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Phosphorus Bearing Substrates in Ring Expansion Reactions

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This is to certify that the dissertation prepared by Bradley Kent Norwood entitled Phosphorus Bearing Substrates in Ring Expansion Reactions has been approved by his committee as satisfactory completion of the requirement for the degree of Doctor of Philosophy in Chemistry.

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Phosphorus Bearing Substrates in Ring Expansion Reactions

A Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry at Virginia Commonwealth University.

By

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Ph.D., Virginia Commonwealth University, December 1995
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DEDICATION

To my beautiful wife Robin, who endured much more than she bargained for. Your love, support and patience have meant more to me than I will ever be able to express.

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List of Abbreviations

1. TBDMS: *tert*-Butyl dimethyl silyl
2. bp: Boiling point
3. bs: Broad singlet
4. DMAD: Dimethyl acetylenedicarboxylate
5. DMSO: Dimethyl sulfoxide
6. d: Doublet
7. dd: Doublet of doublets
8. dq: Doublet of quartets
9. dt: Doublet of triplets
10. GC: Gas chromatography
11. GC/MS: Gas chromatography/mass spectroscopy
12. Hz: Hertz
13. HMPA: Hexamethyl phosphoramide
14. HWE: Horner-Wadsworth-Emmons
15. IR: Infrared
16. LAH: Lithium aluminum hydride
17. m: Multiplet
18. mp: Melting point

19. NMR: Nuclear magnetic resonance
20. q: Quartet
21. s: Singlet
22. t: Triplet
23. THF: Tetrahydrofuran
24. TLC: Thin-layer chromatography.

Phosphorus Bearing Substrates in Ring Expansion Reactions.

Abstract

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry at Virginia Commonwealth University.

Bradley K. Norwood, Ph.D.

Virginia Commonwealth University, 1995

Research Advisor: Dr. Suzanne M. Ruder

A variety of substituted phosphonium salts, phosphorus ylides and phosphonates were studied to assess their utility in ring expansion reactions. The strategy involved formation of fused ring systems whose ring strain could be exploited to accomplish ring expansion to medium sized rings. β-Alkoxy vinylphosphonium salts were found to be unreactive with species such as the dimethylsulfoxonium methylide anion, Simmons-Smith type reagents, and carbenes in attempts to produce cyclopropyl phosphonium salts.

C-Alkylation of β-keto phosphorus ylides using haloalkanes bearing terminal groups that could be converted and reacted with the β-carbonyl, was also examined as a method for accessing strained rings bearing electron donating alkoxy groups and electron withdrawing phosphorus substituents. The presence of C-alkylated phosphonium salt products was detected by NMR analysis of crude reaction mixtures for diiodomethane and dibromoethane, but synthetically useful yields were not obtained except for the reaction with methyl iodide.

Alkynyl phosphonates, however, were found to be adequate substrates for

cycloaddition with enamines to yield ring expanded products. This represents the first ring expansion *via* cycloaddition of alkynyl phosphonates. The reactivities of enamines derived from pyrrolidine or morpholine were compared in the cycloaddition. Efficiency in formation of seven and eight member rings from the enamines of cyclopentanone and cyclohexanone were thus examined. The unsaturated medium sized rings thus obtained were probed for their utility in Michael addition. This method may provide access to the basic framework of a number of natural products found to have biological activity.

Chapter 1:

Introduction

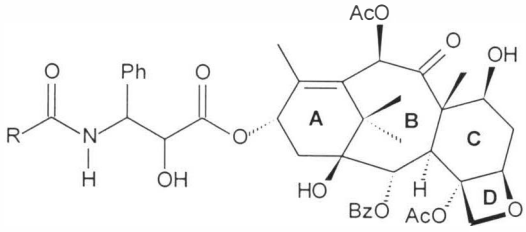
A wide array of highly complex natural products have been isolated and characterized over the past few years. Many of these compounds have been shown to exhibit important biological, agricultural, and chemical properties, making them attractive synthetic targets. Synthetic methodologies leading to the assembly of these complex, biologically active constituents is of great importance, since they occur in extremely low abundance in the flora and fauna of the world. In other words, since isolation from natural sources leads to production of relatively minute amounts of these compounds at relatively high expense, synthetic pathways must be designed to generate useful quantities of these drugs. These limitations have restricted the availability of medicinally useful drugs, "environmentally safe" pesticides and herbicides, as well as compounds with structural or mechanical properties of interest to the industrial sector.

In **Figure 1** are shown several examples of biologically active compounds found in nature. These examples serve to illustrate the wide variety and complexity of natural products. One structural feature shared by all of the compounds shown in **Figure 1** is the presence of a medium sized ring. Medium sized rings are defined as rings comprised of

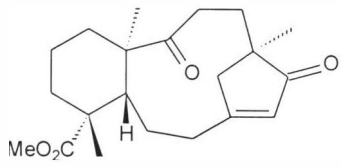
eight to eleven carbons. Another notable feature shared by these compounds is the presence of a double bond at a bridgehead site. The term "bridgehead" is used to denote atoms at either end of a chain shared by two rings such that a three ring system is formed (designated by arrows in **Figure 2**). The bridge can consist of zero to several carbons. For instance, in the structure for Taxol, **1**, the A and B rings are joined by a one carbon bridge. The B and C rings, however, are joined by a zero carbon bridge, that is, a bond directly between the bridgehead atoms, with no other intervening atoms.

Many of the compounds shown in **Figure 1** have been found to exhibit remarkable biological activity as anticancer or antibacterial agents.[1] Taxol, perhaps the most intensely studied of the compounds shown here, is remarkable at least as much for its mechanism of action as for its efficacy.[2] Taxol has been approved by the Food and Drug Administration for the treatment of ovarian cancer, which results in 13,000 deaths annually throughout the United States.[3] Since the survival rate for ovarian cancer is only 35%, this translates into over 20,000 new cases diagnosed annually in the United States alone. Taxol is obtained from the Pacific Yew tree in an overall abundance of 0.02% by weight in the stem bark (less in the heartwood). Unfortunately, this arboreal source of taxol must be destroyed in order to collect the drug.[1a] Clearly, new methods of obtaining useful quantities of taxol or related derivatives must be developed.

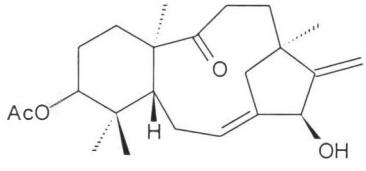
Because of the intense interest in taxol medicinally, structure-activity relationships for many of the prominent features of this compound have been undertaken.[4] The availability of a synthetic route to such compounds may also afford access to even more potent synthetic analogs. Among other key elements, it has been shown that the **A** ring



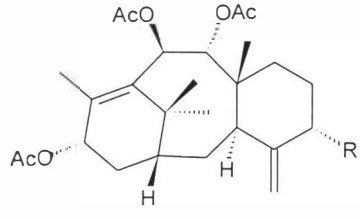
1: Taxol, R = Ph
2: Taxotere, R = $OC(CH_3)_3$
3: Cephalomannine, R = $C(CH_3)CHCH_3$



4: Foetidin



5: Rabdohakusin



6: Taxusin, R = OAc
7: Taxanine, R = $O_2CCHCHPh$

Figure 1: Natural Products With Medium Sized Rings and Bridgehead Double Bonds.

of taxol is necessary for the observed biological activity. Analogs identical to taxol in all other regio- and stereochemical respects, except that an acyclic fragment exists in place of the substituted cyclohexene ring **A**, show markedly reduced activity (between 20 and 40 times weaker than taxol).[5] This suggests that in order to produce a successful synthetic mimic for taxol, and most likely other compounds in the group, the selected method must afford not only the medium sized ring, but also produce the bridgehead alkene. Additionally, there must also be access to further functionalization of the framework.

The goal of the research reported herein has been to develop methods which could be applied to the total synthesis of not only the compounds shown in **Figure 1**, but many other compounds as well. Particular emphasis has been placed on devising a short series of reactions which would lead to the basic carbon framework of the compounds listed in **Figure 1**, consisting of a bridged bicyclic system, including a medium sized ring and a double bond at one bridgehead site (**Figure 2**). To this end, a functional group was sought which could act as an activating group in ring expansion reactions to generate the medium sized rings, and could also participate in formation of the bridgehead alkene.

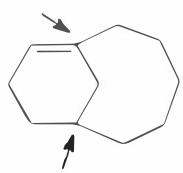


Figure 2: Basic Bridged Bicyclic Medium Sized Ring.

While small rings are relatively easy to form, medium sized rings are more difficult to formand to functionalize. Access to medium sized rings must be either by direct cyclization (a process not favored for rings of this size due to conformational and entropy factors[6]), or by expansion of an existing ring. Shown in **Figure 3** are the three basic pathways for performing expansion of an existing ring by one or more carbons.[7] Method A involves scission of the central bond between two rings of a bicyclic system.[8] Inherent in this approach is the ability to generate the properly functionalized bicyclic system such that cleavage of the shared bond will be promoted to give the desired ring expansion product. Method B consists of the addition of a side chain that can further react with the original ring system by insertion to effect ring expansion.[9] Finally, method C is a reaction of two side chains, usually by some kind of pericyclic reaction (*e. g.* oxy-Cope rearrangement), which will simultaneously form one carbon-carbon bond, while cleaving a bond of the original ring structure.[10] It should be noted that methods B and C often proceed through a transition state or an intermediate analogous to the bicyclic structure depicted in method A.[7] In general, there must be a directing group or leaving group attached at or near the ring junction in order to facilitate cleavage of the central, shared bond, irrespective of the method chosen. The regiospecific cleavage of the shared bond can be accomplished by polarization of this bond with an electron withdrawing group (acceptor) and an electron donating group (donor). If, however, one of the rings is small enough (three or four membered), relief of ring strain alone can be sufficient to promote ring expansion.[11]

Selective cleavage of the shared bond resulting in an expanded ring is illustrated

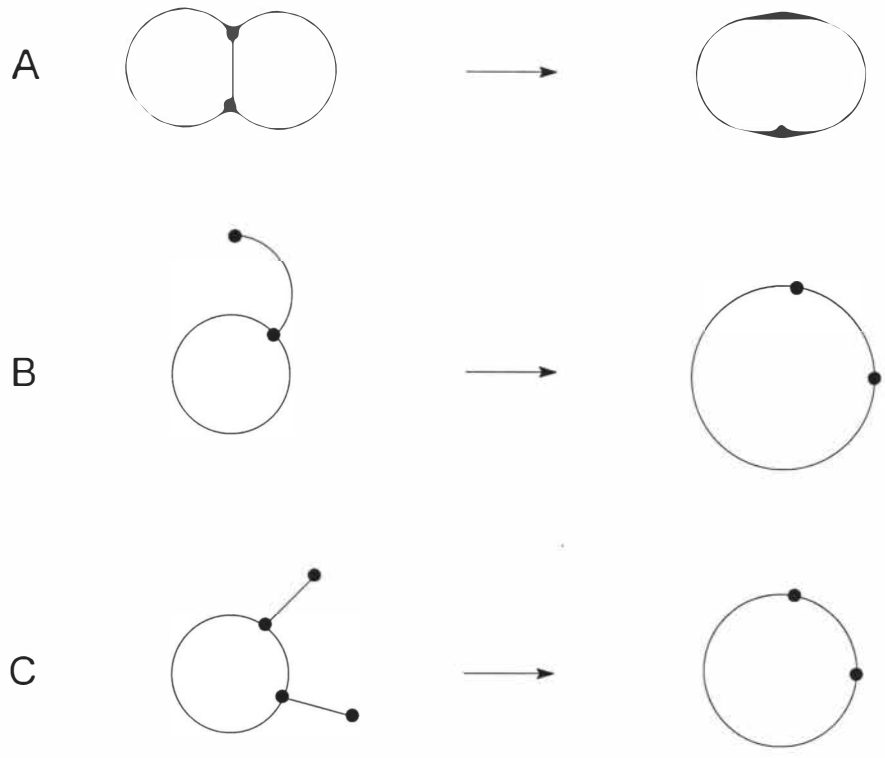
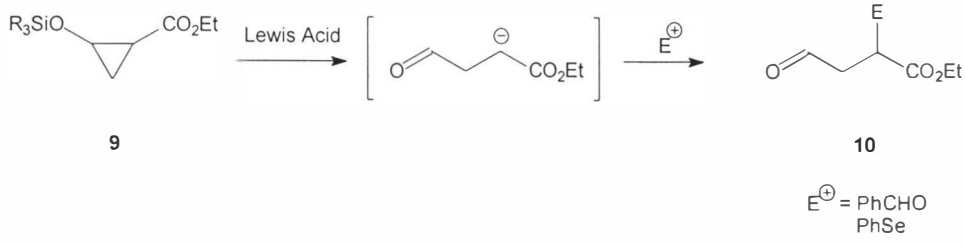


Figure 3: Approaches to Ring Expansion.

by reports of substituted cyclopropyl rings. For example, Reissig and co-workers[12] found that donor-acceptor substituted cyclopropanes, **9**, could be regiospecifically opened to form acyclic product **10** (**Scheme 1**). Cleavage of the silicon-oxygen bond in **9** by a

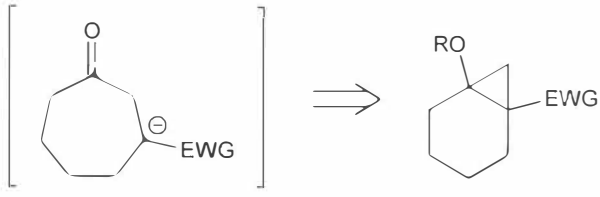


Scheme 1

Lewis acid such as $TiCl_4$ led to formation of the oxy anion. This ion became the "donor", while the ester group acted as the "acceptor", or electron withdrawing group. In this manner, the ester in cyclopropane **9** was used to stabilize the anion generated by scission of the bond between the carbons bearing the donor acceptor pair. The intermediate anion generated by the cleavage of the silyl ether was trapped with a variety of electrophiles (E^+) in order to demonstrate that only one regioisomer was formed, since only one product was obtained.

In a similar fashion, Franck-Neumann and co-workers showed that bicyclic [2.1.0] pentanes bearing an ester and an amino group at bridgehead positions easily underwent regioselective ring expansion to give a five membered ring.[13] It was envisioned that similarly substituted fused systems such as the bicyclo [4.1.0] heptane **12** shown in

Scheme 2 might be predictably opened to form the ring expanded intermediate **11**, affording access to medium sized rings from readily available six membered rings. However, formation of a medium sized ring was only half of the synthetic problem to be addressed. In addition, it was desired that the functional group utilized to promote ring expansion should also be capable of participating in formation of the bridgehead alkene.



