{11}H_8F_3N$: 211.061; Found: 211.061.

α,β-Dimethylcinnamonitriles (49c)

Using the procedure described for the preparation of 49b, this compound was prepared using 0.96 g (0.02 moles) of 50% NaH, 3.54 g (0.02 moles) of 1f, 2.84 g (0.02 moles) of methyl iodide, 0.96 g (0.02 moles) of 50% NaH, and 3.0 g (0.025 moles) of acetophenone. The nmr spectrum and vpc trace (8' Apiezon L, 150°) indicated that the cis- and trans-nitriles were formed in a ratio 24:76. A purified sample (8' Apiezon L, 150°) of cis- and trans-49c exhibited resonances at 1.78 δ (trans-α-CH_3, q, J = 1.8 cps), 2.0 δ (cis-α-CH_3, q, J = 1.2 cps), 2.1 δ (trans-β-CH_3, q, J = 1.2 cps), 2.29 δ (trans-β-CH_3, q, J = 1.8 cps), and at 6.95 - 7.5 δ (phenyl, m).

Diethyl 1-cyano-2-hydroxy-2-phenylphosphonate (50)

This compound was prepared according to the procedure described by Lefebvre and Seyden-Penne (88). To 2.43 g (0.1 moles) of magnesium turnings in 10 mls of dry tetrahydrofuran (THF), was slowly added 12.3 g (0.1 moles) of isopropyl bromide. The mixture was stirred at room temperature for approximately 45 minutes, then cooled in a dry ice-acetone bath. Then 17.7 g (0.1 moles) of 1f was added dropwise and the mixture was stirred for 3 hours. To the resulting phosphonate carbanion was slowly added 10.6 g (0.1 moles) of benzaldehyde in 40 mls of THF. The mixture is stirred again for 3 hours keeping it in a dry ice-acetone bath and then quenched with 200 mls of 2N acetic acid at the same temperature. The resulting mixture is extracted with ether. The ether extracts were washed with water until neutral, dried over anhydrous magnesium sulfate and concentrated to yield white crystals. The crystals were recrystallized from an ether-pentane (70:30) mixture, m.p. 104-106°. The nmr spectrum of the recrystallized material (in $CDCl_3$) exhibited resonances at 1.35 δ (6H, t, J = 7 cps), 3.19 δ (1H, doublet of doublets, J_{HP} = 23 cps, J_{vic} = 2.6 cps), 4.27 δ (5H, m), 5.27 δ (1H, m), and at 7.38 δ (5H, m). Figure 9.

a) After the addition of 5 mg of $Eu(thd)_3$ to the above solution, the resulting nmr spectrum exhibited resonances at 1.13 δ (6H, t, J = 7 cps), 2.49 δ (2H, d, J = 20.5 cps), 4.18 δ (4H, m), 7.1 δ (3H, m), 7.55 δ (2H, m), and at 9.72 δ (1H, s). Figure 10.

b) The nmr spectrum of 50 in benzene-d_6 exhibited resonances at 0.96 δ (6H, q, J = 7 cps), 2.98 δ (1H, doublet of doublets, J_{HP} = 23 cps, J_{vic} = 2.6 cps), 3.67 δ (2H, m), 4.05 δ (2H, m), 5.27 δ (2H, m), 7.0 δ (3H, m),

and at 7.33 δ (2H, m). Figure 11.

c) After the addition of $Eu(thd)_3$ to the nmr spectrum in b), the resulting nmr spectrum was identical with the spectrum obtained in a).

d) When 5 mg of $Eu(DPM)_3$ was added to a solution of 50 in benzene-d_6, the nmr spectrum of the resulting mixture was identical to the spectrum in a).

e) When 5 mg of $Eu(NO_3)_3$ was added to a solution of 50 in $CDCl_3$-benzene, the nmr spectrum of the resulting mixture indicated the presence of benzaldehyde and diethyl α-phosphonoacetonitrile (1f) together with some amount of undissociated 50. With time, the amount of 50 decreased as the benzaldehyde and 1f increased. Probably the slow dissociation of 50, in this case, may be explained by the low solubility of europium nitrate in $CDCl_3$-benzene.