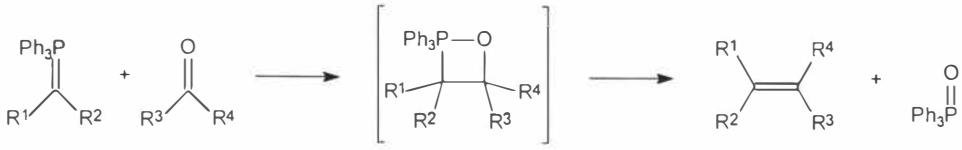
11 **12**

Scheme 2

Bridged bicyclic systems are widely known, with compounds such as camphor and α-pinene being familiar illustrations. However, literature examples of syntheses incorporating a double bond at a bridgehead site are not as common.[14] The preference for all four substituents of an alkene to lie in the same plane is in conflict with the physical requirements of the bridgehead site geometry. This observation, known as Bredt's rule, was first proposed in 1924,[15] but more recent research has shown that under certain circumstances the configuration is allowed. Wiseman found that if the largest ring containing the bridgehead double bond contains eight carbons or more, then the

bridgehead compound should be stable and therefore isolable.[16] Given the conflicting constraints of these complex systems, the synthetic chemist must decide whether formation of the medium sized ring or the bridgehead alkene should be addressed first.[17] As noted above, formation of medium sized rings can be rather difficult. Incorporation of the bridgehead double bond prior to generation of the medium sized ring may not be possible, owing to the implications of Bredt's Rule. Bicylic systems employed in ring expansion reactions, on the other hand, are very common, and many literature methods and approaches have been developed for the purpose of synthesizing such compounds.[18] As a result, the approach used in the course of this research was to first form a properly functionalized bicyclic ring, on which ring expansion to give a medium sized ring could then be performed. Having gained access to a functionalized medium sized ring system, generation of the bridgehead double bond would become the last major step. For this to be achieved most efficiently, the substituents selected for activating the bond scission leading to ring expansion should be participants in the formation of both the bicyclic ring system and the double bond in the final product. Working backwards, the olefination step had to be planned first, with an eye towards the multiple roles that would be demanded of the functional groups utilized in forming the double bond.

The formation of double bonds can be accomplished by a wide variety of methods, but one of the more common techniques is the Wittig reaction.[19,20] This reaction generates a double bond by reaction of a phosphorous ylide, **13**, with an aldehyde or ketone, **14** (**Scheme 3**). The Wittig reaction has become widely used because of the simplicity, efficiency, and the level of control which can be attained with respect to

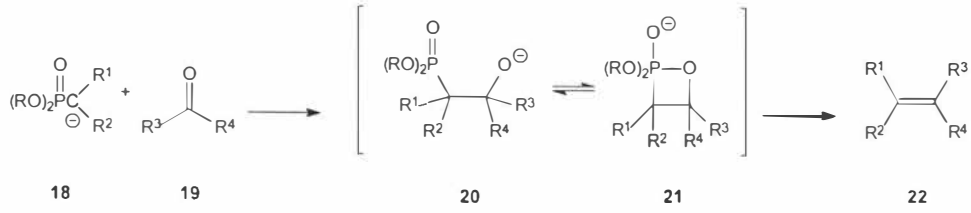


13 **14** **15** **16** **17**

Scheme 3

product geometry.[20a] Based on the choice of the ylide, carbonyl compound, and reaction conditions, high *Z* or *E* selectivity can be attained.[21] The intermediacy of the 1,2-oxaphosphetane **15** was fairly conclusively proven by Vedejs in 1973, based on ^{31}P NMR studies at low temperatures.[22] While it is considered a near certainty that the oxaphosphetane (originally proposed by Wittig himself) is the intermediate, debate continues as to the exact nature of the reaction (stepwise or concerted formation of the oxaphosphetane).[20a] Mechanistic discussions notwithstanding, the Wittig reaction has found wide utility in organic synthesis. Wittig received the Nobel Prize in Chemistry in 1979 for his pioneering work in this area of chemistry.[23]

A variant of the Wittig reaction is the Horner-Wadsworth-Emmons (HWE) reaction (**Scheme 4**), which is the phosphonate analog of the Wittig reaction.[24] In this reaction, phosphoryl stabilized carbanions **18** are reacted with aldehydes and ketones **19** to generate alkenes **22**. Normally, the phosphonate must have a substituent, R^1, capable of stabilizing a negative charge (R^1 = ester, nitrile, sulfonyl, etc).[20a] Unlike the Wittig reaction, the mechanism of the HWE reaction is fairly well established.[25] The stereochemistry of the products can often be controlled by careful selection of reaction

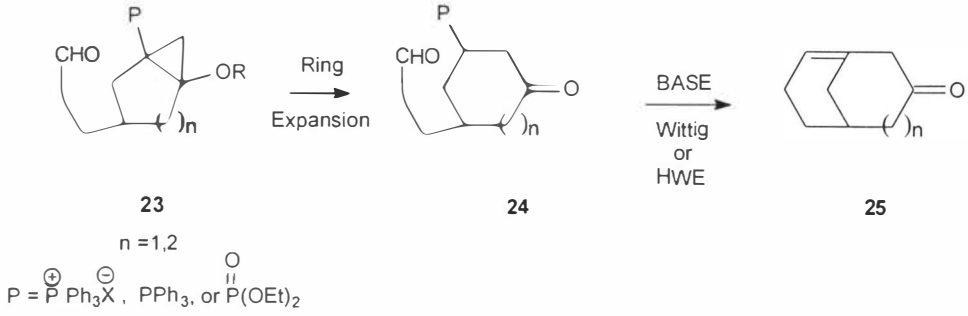


Scheme 4

conditions. A review by Maryanoff and Reitz gives an excellent overview of both the Wittig and HWE reactions.[20a]

The utilization of phosphorus-based olefination reactions became a key element in the development of methods for the formation of bridghead alkenes in bicyclic systems containing a medium sized ring (**Scheme 5**). A five or six membered bicyclic ring system, **23**, bearing phosphorus functionality as part of a donor acceptor substituted strained ring, should undergo ring expansion to afford **24**. A sequence can then be imagined where the expanded product **24** could then undergo an intramolecular Wittig or HWE reaction with a pendant chain bearing an aldehyde or ketone, to generate the desired carbon framework represented by **25**. The application of intramolecular Wittig and HWE reactions for generation of cyclic alkenes has been demonstrated.[26] Chatterjee reported the efficient formation of a fused cyclopentene *via* an intramolecular Wittig reaction.[27] Wiemer and co-workers utilized an intramolecular HWE reaction in their total synthesis of (+)-jatraphone.[28]

The initial focus of these investigations was to develop a method for forming the bicyclic system that would undergo regiospecific ring opening. Regiospecific ring



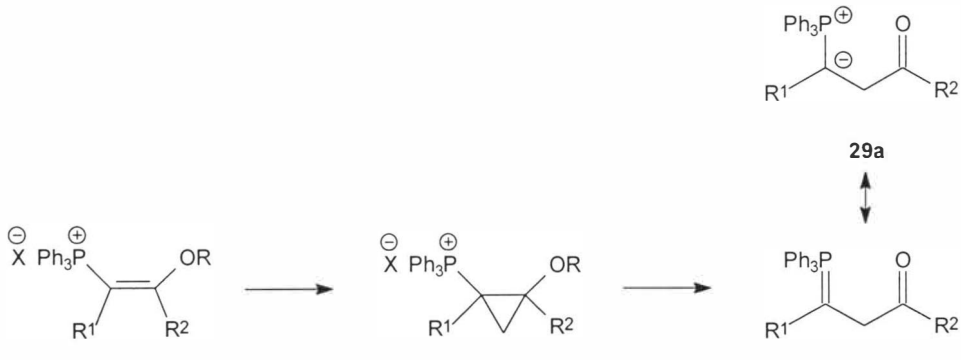
Scheme 5

opening required a bicyclic system containing an electron releasing group (donor) and an electron withdrawing group (acceptor). The objective of this background work was to employ a phosphorus functional group as the acceptor in the ring expansion. A subsequent step could utilize this same functional group to introduce the bridgehead double bond *via* a Wittig or HWE reaction. It was then necessary to identify ring expansion processes in which the phosphorus substituent could either participate as an activating group, or behave as a "spectator" species, having no effect on the reaction.

Initial studies towards formation of the desired medium sized ring systems involved cyclopropanation of β-alkoxy vinylphosphonium salts as model compounds (Chapter 2). The target cyclopropylphosphonium salts, **27**, (**Figure 4**) would mimic the donor-acceptor substituted cyclopropanes, **26**, as reported by Reissig. The acyclic substrates, **28** (**Scheme 6**), were to be used as a model study to develop and optimize the procedure for conversion to the cyclopropyl phosphonium salts, **27**. Once the basic procedure was established on the model system, it would then be utilized in cyclic

26 **27**

Figure 4: Phosphonium Salts as Directing Groups for Ring Opening.

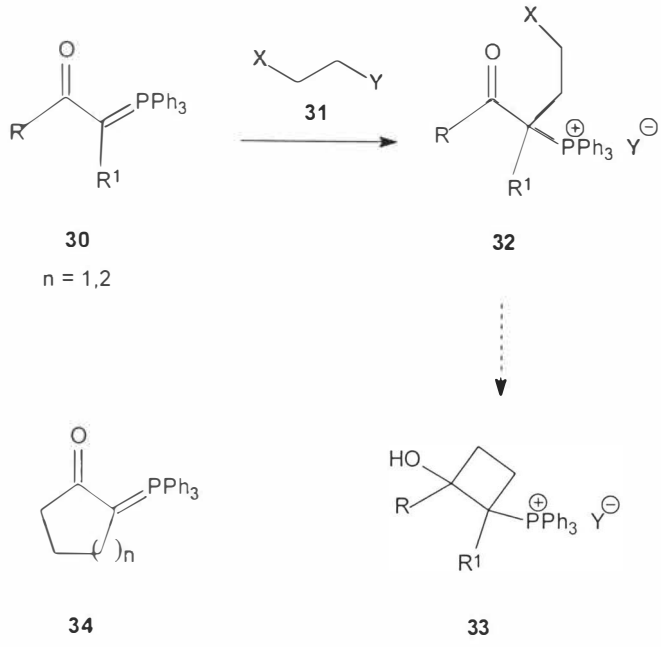


28 **27** **29b**

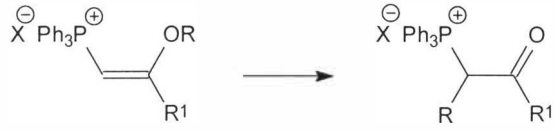
Scheme 6

systems. It was envisioned that the β-alkoxy cyclopropylphosphonium salt, **27**, would be capable of undergoing ring opening analogous to Reissig's system. The electron pair resulting from opening of the three membered ring would reside on the carbon bearing the phosphonium salt (**29a**, **Scheme 6**). The resonance forms of the product, **29a** and **29b**, represent a phosphorus ylide which could, in turn, undergo a Wittig reaction with an aldehyde or ketone to generate a double bond. In the cyclic case, an appropriate pendant chain bearing a carbonyl group would undergo an intramolecular Wittig reaction to close the bicyclic system (**24→26**, **Scheme 5**). In order to gain access to the phosphorus substituted cyclopropanes from β-alkoxy vinylphosphonium salts, **28**, (**Scheme 6**), addition of a number of different reagents was studied, including the addition of a variety of carbon nucleophiles and carbenes. This work served to establish that oxygen nucleophiles such as ethoxide (in addition to the known OH^-)[29] will attack the phosphorus of β-alkoxy vinylphosphonium salts, rather than undergo conjugate addition. This was not the result expected based on published reports.[30] In addition, it was found that β-alkoxy vinylphosphonium salts were unreactive with a wide variety of carbenes.

The second pathway studied involved C-alkylation of β-keto phosphorus ylides, either directly or by rearrangement of β–alkoxy vinylphosphonium salts (Chapter 3). In this approach, small ring systems would be accessed by C-alkylation of β-ketoylide **30** (**Scheme 7**) with a functionalized alkyl chain **31**, to give β-keto phosphonium salt **32**. The reagent **31** would bear a substituent, X, that could be further manipulated to react with the β-carbonyl in order to generate the strained cyclic ring system **33**. After model studies, substrates such as **34** were to be subjected to the same sequence of reactions,



Scheme 7

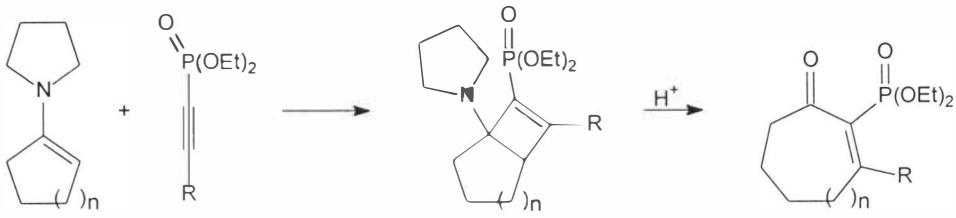


Scheme 8

which would result in the formation of bicyclic systems. There are a number of procedures available in the literature for forming small fused bicyclic ring systems in this manner,[9] one of which is the Barbier reaction.[31] The resulting bicyclic system would again mimic the donor-acceptor ring systems reported by Reissig.[12] The expanded ring, incorporating a phosphorus ylide as a result of bridge bond scission, would then be set up for olefination *via* the Wittig reaction. A number of reaction conditions and substrates were studied to directly C-alkylate the β-keto ylide **30**. Additionally, various β-alkoxy vinylphosphonium salts, **35** (**Scheme 8**) were treated according to conditions reported by Nesmeyanov[32] and Shevchuk[33] to effect rearrangement to C-alkylated phosphonium salts, **36**. This study expanded the scope of substrates reported in the literature on which C-alkylation or rearrangement had been accomplished.

Finally, cycloaddition of alkynyl phosphonates, **38** (**Scheme 9**) with enamines, **37** was examined as a method for incorporating the phosphorus substrate while simultaneously accomplishing the ring expansion (Chapter 4). In this sequence enamines derived from cyclic ketones were reacted with various substituted alkynyl phosphonates, resulting in cycloaddition. Rather than a [2+2] cycloaddition, these results and analogous reports of enamine cycloaddition with vinyl phosphonate,[34] point to a stepwise reaction. Thus, Michael addition of enamine **37** to activated alkyne **38** was followed by an intramolecular aldol-type reaction to form the fused bicyclic ring system **39**. The study of a number of new systems was found to afford quick access to functionalized medium sized rings. Most significantly, these compounds were found to be capable of conversion into compounds which can be used toward the synthesis of a number of natural products

which are composed of bridged bicyclic systems incorporating bridgehead alkenes.



37 **38** **39** **40**

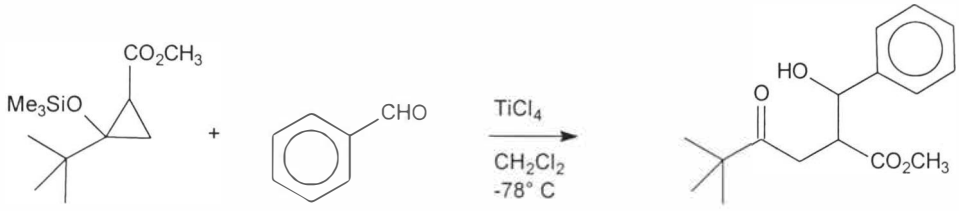
n = 1,2

Scheme 9

Chapter 2:

Cyclopropanation Reactions of β-Alkoxy Vinylphosphonium Salts

Early in the 1980's, Reissig and co-workers reported the regiospecific opening of donor-acceptor substituted cyclopropanes (**Scheme 10**).[12] The classification of "donor-acceptor" was based on the presence of an electron releasing group (donor) and an electron withdrawing group (acceptor) in close proximity to each other on the substrate. Specifically, it was found that the silyl ether group of cyclopropane **41** acted, upon cleavage with a Lewis acid, as an electron donor. The presence of the electron withdrawing ester group on the adjacent ring carbon led to opening of the three membered ring solely at the site alpha to the ester. This result could be readily explained by the fact that the anion generated by cleavage of the C1-C2 bond in **41** was stabilized by the electron withdrawing ester substituent, whereas if the bond between C1 and C3 were broken, an unstable primary carbanion would be formed. The regiospecificity of the reaction was proven by trapping the intermediate anion with electrophiles such as benzaldehyde, benzophenone, and cyclohexanone.[12b] Thus, when



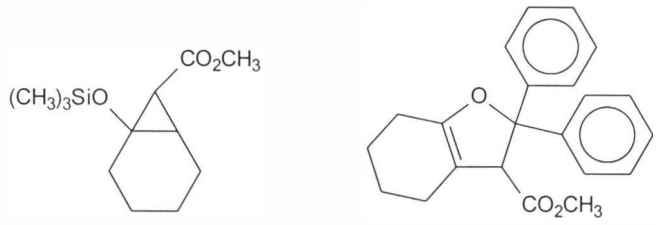
41 42 43

Scheme 10

the reaction of **41** in the presence of benzaldehyde was quenched early at low temperature, regioisomer **43** was formed in 16% isolated yield.[12b]

In addition to simple three membered rings, Reissig and co-workers studied one bicyclic system, **44** as well (**Figure 5**). Treatment of **44** with $TiCl_4$ did not result in ring expansion, because the donor and acceptor were not oriented properly to promote cleavage of the bridge bond. Instead, the three membered ring was cleaved, generating an ester stabilized anion which was subsequently trapped by reaction with benzophenone. The resulting oxy anion attacked the ring carbonyl (formed upon cleavage of the silyl ether) to give the dihydrofuran **45**.[12b]

Reissig and co-workers reported only the use of esters as the acceptor group in the reactions of donor-acceptor substituted cyclopropanes.[12,35] The fact that substituted strained ring systems can be regioselectively opened provides an application to one of the widely used methods for ring expansion, namely method **A**, **Figure 3**. This method of ring expansion involves cleavage of a bridge bond shared by two rings. The process is



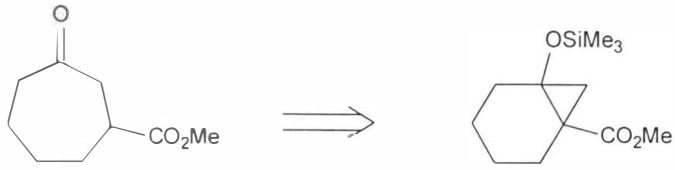
44 **45**

Figure 5: A Donor-Acceptor Substituted Fused Bicyclic System, and the Reaction Product When Cleaved in the Presence of Benzophenone.

promoted by ring substituents that polarize the bridge bond, in order to stabilize the intermediate anion resulting from bond cleavage. The donor-acceptor relationship in Reissig's work on substituted cyclopropanes clearly achieved sufficient polarization of the C1-C2 bond to allow it to be cleaved under the right conditions. Indeed, in addition to esters, nitro groups,[36] sulfones,[37] diketones,[38] and nitriles[39] have all been used to activate cleavage of a bridge bond in ring expansion reactions. To date, though, there are no known reports in the literature where phosphonium salts have been employed as acceptors in ring expansion reactions.

Application of the foregoing methodology to ring expansion would involve a compound such as bicyclo (4.1.0) heptane **48** (**Figure 6**). Here, cleavage of the bridge bond (brought about, for example, by Lewis acid cleavage of the silicon-oxygen bond) would generate the 3-carbomethoxy cycloheptanone **47**. This regiospecific ring opening to give a medium sized ring would, indeed, afford access to one of the key structures of many natural products, that is, functionalized medium sized rings. However, for the

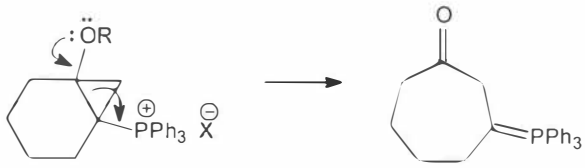
current research, a route was sought that would both generate the medium sized ring, and set the stage for forming the bridgehead double bond, another key feature of a number of these biologically important natural products.



47 **48**

Figure 6: Ring Expansion *via* Cleavage of Donor-Acceptor Substituted Strained Rings.

In order to utilize the Wittig reaction for the formation of the bridgehead double bond of the target structures, access to medium sized rings with phosphorus substituents was needed. This, in turn, led to an examination into the use of phosphorus compounds in ring expansion reactions. The initial investigations were to examine phosphonium salts as the electron withdrawing substituent of donor-acceptor substituted cyclopropanes, and to determine the extent to which they could be utilized to direct the site of ring opening. Phosphonium salts are known to activate the β position of an α,β unsaturated phosphonium salt towards nucleophilic addition,[40] a clear indication of their electron withdrawing capability. The desire was to study cyclopropane systems of the general type **49** (**Scheme 11**), with an alkoxy group as the electron donor (by cleavage of the carbon-oxygen bond) and a phosphonium salt as the acceptor. The anion generated by ring



49 50

Scheme 11

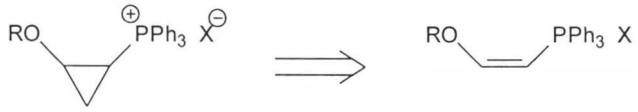
opening would be stabilized by phosphorus in the form of γ-keto ylide **50**. The ylide would then be used to access the bridgehead double bond of the target molecules via the Wittig reaction. Simple phosphorus substituted cyclopropanes were initially examined as models for the fused bicyclic systems **49** which would be required for synthesis of the targeted natural products.

As an analog of the directed ring opening reported by Reissig,[12b] the regiospecificity and conditions required for opening cyclopropanes bearing alkoxy (electron donor) and phosphorus (electron acceptor) substituents was to be studied. Of interest was whether or not the phosphorus substituents would be sufficiently electron withdrawing to effect regiospecific opening of the donor-acceptor system, and if so, to what extent. The acyclic γ-hydroxy ketone **43**, resulting from cleavage of the donor-acceptor cyclopropane **41** in the presence of benzaldehyde followed by quenching at low temperature, was isolated in 16% yield by Reissig and co-workers. This low yield might otherwise have been a cause for concern when considering a method for inclusion in a synthetic scheme. However, the low yield was evidently a result of the high reactivity

of **43** towards formation of dihydrofurans similar to those shown in **Figure 5**, as opposed to inefficient cleavage of the ring. Dihydrofuran **45** was isolated in 88% yield, clearly indicating efficient formation of the ester stabilized anion intermediate, which was the precursor.[12b] The chemical question to be answered was whether or not the phosphorus substituent could activate regiospecific cleavage of the three membered ring. The key of the proposed route to functionalized medium sized rings incorporating bridgehead alkenes became access to the phosphorus substituted three membered ring systems.

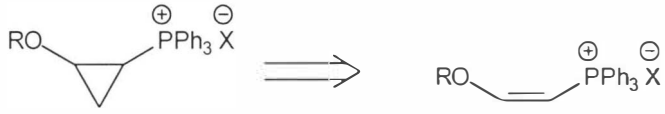
One of the most common approaches to the formation of three membered rings involves addition to a double bond.[41] In order to obtain cyclopropanes functionalized with a phosphonium salt and an alkoxy group by one of these methods, the phosphorus substituent must either be a part of the alkene to be cyclopropanated, or be part of the species attacking the alkene. The simplest approach seemed to be to incorporate the desired donor and acceptor groups into the alkene substrate as shown in **Figure 7**.

The β-keto ylide starting materials (**53a-c**, **Scheme 12**) are all commercially available. (Triphenylphosphoranylidene)acetaldehyde (**53a**) proved to be relatively unstable. Commercially obtained material was sometimes appreciably degraded upon arrival, and continued to degrade upon storage at room temperature. This was evidenced by discoloration of the ylide as purchased and gradually decreasing yields from the alkylation reaction. Storage in the freezer under N_2 in a tightly sealed vial sufficed to reduce decomposition of the material when obtained in satisfactory quality. Alternatively, **53a** could be synthesized from methyltriphenylphosphonium bromide and ethyl formate, (**55**, R = H, **Scheme 13**) in approximately 40% isolated yield. Since 1-



51 52

Figure 7: Three Membered Rings From β-Alkoxy Vinylphosphonium Salts.

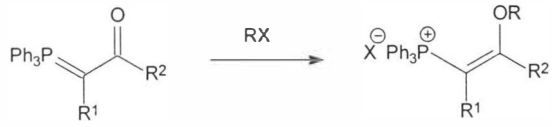


51 52

a: $R^1=R^2=H$
b: $R^1=H$, $R^2=CH_3$
c: $R^1=CH_3$, $R^2=H$

a: R=Et, $R^1=R^2=H$
b: R=Et, $R^1=H$, $R^2=CH_3$
c: R=Et, $R^1=CH_3$, $R^2=H$
d: R=Ac, $R^1=H$, $R^2=CH_3$

Scheme 12



53 54

Scheme 13

triphenylphosphoranylideneacetaldehyde (**53a**) was thus obtained in adequate quantity and purity, aldehyde 2-(triphenylphosphoranylidene)propanal (**53c**) was also synthesized according to the same method. Ethyltriphenylphosphonium bromide, **55**, R = CH_3, was combined with ethyl formate in the same manner as before to give ketoylide **53c** in 29% yield. The products were maintained in the freezer, under Ar or N_2 in order to minimize decomposition.

O-alkylation of the readily available β-keto phosphorus ylides **53a-c** was easily accomplished in high yields (**Scheme 12**) to give the β-alkoxy vinylphosphonium salts, **54a-d**.[42] Typically, the β-ketoylide was dissolved in the alkyl halide (neat), and stirred at room temperature to give the desired vinylphosphonium salt. The resulting compound could then be recrystallized from hexanes/dichloromethane/ethyl acetate. This procedure normally resulted in excellent yields (≥90%) of the desired product in a few hours. A major exception to this was the attempted reaction of ketoylide **53a** with acetyl chloride. In fact, none of the desired β-acetoxy vinylphosphonium salt **54** (R ,= Ac, $R^1 = R^2 =$ H) was isolated. It must be assumed that the reason for this lies in the lability of the aldehyde carbonyl in **53a**, since the product **54d** (where R^2 is CH_3) was obtained easily and in good yield by combining ketoylide **53b** with acetyl chloride in dry benzene.

Examination of the ^{1}H NMR spectrum of 2-ethoxy vinyltriphenylphosphonium bromide (**54a**) showed that, under various conditions, the *E*:*Z* product ratio could be controlled. When the reaction was carried out in refluxing ether, the *E* isomer predominated in a 4:1 ratio. This effect could also be seen to a lesser degree in reactions carried out in neat alkyl halide at room temperature and high concentration, where *E*:*Z*

ratios were about 2:1. Reactions carried out at room temperature under dilute conditions gave *Z*:*E* ratios of >13:1. *E* and *Z* isomers were easily distinguished by evaluating the proton-proton coupling constants, while the ratios were determined based on the integration of the assigned peaks. Both the chemical shift values and coupling constants were consistent with the assignment reported in the literature.[43] The ^{1}H NMR spectra for both *Z* and *E* isomers of (2-ethoxy)vinyltriphenylphosphonium bromide (**54a**) have been shown in **Figure 8**. For the *Z* isomer, the proton located *alpha* to the phosphonium salt, H_a, appears as a doublet of doublets at 5.75 ppm with coupling constants of 17.3 and 7.3 Hz. The doublet of doublets at 8.35 ppm integrated to one proton, with J = 33.4 and 7.3 Hz. This was consistent with a proton (H_b) located *trans* and *beta* to the phosphonium salt as reported by Snyder and Bestmann.[43] For the *E* isomer, the *alpha* proton, H_c, appeared as a doublet of doublets at 6.75 ppm (J = 13.8, 13.8 Hz) and the *cis*, *beta* proton H_d appeared as a doublet of doublets at 6.9 ppm (J = 13.8, 13.8 Hz). Note that in the *Z* product, the coupling value ($J_{H\text{-}H}$) for the two vinyl protons was ~7 Hz, where the $J_{H\text{-}H}$ value for the *E* isomer was ~14 Hz, in agreement with accepted values. The assignment of protons could also be verified by stirring a solution of nearly pure *Z* **54a** (>13:1) in dichloromethane with an excess of triethylamine. A 7:1 mixture (*E*:*Z*) of the two β-alkoxy vinylphosphonium salts resulted after stirring at room temperature for 48 hours. For vinylphosphonium salt **54b**, the chemical shift of 5.65 ppm, as well as the $J_{H\text{-}P}$ of 18.3 Hz supported the assignment of the *Z* configuration to the major product (yield: 94%; *Z*:*E* >30:1). Interestingly, the vinylphosphonium salt derived from the third ketoylide used, **54c** (R^1 = CH_3, R^2 = H) appeared, based on the vinylic doublet at 6.7