Ethyl α-methyl-β-hydroxy-β-phenyl-propionate (52)

This compound was prepared according to the procedure described by Hauser and Breslow (107) for the preparation of ethyl β-phenyl-β-hydroxy-propionate. To 8 g (0.12 moles) of granular zinc was added 10 mls of a solution of 18.1 g (0.1 moles) of ethyl α-bromopropionate, and 1.3 g (0.12 moles) of benzaldehyde in 40 mls of benzene and 10 mls of ether. The flask is then warmed until the reaction started. The reaction mixture was stirred and the rest of the benzaldehyde solution was added slowly. After addition, the reaction mixture was refluxed for 2 hours and then cooled in an ice bath. Approximately 100 mls of cold 10% sulfuric acid was added with vigorous stirring. The acid layer was drawn off and the benzene-ether

solution was extracted twice with 25 mls of 5% sulfuric acid and washed consecutively with 15 mls of 10% sodium carbonate, 15 mls of 5% sulfuric acid, and with 25 mls of water. Vacuum distillation yielded 8.5 g (40%) of 52, b.p. 90-91°/1 mm [lit. (108) b.p. 120-125°/6.5 mm].

Dissociation of 50 in the presence of m-chlorobenzaldehyde

To a mixture of 0.283 g (1 m mole) of diethyl 1-cyano-2-hydroxy-2-phenylphosphonate (50), 0.048 g (3 m moles) of m-chlorobenzaldehyde, and 20 mls of 1,2-dimethoxyethane was added 0.048 g (1 m mole) of 50% NaH. Bubbling occurred immediately upon addition of sodium hydride. The mixture was stirred at room temperature for 15 minutes; quenched with 30 mls of water; and extracted with ether. The ether extract was concentrated to yield an oil. Vpc analysis (8' Apiezon L, 190°) of this oil indicated that the m-chlorocinnamonitriles and cinnamonitriles were formed in a ratio of 92:8.

Reaction of diethyl α-phosphonoacetate (1a) with acetophenone at low temperatures A phosphonate carbanion was prepared in the usual manner using 0.96 g (0.02 moles) of 50% NaH and 4.48 g (0.02 moles) of 1a. The resulting phosphonate anion solution was then cooled to -5°. To this cooled solution was slowly added 2.4 g (0.02 moles) of acetophenone. The mixture was stirred for 30 minutes at -5° after the addition. The reaction was quenched with 2N acetic acid and extracted with ether. The ether extracts were washed with water until neutral, dried over anhydrous magnesium sulfate, and concentrated to yield a yellow liquid. The nmr spectrum of this liquid indicated that ethyl β-methylcinnamates (41a) were

formed (cis/trans = 17:83).

Reaction of diethyl α-phosphonoacetonitrile (1f) with acetophenone at low temperatures a) A phosphonate carbanion was prepared in the usual manner using 0.96 g (0.02 moles) of 50% NaH and 3.54 g (0.02 moles) of 1f. The resulting phosphonate anion solution was cooled to -50°. To this cooled solution was slowly added 2.4 g (0.02 moles) of acetophenone. The mixture was then stirred for 45 minutes at -50°. The reaction was quenched with 2N acetic acid and extracted with ether. The ether extracts were washed with water until neutral, dried over anhydrous magnesium sulfate, and concentrated to yield a yellow liquid. The nmr spectrum of this liquid indicated the presence of β-methylcinnamonitriles (cis/trans = 12:88).

b) The same reaction as in a) was carried out at -70°. The nmr spectrum of the resulting product mixture showed that cis- and trans-β-methylcinnamonitriles were formed in a ratio of 13:87.

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