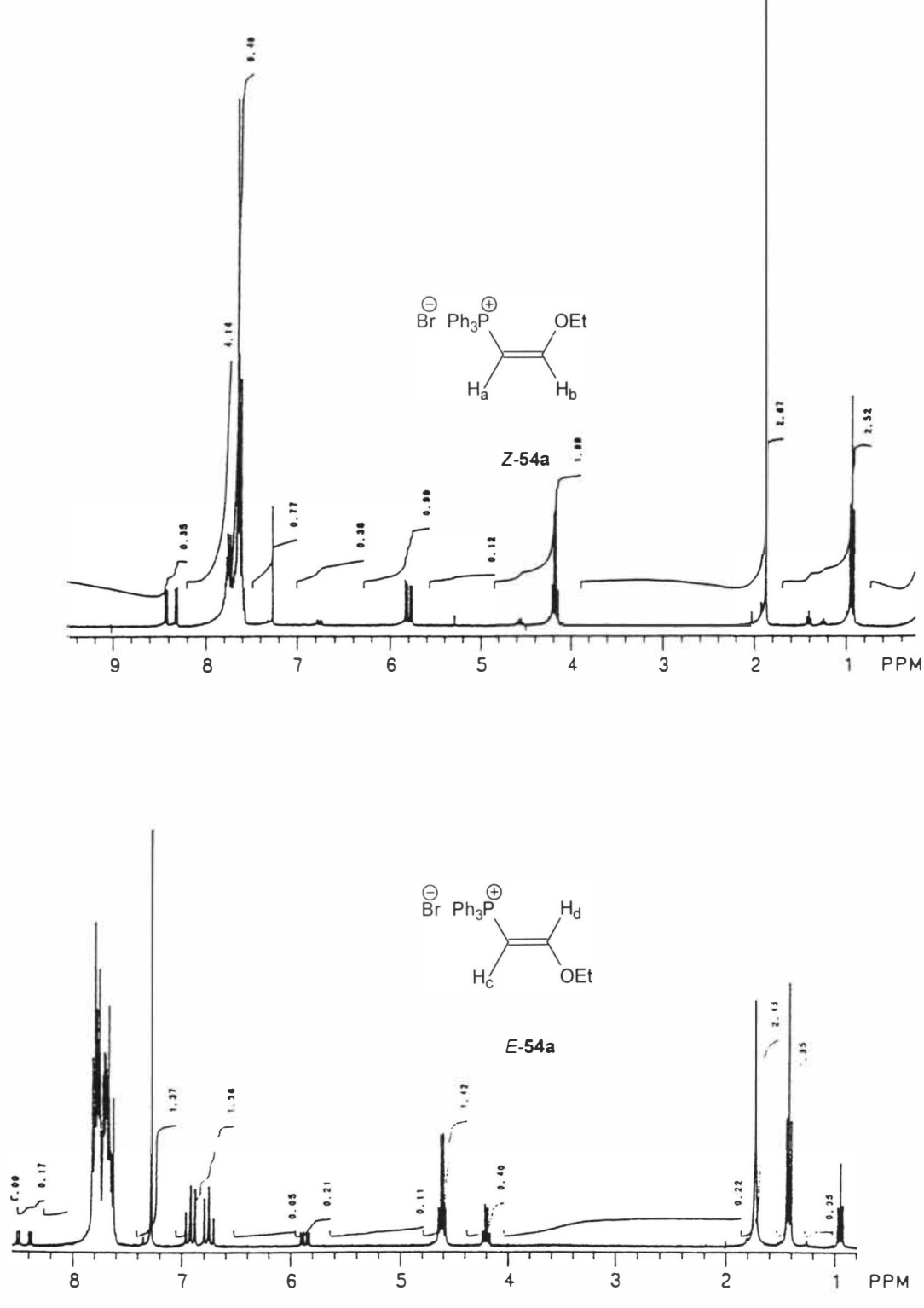
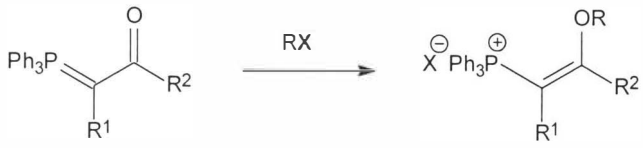


Figure 8: Comparison of *Z* and *E* 1-Triphenylphosphoranylideneacetaldehyde (**54a**).



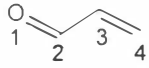
53 **54**

Entry	R	R^1	R^2	X	Compound	Yield (%)
1	Et	H	H	Br	**54a**	94
2	Et	H	CH_3	Br	**54b**	94
3	Et	CH_3	H	Br	**54c**	79
4	OAc	H	CH_3	Cl	**54d**	70
5	OAc	H	H	Cl	**54e**	–

Table 1: O-Alkylation of β-Keto Phosphorus Ylides

ppm, to be produced with a *Z*:*E* ratio of 1:10. A small doublet at 8.25 ppm having a large coupling constant was indicative of a small amount of the *Z* isomer. The compounds produced as substrates to be used for cyclopropanation have been summarized in **Table 1**.

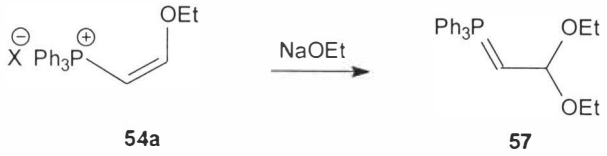
With ready access to the desired β-alkoxy vinylphosphonium salts **54a-d**, work was begun in earnest to synthesize the alkoxyphosphonium cyclopropanes. The reactivity of α,β-unsaturated phosphonium salts has been well reported. Alcohols,[44] thiols,[45] primary amines[46] and carboxylic acids[47] are all known to add to the double bonds of these salts in a Michael-type reaction. Michael addition, also called conjugate addition or 1,4 addition, involves addition to the end (carbon 4) of a conjugated system (**Figure 9**).



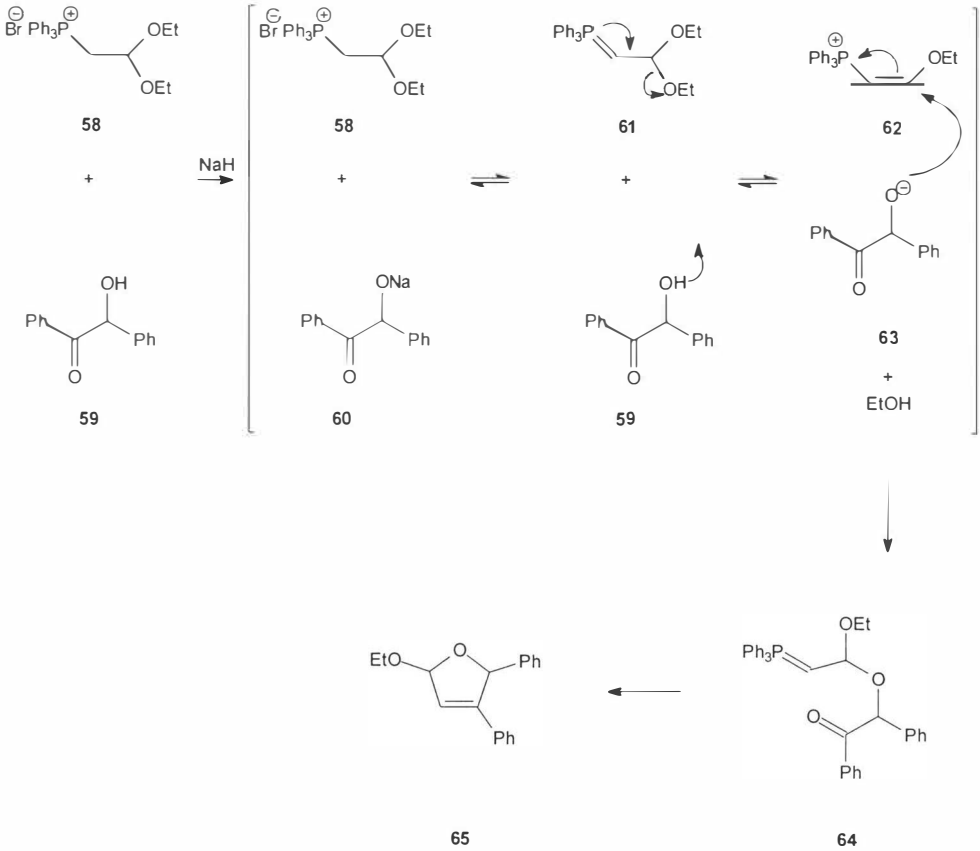
56

Figure 9: A Conjugated System, Michael Acceptor.

Bestmann and co-workers reported that β-alkoxy vinylphosphonium salts underwent Michael-type addition with oxygen nucleophiles.[30a,b] They treated 2-ethoxy vinyltriphenylphosphonium bromide with sodium ethoxide, and reported isolation of diethoxy ylide **57** (**Scheme 14**). Others have reported formation of furans from ethoxy substituted vinyl phosphonium salts and α-hydroxy ketones such as benzoin.[48] The proposed mechanism, shown in **Scheme 15**, was believed to involve several steps: first,



Scheme 14



Scheme 15

abstraction of the hydroxyl hydrogen of benzoin (**59**) with sodium hydride. The benzoin anion, **60**, then abstracted a proton from diethoxy phosphonium salt **58**, generating the phosphorus ylide 61. The ylide then underwent elimination of ethoxide, which abstracted the proton from the hydroxy group of benzoin, forming an ion pair consisting of the β-alkoxy vinylphosphonium cation **62** and benzoin anion **63**. Conjugate addition of the oxyanion to the vinyl phosphonium salt led to formation of the ketoylide **64**. This then underwent an intramolecular Wittig reaction to form the dihydrofuran **65**. The step of relevance to the current investigation was the Michael addition to β-alkoxy vinylphosphonium salt **62**. Other reports of vinylphosphonium salts as Michael acceptors also occur in the literature.[49,50] Together, these facts were taken to be good evidence that the vinyl phosphonium salts **54a-d** should be adequate Michael acceptors, even in the presence of an electron donating alkoxy substituent. These Michael acceptors were key reagents in the generation of the donor-acceptor cyclopropane systems.

With the literature basis for the work established, a series of reactions aimed at converting **54a-d** to substituted cyclopropanes was begun. In 1965 Corey and Chaykovsky[41b] described the use of dimethylsulfoxonium methylide and dimethylsulfonium methylide (collectively referred to as the "dimsyl reagent") in forming epoxides and cyclopropanes. Formed by abstraction of an acidic hydrogen from tri-coordinated sulfur salts or penta-coordinated sulfoxide salts, Corey and co-workers found that the reagent exists in the form shown in **Figure 10**. The ylide reagent can be formed in dimethyl sulfoxide (DMSO), tetrahydrofuran (THF), or dioxane, and stored for long periods of time at 0 °C. Additionally, they found that dimethylsulfoxonium methylide

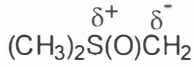
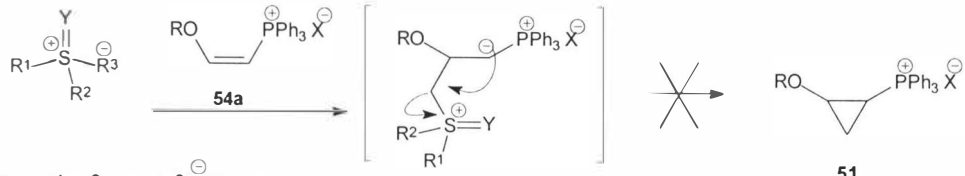


Figure 10: Dimethylsulfoxonium Methylide (Dimsyl).

(**66**) could selectively cyclopropanate α,β unsaturated systems in the presence of γ,δ extended conjugated systems and isolated double bonds.[41b] Since that time, these reagents have become widely used, at least partly due to their ease of formation, stability and generally high yields. The continuing popularity of these reagents was demonstrated by a literature search which revealed that the initial report, though published 30 years ago, has been referenced over 150 times since 1990. Interestingly, in α,β-unsaturated systems, the dimethylsulfoxonium ylide was found to preferentially add to the double bond, while the dimethylsulfonium ylides added exclusively to the carbonyl carbons of these compounds. The cyclopropanation mechanism involves conjugate attack of the carbanion on the activated alkene, followed by back attack from the α carbon onto the methylene of the sulfur ylide closing the three membered ring and eliminating a molecule of DMSO.[51] This mechanism is reflected in the intermediate depicted in **Scheme 16**.

In a typical procedure, the dimsyl reagent **67** was formed by stirring trimethylsulfoxonium iodide in DMSO with sodium hydride. After a few minutes, liberation of hydrogen ceased and the mixture turned from cloudy to clear. After one



67a: $R^1=R^2=CH_3$, $R^3=\overset{\ominus}{C}H_2$, Y=O

b: $R^1=R^2=CH_3$, $R^3=\overset{\ominus}{C}H_2$, Y= :

c: $R^1=R^2=CH_3$, $R^3=\overset{\ominus}{C}HCO_2CH_2CH_3$, Y = :

Scheme 16

hour, the β-alkoxy vinylphosphonium salt **54a** was dissolved in DMSO and added to the solution of the methylide. This was stirred under nitrogen at room temperature. Initially, the reaction was monitored by thin-layer chromatography (TLC), and at 15 hours showed no change from the appearance (by TLC) at 15 minutes. The reaction mixture was then quenched with water, extracted into dichloromethane, washed with saturated sodium bicarbonate and brine, and then dried over potassium carbonate.

^{1}H NMR analysis of the crude reaction products of **54a** with dimsyl indicated that the resultant mixture contained no starting material, but no cyclopropanated product, either. Comparison of the ^{1}H NMR spectra of starting material **54a** and the reaction product (**Figure 11**) points out the distinct differences between them. The vinyl protons of vinyl phosphonium salt **54a** appear as two doublet of doublet groups at 5.75 and 8.35 ppm. In the product, there were still two doublet of doublet groups, but they now appeared at 5.28 and 7.05 ppm.

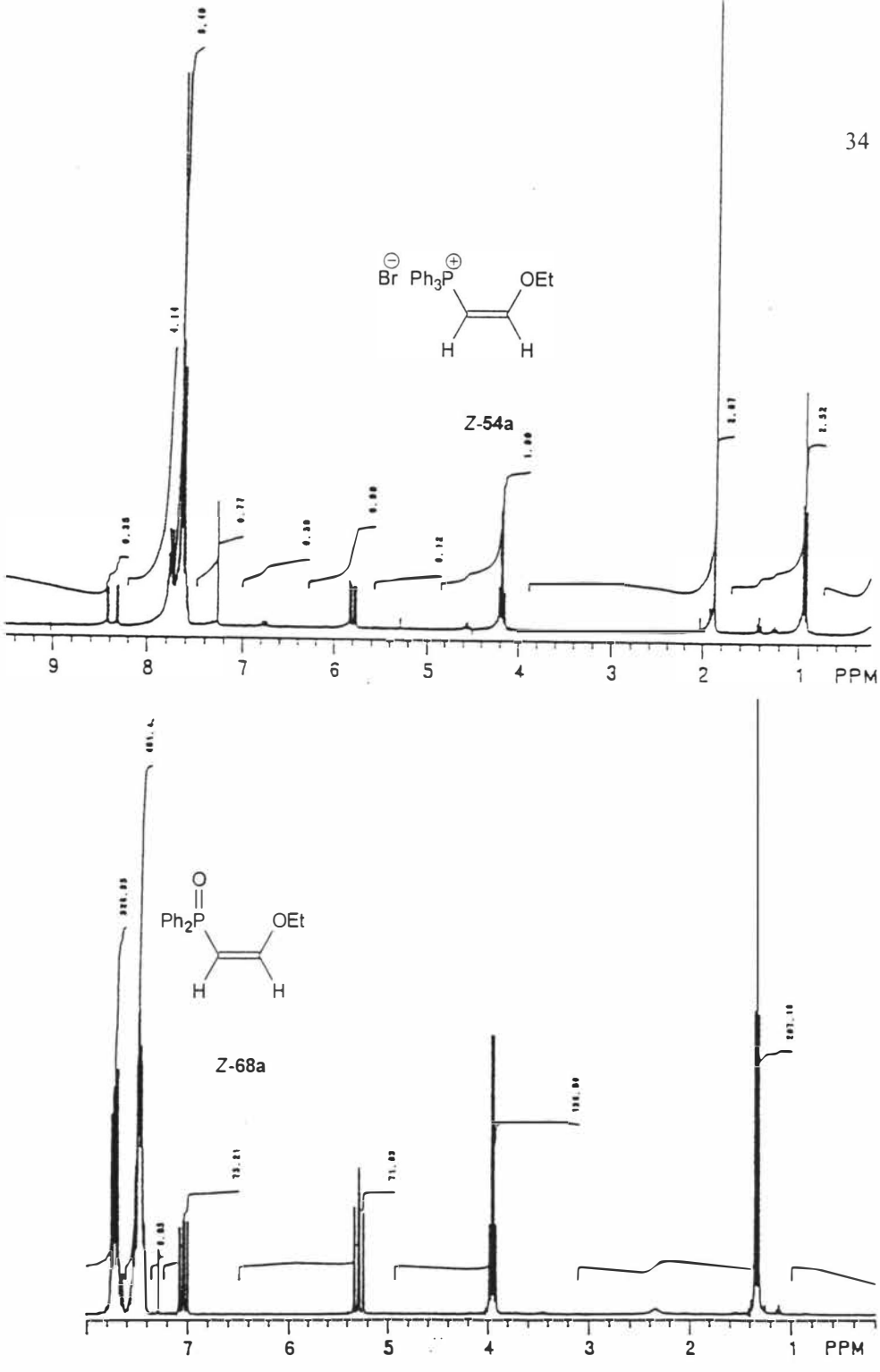


Figure 11: Comparison of the ^1H NMR Spectra of β-Alkoxy Vinylphosphonium Salt **54a** and Diphenyl Phosphine Oxide **68a**.

Additionally, the ratio between phenyl and vinyl protons was no longer 15:1. This was attributed to the probability that more than one species (*e.g.* triphenylphosphine, etc.) was present in the crude mixture. This compound was later determined to have the structure shown in **Figure 11** as compound **68a** (*vide infra*).

Believing that moisture was perhaps interfering with the formation of the dimsyl anion, attempts were made to rigorously exclude sources of moisture from the reaction. Even after flame drying the glassware and doubly distilling the DMSO after stirring it over barium oxide, the same product as before was isolated, without any trace of the desired three membered ring. The reaction was repeated with temperatures up to 100 °C for between 4 and 240 hours. In all cases, the products were mixtures of the undesired product as well as starting material. The general trend appeared to be that the longer the trimethylsulfoxonium iodide and sodium hydride were stirred together prior to addition of the vinylphosphonium salt, the more starting material was recovered. This seemed to indicate that something (presumably moisture) might be destroying the dimsyl anion precluding its addition to the vinylphosphonium salt. The β-alkoxy vinylphosphonium salts were also combined with the related dimethylsulfonium methylide reagent, **67b**, formed by treating trimethylsulfonium iodide with sodium hydride base. After reaction at -78 °C for several hours and warming to room temperature for 36 hours, only starting material was isolated.

Efficient cyclopropanation of β-carbomethoxy vinylphosphonium salts has also been reported using a stabilized sulfur ylide, **67c**.[52] This compound was prepared and isolated, and could be stored for extended periods of time at -10 °C.[53] Since the ylide

was stable and isolable as a yellow oil, the mechanics of the reaction were remarkably simple. The β-alkoxy vinylphosphonium salt **54a** was dissolved in CH_2Cl_2 and placed in a round bottomed flask. The sulfur ylide **67c** was added as a solution in CH_2Cl_2. The solution was then maintained at room temperature for up to six hours before heating to reflux. Highly complex mixtures were the result of this reaction, with as many as six separate triplets apparent between 0.8 and 1.5 ppm in the ^{1}H NMR spectrum. The crude product was placed on a silica preparatory TLC plate, and eluted with 50% hexanes/35% CH_2Cl_2/15% absolute ethanol. This did little to improve the complexity of the proton spectrum, as evidently several components co-eluted under these conditions. In order to simplify the spectrum, a portion of the reaction product was treated with lithium aluminum hydride in order to reduce the ester to an alcohol. In theory, this should have simplified the region of the spectrum caused by the two ethoxy groups. In practice, the material recovered showed only phenyl protons in the ^{1}H NMR.

In order to establish the ability of the vinylphosphonium salts to act as Michael acceptors, an attempt was made to duplicate the previous reports of Bestmann and co-workers.[30a,b] When **54a** was stirred in anhydrous THF in the presence of sodium ethoxide, the identical product to that obtained in the dimsyl reactions was isolated. The ^{1}H NMR of the product obtained in our hands did not match that reported by Bestmann for 1-(triphenylphosphoranylidene)-2,2-diethoxyethane (**57**, **Scheme 14**)

In continued attempts to duplicate Bestmann's work, stringent measures were implemented to exclude moisture and ensure fresh reagents. Initially, sodium ethoxide off the shelf had been utilized, but none of the reported product was detected. Use of

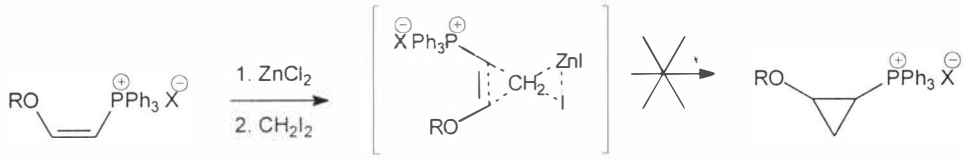
fresh sodium ethoxide, under the identical conditions reported by Bestmann and co-workers, still failed to produce detectable amounts of diethoxy ylide **57** in the product mixture. Other measures taken to ensure that there was no water or hydroxide present included distillation of solvents from lithium aluminum hydride, laboratory preparation of fresh sodium ethoxide, purification of the sodium ethoxide by sublimation, and preparation of sodium ethoxide *in situ*. In all cases, these reactions resulted in isolation of mixtures of starting materials and the undesired byproduct. After many attempts with strict precautions to maintain anhydrous and inert conditions, Bestmann's reported adduct could not be formed.

The report by Corey and co-workers indicated that the success of cyclopropanations with dimsyl may be affected by steric conditions near the alkene.[41b] Though steric effects had no bearing on the inability to duplicate the product reported by Bestmann, there were concerns about the three phenyl groups on the phosphorus and how they might affect the dimsyl cyclopropanation. Additionally, the indications were that the β-alkoxy vinylphosphonium salts were not nearly as reactive towards Michael addition as were vinylphosphonium salts. In light of these two observations, it was determined that other methods for converting the β-alkoxy vinylphosphonium salts to three membered rings should be considered.

Carbenes are another class of reagents known to add to alkenes to give three membered rings. Depending on the type of carbene used, selectivity based on steric conditions can vary greatly.[54] Carbenes can be either electrophilic or nucleophilic.[55] As a result, they have been shown to add to electron rich[56] as well as electron deficient[57]

alkenes. A wide variety of carbene reactions have been recorded in the literature. One method of cyclopropanation involving a carbene insertion into a double bond is the Simmons-Smith reaction.[41a]

The Simmons-Smith reaction involves complexation of diiodomethane with an activated zinc-copper couple. As such, instead of a free carbene, an organometallic complex is formed that attacks alkenes to effect methylene transfer (**Scheme 17**). This reagent generally gives better yields with alkenes that are not electron deficient, but since the earlier studies produced some evidence that the β-alkoxy vinylphosphonium salts



54a **51**

Scheme 17

were not acting as good Michael acceptors, there was reason to believe that the alkoxy substituent was adding enough electron density to offset the electron withdrawing effects of the phosphonium salt. Perhaps more importantly, Simmons-Smith cyclopropanation is less susceptible than the dimsyl reagent to steric interactions with the substrate. Although the reaction appears to work best on terminal alkenes, some tetrasubstituted alkenes are activated towards cyclopropanation by the Simmons-Smith reagent compared to cyclohexene.[58] Thus, cyclopropanes can be generated from tetrasubstituted alkenes.[59]

In a slight modification of a literature method for formation of the zinc-copper couple,[59] clean, dry zinc granules and copper(I) chloride were combined in refluxing diethyl ether or dioxane for 30 minutes, followed by addition of the β-alkoxy vinylphosphonium salt. Lastly, diiodomethane was added, and the reaction was stirred under nitrogen. Great care had to be exercised in order to ensure that the zinc was clean and dry, hence it was first washed with 10% HCl, rinsed with de-ionized water, then dried overnight in a vacuum oven (0.1mm Hg, 110 °C). Later reactions were run using zinc dust, which was dried under vacuum and heat overnight prior to use. Additionally, the solvents utilized were kept scrupulously dry. Initially, diethyl ether from a sodium/benzophenone still was used for the reactions, however, the vinylphosphonium salts were not very soluble in ether, and though the reaction was attempted, only starting materials were recovered. Since it was determined that the vinylphosphonium salts were, to some extent, soluble in dioxane, it was substituted for diethyl ether in another series of reactions. Despite all the attempts to ensure pure reagents and dry reaction conditions, reactions employing the zinc-copper couple resulted in recovery of starting material only.

There have been several reports in the literature on improving the effectiveness of Simmons-Smith cyclopropanation. One such report noted that addition of trace amounts of acetyl chloride could facilitate the reaction.[60] The normal Simmons-Smith procedure was followed, except that after addition of the diiodomethane, acetyl chloride was added to the reaction mixture. The appearance of the zinc powder in the flask changed from light grey to a dark grey, an indication which was specifically mentioned in the paper by Friedrich and co-workers.[60] Temperatures from 60 °C (in a round

bottomed flask) to 150 °C (in a sealed tube) along with reaction times of between 2 and 46 hours were attempted in order to effect cyclopropanation, with negative results.

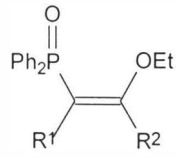
Sonication has also been reported to improve Simmons-Smith cyclopropanation for compounds where more forceful conditions cannot be tolerated by the substrate.[61] The collapse of solvent bubbles formed by the ultrasound energy generates high temperatures and pressures in the locality of the bubble itself, without raising the temperature of the whole mixture. It should be noted, however, that upon extended sonication, the water bath temperature did reach into the 40-50 °C range. In addition, a heated oil bath apparatus was constructed to fit inside the ultrasonic bath, such that the sample could be heated. Using this apparatus, reaction temperatures of 80 °C to 100 °C were maintained, using diglyme, dioxane, or triglyme solvents in either round bottomed flasks (atmospheric pressure) or sealed tubes. Each of these modifications was individually applied to the attempted Simmons-Smith cyclopropanation of the β-alkoxy vinylphosphonium salt **54a**, but unreacted starting material was recovered as the only product observed. Simultaneous use of sonication along with catalytic amounts of acetyl chloride was also attempted in order to promote successful cyclopropanation. Only starting materials were recovered from the reaction mixture.

An alternate method of forming the zinc-diiodomethane intermediate for cyclopropanation of alkenes involves reaction of diethylzinc and diiodomethane.[59] Diethylzinc was obtained as a solution in hexanes from Aldrich Chemical company. In this attempt, even temperatures of 100 °C in a sealed tube and large excesses of diethylzinc and diiodomethane in the presence of β-ethoxy vinyltriphenylphosphonium

bromide (**54a**) failed to produce detectable amounts of the desired (2-ethoxycyclopropyl)triphenylphosphonium bromide (**51**, **Scheme 17**). It became evident that a more reactive species was needed in order to carry out the cyclopropanation of the β-alkoxy vinylphosphonium salts **54**.

Another highly reactive carbene, dichlorocarbene, was formed *in situ* by adding 50% NaOH to a vigorously stirred solution of **54a** in chloroform, in the presence of the phase transfer catalyst benzyltriethyl ammonium chloride.[62] Surprisingly, the only product recovered was identical to the product from the earlier series of dimsyl reactions. This should not have been the case, as the reaction types and conditions were markedly different. Examination of the purified product by a variety of spectroscopic techniques was helpful in determining its structure and origin. The GC/MS of the product indicated a molecular weight of 272 g/mole. The ^{1}H NMR spectrum showed 10 phenyl protons in addition to the vinyl protons and those representing the ethoxy group. An IR spectrum taken on a salt plate showed a strong absorbance at 1265 cm^{-1}, indicative of a phosphorus-oxygen double bond. These factors taken together pointed to 2-ethoxy vinyldiphenylphosphine oxide (**68a**, **Figure 12**) as the product obtained. While the mechanism leading to formation of phosphine oxides from phosphonium salts reacting with hydroxide anions has been reported,[29,63] the range of known possible products includes trialkylphosphine oxides, dialkylphosphine oxides, ylides, and vinyl phosphonium salts.[64] Thus, the formation of phosphine oxide **68a** was thereby easily explained in the phase transfer catalyzed formation of dichlorocarbene (50% aqueous NaOH). The formation of the same product in the sulfur ylide reactions was slightly more obscure,

especially in light of the extensive efforts undertaken to exclude moisture from the reaction mixture. Clearly, the sulfoxy anion form **69b** (**Scheme 18**) of the methylide **69** (or DMSO solvent when reacted with a hydride base) has a significant contribution to the

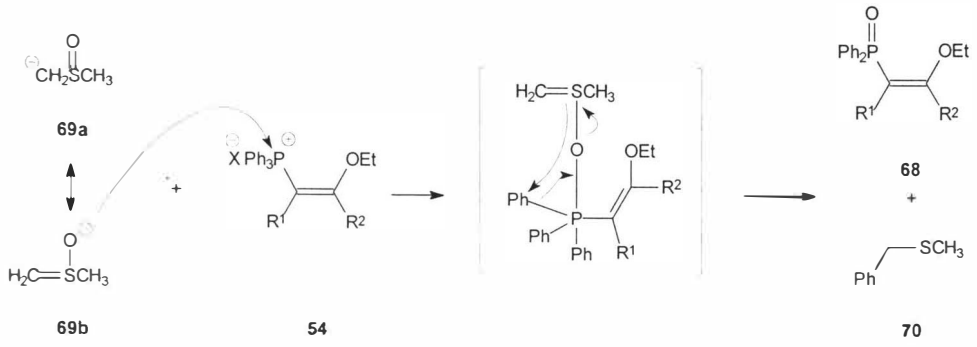


68a: $R^1 = R^2 = H$
b: $R^1 = H$, $R^2 = CH_3$
c: $R^1 = CH_3$, $R^2 = H$

Figure 12: Diphenylphosphine Oxides From β-Alkoxy Vinylphosphonium Salts.

structure of the ylide. Indeed, DMSO can oxidize primary alkyl halides to give aldehydes by oxygen attack on the carbon bearing the halogen.[65] It is not altogether surprising, then, that sulfoxonium attack could occur at the phosphorus. The proposed sequence for the reaction of the β-alkoxy vinylphosphonium salts in DMSO is shown in **Scheme 18**. It is believed that the initial attack occurs by the oxygen anion, **69b**, at the positive phosphorus center of vinylphosphonium salt **54**. An electrocyclic reaction then ensues, initiated by formation of a second bond to the phosphorus by a lone pair on the oxygen. As the new phosphorus - oxygen bond forms, one of the phosphorus - phenyl bonds is cleaved, and the resulting species attacks the methylene of the methylsulfoxonium methylide, with final expulsion of benzylmethyl sulfide.[42] This mechanism was supported by detection (by GC/MS) of benzylmethylsulfide (**70**) in crude reaction mixtures. The

significance of the reaction shown in **Scheme 18** was that when β-alkoxy vinylphosphonium salts were reacted with oxygen nucleophiles (*e.g.* hydroxide, sulfoxy or alkoxy anion), the only product obtained was phosphine oxide **68**. In fact, in reactions



Scheme 18

where **68** was the intentional product, the phosphine oxide could be produced in nearly quantitative yield by combining the β-alkoxy vinylphosphonium salt with n-butyllithium in DMSO. The presence of an oxygen nucleophile was required, since experiments in which the vinylphosphonium salt was treated with sodium hydride in dichloromethane yielded only traces of the phosphine oxide product, presumably from small amounts of sodium hydroxide present in the hydride reagent. Additionally, it was shown that stirring the vinylphosphonium salt **54** in DMSO in the absence of base led to no reaction whatsoever.

In an attempt to make use of the phosphine oxide product **68**, it was subjected to the original cyclopropanation conditions. It was believed that since the phosphorus had

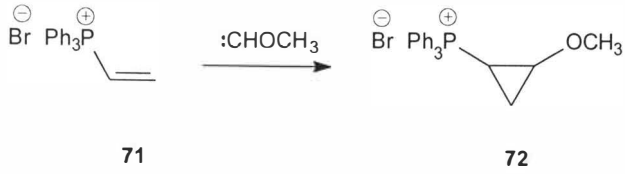
already reacted to form the phosphine oxide, oxygen nucleophiles would no longer attack the phosphorus. As a result, the carbanion form of the dimsyl reagent could add to the double bond, which would then allow formation of the desired cyclopropanes. However, when the reaction mixture was stirred in a sealed tube at 150 °C for 90 hours, no reaction between the dimsyl anion and 2-ethoxy vinyldiphenylphosphine oxide (**68a**) was seen.

Samarium iodide, a versatile reagent, has been shown to accomplish two different chemical reactions which had direct bearing on the continuing investigation. Imamoto and co-workers[66] reported that SmI_2 could be used in conjunction with CH_2I_2 in cyclopropanations of enolates, while Handa and co-workers[67] reported its utility as a reducing agent for phosphine oxides. While other researchers[68] have attempted cyclopropanation of unsubstituted vinylphosphonium salts *via* this reagent, the reaction was also attempted with the β-alkoxy vinyldiphenylphosphine oxide **68**. Samarium iodide can either be purchased as a solution in THF, or samarium metal can be purchased and the reagent prepared. Due to some undesirable side reactions that can occur with acid halides in the presence of THF, a method has been developed for formation of SmI_2 in acetonitrile.[69] However, since in this particular case, coupling with THF was not expected to be a problem, and since the vinyldiphenylphosphine oxides were soluble in THF, the 0.1 M solution of samarium iodide available from Aldrich was used. Upon addition of the solution of SmI_2 to the stirred solution of the phosphine oxide, the blue-green color was initially dissipated. As the addition continued, however, the color stabilized, and the solution took on the color of Sm^{2+}. The dark color persisted for 15 minutes, until the CH_2I_2 was added. Upon addition of diiodomethane, the solution lightened somewhat, but

maintained a green color. Over several hours, the green color was completely discharged. Upon workup, only the unreacted β-alkoxy vinyldiphenylphosphine oxide was found in the reaction mixture. This indicated that either the β-alkoxy vinyldiphenylphosphine oxides were unreactive to the SmI_2 reduction, the electron-transfer intermediate was not formed, or the intermediate was quenched by the presence of trace amounts of water in the reagents. The latter possibility was unlikely, given the extreme measures undertaken to completely exclude moisture from the reaction system.

Two other carbenes were used in an effort to gain access to donor-acceptor substituted cyclopropanes. Since the β-alkoxy vinylphosphonium salts were clearly sensitive to reaction conditions involving hydroxide or alkoxide nucleolphiles, a carbene which could be formed without the use of such species was desired. Difluorocarbene can be easily formed under neutral conditions from combination of triphenylphosphine, dibromodifluoromethane, and potassium fluoride in triglyme.[70] Burton and co-workers reported efficient cyclopropanation of tri- and tetrasubstituted alkenes with difluorocarbene. β-alkoxy vinylphosphonium salts **54a** and **54b** were each treated with the difluorocarbene reagent, with the result that starting material was recovered.

An alternate approach involved reaction of vinyl triphenylphosphonium bromide, **71**, with a carbene bearing a methoxy group (**Scheme 19**). In this manner, an alkene bearing a phosphonium salt could be treated with a carbene that would, by insertion into the bond, deliver the alkoxy group needed for regiocontrolled ring opening. The methoxy carbene was formed by treatment of chloromethylmethyl ether with either lithium dicyclohexylamide or lithium 2,2,6,6-tetramethylpiperidide.[71] The base was prepared by



71 72

Scheme 19

combining the amine with n-butyllithium at -23 °C. The base solution was then combined by inverse addition to a solution of the vinyltriphenylphosphonium bromide (**71**). The only material consistently isolated from these reaction mixtures was a considerable amount of starting material. On some occasions, the reaction mixtures were highly complex, other times pure starting material was recovered. No products were isolated that could be credibly assigned as the desired cyclopropyl phosphonium salts **72**.

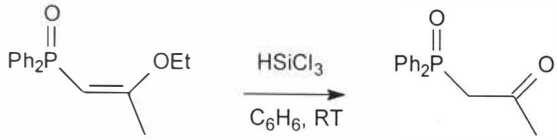
It was clear that the nature of the phosphorus substituent had an immense impact on the reactivity of the alkene. The β-alkoxy vinylphosphonium salts were reactive with oxygen nucleophiles in ways that were unanticipated, and were therefore unsuitable for cyclopropanation *via* dimsyl reagents. The double bonds of these systems were completely unreactive towards carbenes, as were the phosphine oxides. As a result, it was believed that some other alterations in the electronic environment of the double bond might enhance its reactivity towards cyclopropanation. In an effort to transform the β-alkoxy vinyldiphenylphosphine oxide **68a** into a more electron rich alkene, reduction to the corresponding phosphine was attempted. Imamoto and co-workers reported that combination of phosphine oxides with lithium aluminum hydride (LAH) in the presence of $CeCl_3$ effected rapid and efficient reduction to the phosphine.[72] The β-alkoxy

vinylphosphine oxide was added to a solution of LAH and $CeCl_3$ in dry THF. When the reaction was allowed to proceed for 45 minutes at 40 °C, material that by ^1H NMR appeared identical to starting material was recovered. The presence of a strong absorption at 1193 cm^{-1} in the IR spectrum of the material collected after workup of the reaction mixture verified the presence of a phosphorus oxygen double bond, indicating that, in fact, no reduction had occurred.

Reduction of phosphine oxides to phosphines by samarium iodide, reported by Handa and co-workers[67] was also attempted. This procedure utilized electron transfer with a SmI_2-THF-HMPA complex. Though the reduction of triphenylphosphine oxide required the most time (16 hours) of any of the organic heteroatom oxides reported by Handa, this method still represented a mild and relatively efficient method for reducing phosphine oxides. When phosphine oxide **68b**, HMPA, and samarium iodide were mixed, the solution immediately turned a deep purple color which persisted for no more than a few minutes. After 12 hours, IR analysis of the product mixture showed that the phosphine oxide was still present.

Another method reported to effect reduction of phosphine oxides utilizes a silane reagent.[73] Unfortunately, in contrast to the other reductions already attempted, the β-alkoxy vinyldiphenylphosphine oxide proved to be reactive with trichlorosilane, and cleavage of the ethoxy group occurred, such that acetonyl diphenylphosphine oxide **73** (**Scheme 20**) was the product isolated after as little as four hours' reaction time.

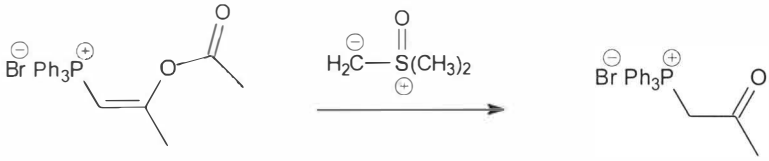
In an attempt to enhance the electron deficient nature of the β-alkoxy vinylphosphonium salts, the acetoxy derivative **54d** was made. Since resonance forms



68b **73**

Scheme 20

of the ester could be drawn in which the lone pairs of the ester oxygen participated by donation towards the carbonyl carbon, it was hoped that **54d** (**Scheme 12**) would represent a slightly more electron deficient alkene than the β-alkoxy vinylphosphonium salts had proven to be. However, reaction of 2-acetoxy vinyltriphenylphosphonium chloride (**54d**) and dimsyl produced only the β-keto phosphonium salt **74** (**Scheme 21**). It is interesting to note, however, that none of the diphenylphosphine oxide that would have been expected to form as a result of oxyanion attack on phosphorus was detected in the product mixture.

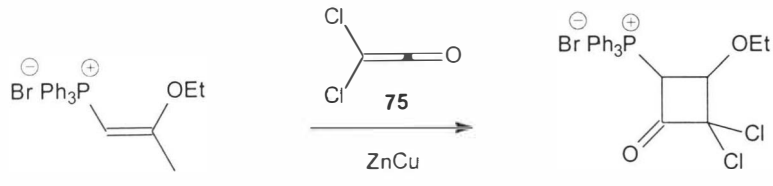


54d **74**

Scheme 21

Cyclopropanation of cyclic β-alkoxy vinylphosphonium salts should result in overall (n+1) ring expansion when the cyclopropyl ring were opened. This reaction would afford access to eight to eleven membered rings from seven to ten membered starting materials. In order to effect an (n+2) ring expansion, formation of donor-acceptor cyclobutane ring systems would be required. The ability to expand rings by two carbons as well as one-carbon expansion would not only add versatility to the method, but in addition would allow formation of functionalized eight membered rings from commonplace six membered rings. To this end, investigations into reactions that might be used to form cyclobutanes from alkenes were initiated. One such method was the reaction of ketenes with silyl enol ethers.[74] Consequently, preliminary investigations were begun into the use of ketenes for cycloadditions with β-alkoxy vinylphosphonium salts (**Scheme 22**).

Dichloroketene was formed by addition of a solution of trichloroacetyl chloride



54b **76**

Scheme 22

to a flask containing the vinylphosphonium salt **54b** and the zinc-copper couple in dry diethyl ether. The addition of ketenes to alkenes is a concerted reaction and therefore mechanistically different than many of the cyclopropanation methods previously attempted on the β-alkoxy vinylphosphonium salts. However, the ^{1}H NMR of the material collected after aqueous workup showed predominantly starting material. An IR spectrum was obtained, and showed a moderate peak at 1759 cm^{-1}, which was lower than the 1800 cm^{-1} expected for cyclobutanones.

The preceeding series of experiments served to show that β-alkoxy vinylphosphonium salts are not very good Michael acceptors. Additionally, it revealed a strong reactivity of these compounds with oxygen nucleophiles to form phosphine oxides in nearly quantitative yields. Overall, the β-alkoxy vinylphosphonium salts proved to be poor substrates for cyclopropanation *via* a number of reaction types and combinations. Clearly, another route to phosphorus substituted strained ring systems (and fused strained ring systems) was required.

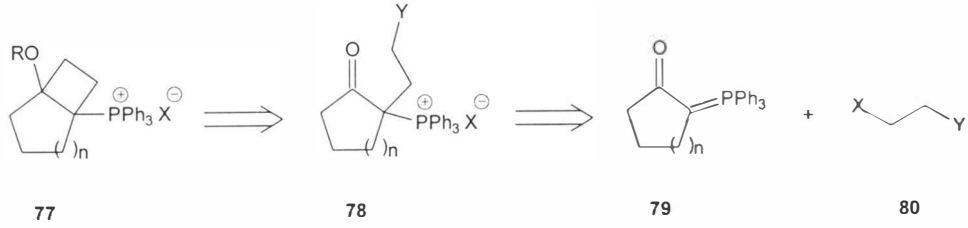
Chapter 3:

C-Alkylation of β-Keto Phosphonium Salts

The primary focus of most of the work discussed to this point was the formation of three membered ring systems bearing an electron donating alkoxy group (donor) and a phosphonium salt (acceptor). The interest in donor-acceptor substituted strained rings was an integral part of a plan to form bicyclic systems *via* the procedures worked out for the acyclic model compounds. Cleavage of the bridge bond in a [n.1.0] ring system would result in ring expansion by one carbon unit (n+1). For broader utility, access to (n+2) ring expansion was also needed. Consequently, a method for formation of fused bicyclic systems of the [n.1.0] and [n.2.0] type was sought. While cycloaddition of ketenes to cyclic alkenes would result in formation of fused bicyclic systems incorporating four membered rings, this approach was unsuccessful in attempts with β-alkoxy vinylphosphonium salts.

Since cyclopropanation of β-alkoxy vinylphosphonium salts was evidently not a viable pathway to the desired phosphorus substituted strained ring systems, an alternate route was needed. One alternative affording access to three and four membered rings

(and, therefore, (n+1) and (n+2) ring expansion) has been illustrated retrosynthetically in **Scheme 23**. Bicyclic phosphonium salt **77** is representative of compounds which could undergo ring expansion to give medium sized rings. As an initial target, **77** would result from intramolecular reaction of the side chain on cyclic β-ketophosphonate **78**. β-Ketophosphonate **78**, in turn, could be obtained by C-alkylation of cyclic β-keto phosphorus ylide **79** with the difunctional alkane **80**. Though any chain length could be chosen for the alkylation agent **80**, the focus on (n+1) and (n+2) ring expansions *via* donor-acceptor substituted strained ring systems meant three and four membered fused bicyclic systems were to be studied. Thus, the interest, for the present, was in addition of one and two carbon units to the ylide substrates. Substituents on **80**, represented by



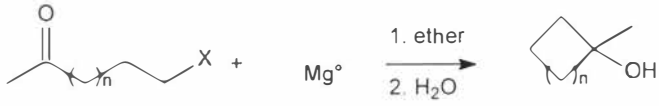
77 **78** **79** **80**

Scheme 23

X and Y, needed to meet only two criteria. One substituent (*e.g.* X) must be suitable for C-alkylation of the carbon bearing the phosphorus ylide. The remaining functional group (*e.g.* Y) had to be something that could, either in its native form or after conversion to another reactive species, attack the beta carbonyl, generating **77**.

The Barbier reaction is one of several synthetic methods which can afford access

to the desired bicyclic systems.[9,31] First reported in 1899, this reaction is a simple one-step process for formation of alcohols from alkyl halides and carbonyl compounds by way of magnesium metal.[75] It was Barbier's own student, Victor Grignard, who reported a two-step procedure the following year that would overshadow the one-step process (and won the 1912 Nobel Prize in Chemistry for the discovery). There is good evidence that the Barbier and Grignard reactions differ in mechanism, because different products are obtained from the same substrates depending on the procedure used.[76] The Barbier reaction, among other things, has been useful in formation of four and five membered rings by an intramolecular process (**Scheme 24**).[31] Given β-keto phosphonium salt **78** (**Scheme 23**), the Barbier reaction is one of several methods that would provide access



81a: n = 1
b: n = 2

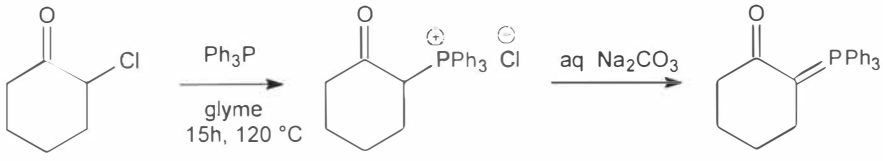
82a: 60%
b: 65%

Scheme 24

to the desired fused bicyclic systems. The substituents of compound **77** (**Scheme 23**) have been positioned so as to activate cleavage of the bridge bond to give the desired medium sized rings. Once again, the phosphonium salt was to act as electron acceptor. The alkoxy substituent, upon cleavage of the carbon-oxygen bond by the appropriate reagent, was to be the electron donor, the two substituents together capable of promoting

and directing ring opening to give an overall (n+2) ring expansion.

Cyclic β-ketoylides such as that represented by **79** are formed by base treatment of the corresponding β-keto phosphonium salts. These, in turn, are formed by the reaction of cyclic α-halo ketones and triphenylphosphine (**Scheme 25**).[77] The formation of cyclic β-ketoylides is much less efficient than for the acyclic counterpart. This limitation in the synthesis of cyclic β-keto phosphonium salts results from the mechanism of their formation. In the acyclic case, triphenylphosphine attacks the carbonyl, and *via* an epoxide-like transition state, the halogen is eliminated during formation of the



83 **84** **85**

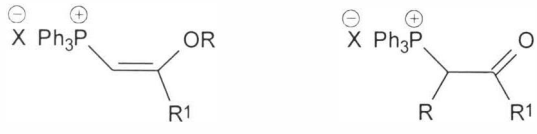
Scheme 25

carbonyl. The geometry of the cyclic systems precludes such an epoxide intermediate, and thus, direct S_N2 displacement of the halogen by triphenylphosphine probably occurs. Steric hindrance due to 1,3 hydrogen interactions, and the halogen itself, results in lower than ideal yields.[77]

Due to the more arduous route to the cyclic β-keto phosphonium salts, initial model studies were performed using acyclic systems. As a result, the same β-keto phosphorus ylides used as precursors in the cyclopropanation studies became the model

compounds in these investigations.

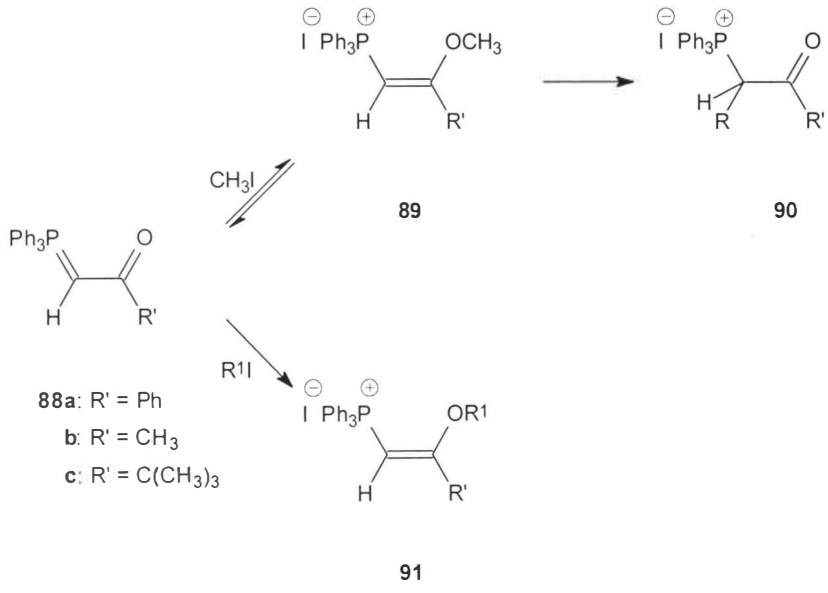
For this approach, the key step was to selectively C-alkylate the β-keto phosphorus ylide. As was shown in the previous chapter, O-alkylation of these substrates at room temperature is highly efficient. Additionally, precedent for simple conversion of **86** to **87** (**Figure 13**) can be found in the literature. Nesmeyanov and co-workers reported in



86 **87**

Figure 13: O-Alkylation vs. C-Alkylation of β-Keto Phosphorus Ylides.

1975 that acyclic β-keto ylides **88a,b** (**Scheme 26**) could, in effect, be C-alkylated with methyl iodide to give the β-keto phosphonium salts **90** (R = CH_3).[32] C-alkylation was reported for R' = C_6H_5 and CH_3. When these ylides were treated with either iodoethane or iodopropane (R^1 = CH_2CH_3 or $CH_2CH_2CH_3$) , only the O-alkylated products **91** were isolated. The fact that the relatively large phenyl substituent did not prevent the formation of the desired product would seem to support the conclusion that steric considerations are not the sole determinant in directing the site of alkylation. Nesmeyanov and co-workers reported that C-alkylation was the result of rearrangement from the readily formed O-alkylated salts **89** to form the desired β-keto phosphonium salts **90** upon heating in a sealed tube for 1-5 hours in toluene. No other conditions,


I Ph3P OCH3
H R'
I Ph3P O
H R R'
CH3I
89
90
Ph3P O
H R'
R1I
I Ph3P OR1
H R'
88a: R' = Ph
b: R' = CH3
c: R' = C(CH3)3
91

Scheme 26

solvents or substrates were reported.[32]

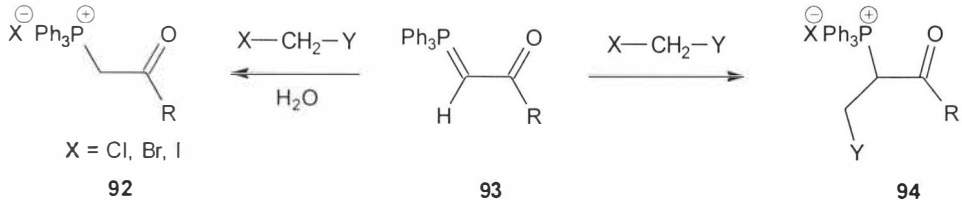
In related work, Shevchuk and co-workers reported C-alkylation of the β-ketoylides **88c** with chloromethyl methyl ether to give **90** ($R = CH_2OCH_3$).[33] Alkylation of the tertiary butyl substituted ylide indicates relative insensitivity to steric bulk of the R' group adjacent to the ketone. This was encouraging, in light of the fact that this procedure was to be utilized on cyclic β-ketoylides, which have inherently more steric crowding due in part to ring puckering.

In order to conduct a thorough study of reaction conditions and substrates, a variety of bifunctional compounds were stirred with β-ketoylides to attempt C-alkylation. **Scheme 27** and **Table 2** summarize the reactions attempted. The commercially available acyclic substrates **93** were examined as models for the less accessible cyclic β-keto phosphorus ylides of the general form of **85** (**Scheme 25**). The immediate goal was to determine the feasibility and optimal conditions for direct C-alkylation of β-keto ylides. Compounds **94b-g** could undergo coupling using tributyltin hydride[9] to form three membered rings. Compounds **94h-j** would provide four membered rings after attack of the side chain at the β carbonyl. As models for the cyclic cases, compounds **94b-j** therefore represent access to ring expansions of (n+1) and (n+2).

In a typical procedure, the ketoylide **93** ($R = CH_3$) was stirred in dry benzene with 5 equivalents of methyl iodide (**Table 2**, entry **1**). The flask was then placed in an oil bath at 77 °C and stirred for 4.75 hours under nitrogen. The product **94a** was purified by preparatory thin-layer chromatography on silica gel, eluted with 1:3:2 CH_2Cl_2/EtOAc/Et_2O to give the product in 11% yield. In cases where this proceedure

failed to yield the desired (1-alkyl acetonyl) phosphonium salt **94**, a number of reaction parameters were varied in an attempt to find conditions that would best promote C-alkylation. For instance, reactions were carried out at temperatures between 0 °C and 90 °C, in benzene, THF, toluene, ethyl acetate, and diglyme. The solvent was rigorously dried, since the presence of water in the reaction mixture led to isolation of the β-keto phosphonium salt **92**. Reaction times were also varied, from 50 minutes to 78 hours. In all cases, the major product was either the O-alkylated product **89** or the β-keto phosphonium salt **92**. Traces of material consistent with C-alkylated products were detected in the ^{1}H NMR spectra of the crude product mixtures. Of the reactions **94a-g**, **94a** produced the highest yield of C-alkylated product, with an isolated yield of 6%. ^{1}H NMR of the crude reaction mixture for **94d** showed just over 3% was the desired product (by integration), after heating overnight in ethyl acetate at 75 °C. Higher temperatures (greater than 100 °C) or long reaction times (greater than 12 - 18 hours) rarely showed any evidence of C-alkylation, but rather the formation of the phosphonium salt. These results were in agreement with the findings of Nesmeyanov.[32]

In the case of entry **8** (**Table 2**), the β-alkoxy vinylphosphonium salt (O-alkylation product) was isolated, purified by recrystallization, and then attempts were made to effect rearrangement by heating in various solvents. As with the formation of β-alkoxy vinylphosphonium salts **54** (**Table 1**), O-alkylation could be accomplished in high yield (86%). In attempts to effect thermal rearrangement of the O-alkylated vinylphosphonium salt (corresponding to compound **86** in **Figure 13**, R = CH_2CH_2Br; R^1 = CH_3) to the C-alkylated keto ylide **94h**, polar solvents such as chloroform seemed, based on ^{1}H NMR



Scheme 27

Entry	R	X	Y	Compound
1	CH_3	I	H	**94a**
2	H	Cl	OCH_3	**94b**
3	CH_3	Cl	OCH_3	**94c**
4	CH_3	Br	OCH_3	**94d**
5	CH_3	I	I	**94e**
6	CH_3	Cl	I	**94f**
7	$C(CH_3)_3$	Cl	OCH_3	**94g**
8	CH_3	Br	CH_2Br	**94h**
9	CH_3	Cl	CH_2Br	**94i**
10	CH_3	Br	CH_2OCH_3	**94j**

Table 2: Reaction of β-Keto Phosphorus Ylides with Haloalkanes or Water. Attempted C-Alkylation.

analysis of the crude reaction mixtures, to provide the highest proportion of C-alkylated material. However, while rearranged products could be detected by ^{1}H NMR, the isolated yields proved to be insufficient to be synthetically useful. In no other case was C-alkylated product detected in more than trace quantities (*i.e.* no more than a few percent by ^{1}H NMR) in crude reaction mixtures.

Other modifications on this basic theme were utilized in the effort to effect C-alkylation. In one attempt, LiBr was added to the reaction mixture in addition to the ketoylide and haloalkane. The intent was to complex the carbonyl oxygen so that O-alkylation would be less likely. In another series of reactions, phenyllithium was used to generate the ylide *in situ* from β-keto phosphonium salts, **92**. This was followed immediately by addition of an alkyl halide to the reaction mixture. No more than trace amounts of the desired products were detected by ^{1}H NMR. It was of particular interest that combination of the β-keto phosphonium salt **92** and methyl iodide in the presence of phenyllithium failed to produce the C-alkylation product **94a** which was accessed *via* the method of Nesmeyanov (*vide supra*).

As a result of these studies, the difficulties of functionalizing the carbon bearing the triphenylphosphonium salt was highlighted. It is indeed probable that the bulk of the phenyl groups on the phosphorus were responsible for the limited success in alkylation at this site, especially in light of the fact that simple compounds such as methyl iodide could be added, but any other group could not be forced to add to any useful extent. Consequently, the desired phosphorus containing donor-acceptor substituted strained bicyclic systems must be accessed *via* a pathway other than one involving Barbier-type

reactions of β-keto phosphonium salts.

Chapter 4:

Cycloadditions of Enamines With Alkynylphosphonates

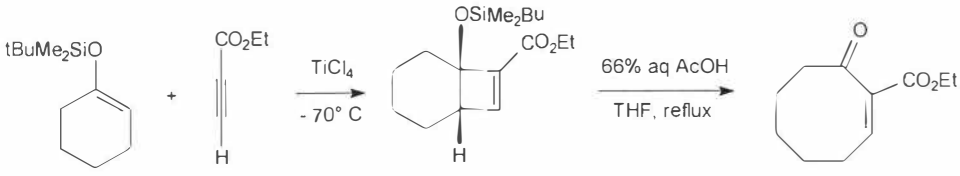
The route to formation of phosphorus substituted medium sized rings discussed thus far involved formation of a bicyclic ring precursor from a system already containing the phosphonium salt functional group. One problem with this approach that was unanticipated, however, was the electronic and steric effects of the large triphenylphosphonium salts on the reactivity of alkenes toward cyclopropanation and ylides toward C-alkylation. Interestingly, vinyl phosphonate **95** (**Figure 14**) has been shown to undergo cycloaddition with monochloroketenes,[78] while vinyl phosphonium

95 **96**

Figure 14: Cycloadditions of Vinyl Phosphonates vs. Vinyl Phosphonium Salts.

salt **96** was found to be unreactive to a variety of carbenes as well as dichloroketene. Clearly, the nature of the phosphorus containing group strongly affects the reactivity of the alkene bearing it. The goal of forming a medium sized ring bearing a phosphorus reagent capable of undergoing an olefination reaction (Wittig, HWE etc.) was still unrealized as yet. An alternative approach to those already described involved introduction of phosphorus coincidentally with formation of the bicyclic system itself. In other words, a phosphorus containing reagent would be utilized to generate the three or four membered ring from alkenes containing an electron donor group. The question then became one of identifying a phosphorus reagent capable of carrying out such a transformation.

In 1979, Clark and Untch reported a method for formation of medium sized rings by cycloaddition of silyl enol ethers with ethyl propynoate.[79] Reaction of the silyl enol ether of cyclohexanone (**97**, **Scheme 28**) and ethyl propynoate (**98**) initially gave the bicyclic adduct **99** which was isolated in 37% yield. Bicyclic adduct **99** was refluxed in THF containing aqueous acetic acid with 5 drops 85% phosphoric acid for 20 hours, to give the ring expanded product **100** in 58% yield. Analogously, enamines have been

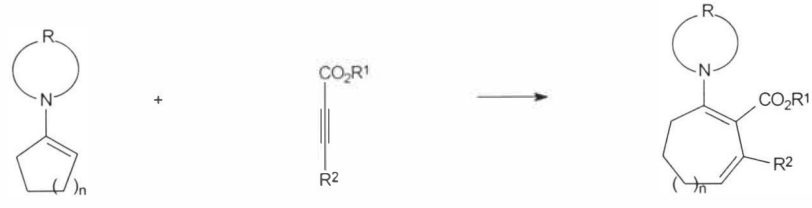


97 **98** **99** **100**

Scheme 28

reacted with acetylenic monoesters to give ring expanded products.[80] Heubner and co-workers[81] added a solution of ethyl propynoate (**102a**) in dioxane to a solution of 1-pyrrolodinylcyclopentene (**101a**) in dioxane. After being heated for 15 minutes on a steam bath followed by purification, the enamino intermediate **103** was stirred for 12 hours in 20% aqueous acetic acid to give the hydrolyzed product in 66% yield from the intermediate. In addition, these and other researchers studied the reactions of enamines with dimethyl acetylene dicarboxylate (DMAD, **102b**), and obtained similar ring expanded products (**Scheme 29**).[82] Cycloaddition of an enamine with DMAD has also been used in the synthesis of a number of lactarane terpenoids.[83] The fact that an ester group was adequate to activate an alkyne in a cycloaddition reaction suggested that a phosphorus containing substituent might also serve to activate alkenes and alkynes towards cycloaddition.

Bearing in mind the goal of using a phosphorus functional group to accomplish



101a: n = 1, R = -$(CH_2)_4$-
b: n = 2, R = -$(CH_2)_2O(CH_2)_2$-

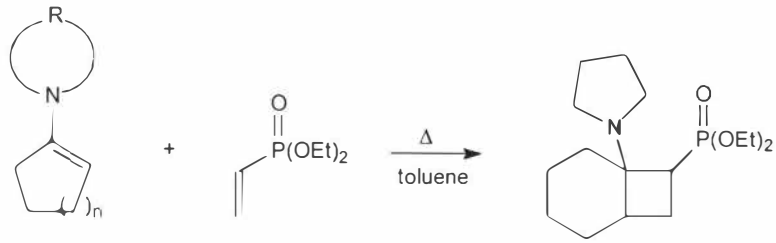
102a: R^1 = Et, R^2 = H
b: R^1 = Me, R^2 = CO_2CH_3

103a: n = 1, R = -$(CH_2)_4$-, R^1 = Et, R^2 = H
b: n = 2, R = -$(CH_2)_2O(CH_2)_2$-, R^1 = Me, R^2 = CO_2Me

Scheme 29

ring expansion and bridgehead alkene formation, attention was turned from phosphonium salts to phosphonates. The vinyl phosphonium salts which had been used thus far did not afford products useful for utilization as ring expansion precursors. It had been anticipated that the electron deficient nature of the phosphonium salt would result in activation of the alkene towards Michael addition. This was a key component of the early attempts at forming donor-acceptor substituted strained ring systems, and was a premise well supported by the literature. Unfortunately, it was discovered that the presence of the phosphonium salt and/or the alkoxy substituent radically reduced the reactivity of the alkene, to the extent that even procedures that were known to effect cyclopropanation in electron rich and electron poor alkenes failed to produce the desired cycloadducts in these systems. The discovery by Ruder and Kulkarni that anions generated from β-keto phosphonates underwent cycloaddition with DMAD, led to the consideration of employing phosphonates in alternate cycloaddition reactions.[84] Since phosphonates undergo the HWE olefination reaction, they conformed to the desire that the same functional group used in forming the medium sized ring also participate in the formation of the bridgehead double bond. The HWE reaction utilizes phosphonates which (usually) bear an α substituent capable of stabilizing a carbanion (*e.g.* a carbonyl, ester, cyano group) to react with aldehydes and ketones to form alkenes.[20a]

Several groups have reported reactions in which an alkene or alkyne was activated by a phosphonate functional group.[85] At least one report, by Darling and Subramanian, described cycloaddition reactions of vinyl phosphonates (**Scheme 30**).[86] They found that combination of the pyrrolidine enamine of cyclohexanone, **101c**, with diethyl vinyl

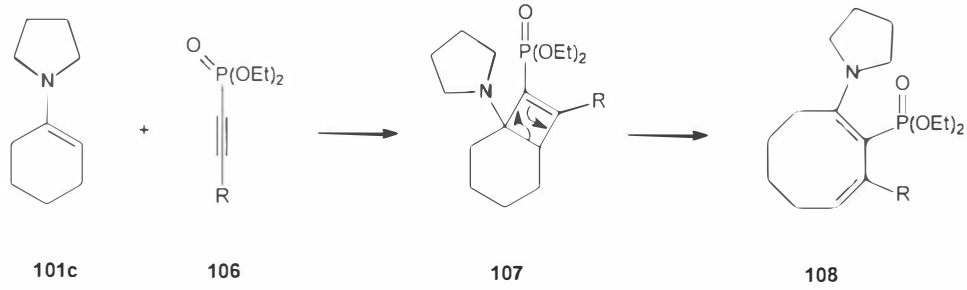


101c: n = 2, R = $-(CH_2)_4-$ **104** **105**

Scheme 30

phosphonate (104) produced the bicyclic [4.2.0] system **105**. This was a direct analog of the reactions of ethyl and methyl propiolate with enamines. The bicyclic phosphonate 105 did not undergo ring expansion for two reasons. First, the electron donating substituent (the amine) and the electron withdrawing substituent (the phosphonate) are not situated properly to polarize the bridge bond. Second, there are no π electrons which could participate in an electrocyclic rearrangement leading to cleavage of the bridge bond. However, if an alkynyl phosphonate such as **106** (**Scheme 31**) were utilized rather than vinyl phosphonate **104**, the resulting product would bear a double bond, and ring expansion would therefore be possible.

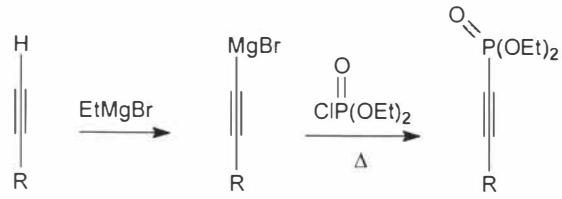
While enamines are common reagents in organic synthesis, and are easily made by well-established procedures,[87] alkynyl phosphonates are rather obscure compounds that are not commercially available. There were two main approaches to procuring the desired alkynyl phosphonate compounds,[88] neither of which were found to be particularly convenient in terms of providing high yields of relatively pure alkynyl phosphonates. The



101c 106 107 108

Scheme 31

first method involved addition of an alkynyl Grignard to diethylchlorophosphate.[88a] The alkynyl Grignard was formed by reaction of a monosubstituted alkyne with ethylmagnesium bromide, and the resulting solution was added to a solution of diethylchlorophosphate. This method reportedly gave fair to good yields (52% - 76%) for alkynes which had alkyl or aryl substituents (**Scheme 32**, **109a,b**).[88a] However, when an attempt was made to produce diethyl ethynylphosphonate (**106**, R=H) by combining ethynyl magnesium bromide and diethylchlorophosphate in ether at 0 °C, a very dark red/black solution resulted in which no product was detectable by ^{1}H NMR. Slowing the addition rate of the ethynyl magnesium bromide to the ice cold solution of diethylchlorophosphonate resulted in formation of a yellowish grey solution that over 30-45 minutes gradually darkened, finally reaching the same red/black solution earlier encountered. However, the yield did improve to 12% based on ^{1}H NMR of the crude reaction mixture. Additions carried out at -78 °C and at room temperature gave much lower yields (3% and 1.5% respectively). Acheson and co-workers noted this problem as well, and attributed the low yields and the formation of tars to reaction of the ethynyl



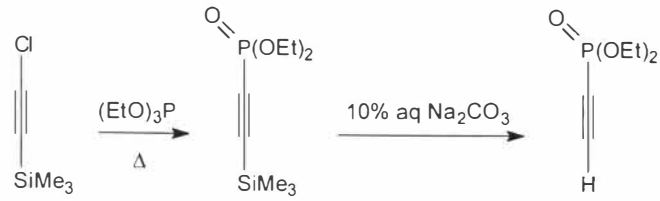
109a: R = alkyl **110** **106**
b: R = aryl
c: R = TBDMS

Scheme 32

anion with the chlorine of the diethyl chlorophosphate rather than the phosphorus.[88c]

As a result of concern that the poor performance of this proceedure may have been due in part to the acidic nature of the alkynyl proton, an attempt was made to form the *tert*-butyl dimethylsilyl (TBDMS) protected ethyne **109c** by reaction of ethynyl magnesium bromide with TBDMSCl. Ethyl magnesium bromide was then added to the resulting *tert*-butyl dimethyl ethynyl silane at 0 °C, to give the silyl protected alkyne (**110**, R=TBDMS). This solution also appeared black at the end of the reaction, and after hydrolysis by shaking with aqueous sodium carbonate, a 7% yield of the desired diethyl ethynylphosphonate was isolated.

The second method for formation of diethyl ethynylphosphonate (**106**, R = H) was initially reported by Burt and Simpson (**Scheme 33**).[88b] They used trialkylsilyl substituted haloacetylenes in an Arbuzov reaction with triethylphosphite. This reaction worked adequately, but obtaining 1-chloro-2-trimethylsilylethyne (**111**) was not trivial.

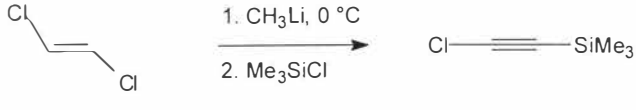


111 **112** **106** (R = H)

Scheme 33

Haloalkynes can be explosive, neccessitating the use of the trimethylsilyl protecting group. Of the several syntheses reported for **111**,[89,90] two methods for making it were attempted.

In the first method which was used, a solution of *trans*-dichloroethylene (**113**) in ether was added dropwise to 2.2 equivalents of methyllithium in dry ether at 0 °C (**Scheme 34**), and was then allowed to warm to room temperature. The mixture was then cooled to -78 °C, and trimethylsilyl chloride was added dropwise. The 1-trimethylsilyl-2-chloroethyne (**111**) was purified by distillation. The reported yield for this reaction was 96%,[89] but yields obtained in the course of this research never exceeded 66%.



113 **111**

Scheme 34

Alternatively, the silylated chloroalkyne **111** was prepared from tetrachloroethylene by reaction with lithium metal (**Scheme 35**).[89] A large excess of lithium metal was placed in THF, and cooled to -78 °C, followed by addition of tetrachloroethylene (**114**). This reaction mixture was kept at -78 °C for 36 hours, after which time it was a thick, grey slurry which was then added *via* cannula to a stirred solution of chloro trimethylsilane in THF at -78 °C. After warming to room temperature, THF was distilled from the clear yellow solution, and the product was distilled in a *Kugelrohr* apparatus to give a 38% yield of the desired chloroethynyltrimethylsilane (**111**).

1-Trimethylsilyl-2-chloroethyne (**111**) was then used as the starting material for the formation of diethyl ethynylphosphonate **106** (**Scheme 33**).[88b] The chloroalkyne **111**

114 **111**

Scheme 35

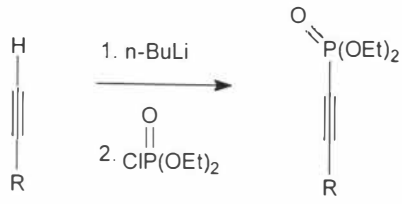
was refluxed with freshly distilled triethylphosphite under nitrogen for 5 hours, followed by removal of the trimethylsilyl group by hydrolysis with 10% Na_2CO_3. This method provided the desired ethynyl phosphonate **106**, but removal of unreacted triethylphosphite was difficult. The best GC yield using the chloroalkyne was 78%, but isolated yields were normally in the range of 30% to 40%, primarily due to repeated distillations which were necessary in order to purify the product.

In an effort to produce the desired diethyl ethynylphosphonate in higher yield, the

procedure used by Chattha and Aguiar[88a] was modified slightly. Their method used Grignard reagents to deprotonate terminal alkynes. However, the treatment of a terminal alkyne with a base such as n-butyllithium affords the alkynyllithium reagent, which should cleanly add to diethyl chlorophosphate to give substituted alkynyl phosphonates (**Scheme 36**). The terminal alkyne trimethylsilylethyne (**115a**) could be synthesized from trichloroethene by a literature procedure,[91] and was also available commercially. Reaction of **115a** *via* this method did give good yields, on the order of 60-70% for **106a** after hydrolysis of the trimethylsilyl group with aqueous sodiuim carbonate. The simplicity of this sequence, in conjunction with the ease with which the starting materials could be obtained, made this the method of choice for obtaining all of the alkynyl phosphonates utilized. It also provided a general method for formation of 1-phosphonyl alkynes, because any monosubstituted alkyne could be added to diethyl chlorophosphate in this manner. **Table 3** summarizes the results for the alkynyl phosphonates synthesized in the course of this work.

With the alkynyl phosphonates in hand, their reactivity towards cycloaddition with enamines could be experimentally compared to the earlier work involving ester-activated alkynes.[79-82] The work by Darling and co-workers had already shown that phosphonates activate alkenes towards cycloaddition with enamines.[34] Their work served as the bridge linking the two methodologies by which the formation of the bicyclic systems comprised of a medium sized ring with a bridghead double bond could be accomplished.

Cycloadditions of propynoates and DMAD have been reported with both silyl enol ethers[80] and enamines.[80-82] Clark and Untch reported that, by carrying out cycloadditions



115a: R = $SiMe_3$
b: R = $(CH_2)_2CH_3$
c: R = CH_2OCH_3
d: R = C_6H_5

112: R = Me_3Si
106 a: R = H
b: R = $(CH_2)_2CH_3$
c: CH_2OCH_3
d: C_6H_5

Scheme 36

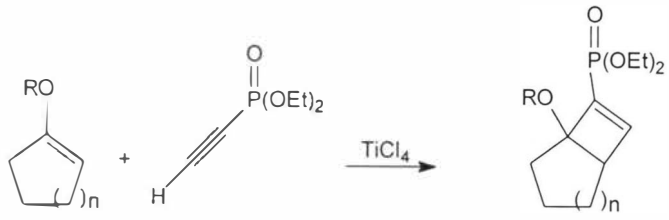
106

Entry	R	% Yield	Compound
1	H	60	**106a**
2	$(CH_2)_2CH_3$	63	**106b**
3	CH_2OCH_3	69	**106c**
4	Ph	75	**106d**

Table 3: Synthesis of Alkynyl Phosphonates.

of silyl enol ethers with ethyl propynoate at -70 °C, they were able to isolate the bicyclic intermediate.[79] Correspondingly, diethyl ethynylphosphonate (**106a**) and $TiCl_4$ were combined in diethyl ether at -78 °C (**Scheme 37**), followed by addition of 1-(*tert*-butyldimethylsilyloxy)cycloheptene (**116a**). The reaction was allowed to warm to room temperature overnight, and after 24 hours, the reaction was worked up, and the ^{1}H NMR spectrum of the crude reaction mixture was taken. Based on the absence of any vinyl protons, it was determined that cycloaddition had not taken place. In order to minimize the steric bulk around the enol ether, **116b** was prepared and combined with the alkynyl phosphonate **106a**. As before, no cycloadduct was detected in the ^{1}H NMR of the crude reaction mixture. Attempts to duplicate the reactions reported by Clark and Untch on identical compounds met with very limited success.[92]

Consequently, it was decided to turn to enamines as the source of the activated alkene for cycloaddition. In cycloadditions of enamines with activated alkynes, several literature reports have indicated that the nature of the desired products has a direct bearing on the selection of the amine from which to form the enamine. Berchtold and co-workers reported that, compared to morpholine enamines, pyrrolidine enamines gave superior yields in cycloadditions with DMAD.[82] Brannock and co-workers noted that the occurrence of products, byproducts, and rearrangements depended on whether dimethylamine, pyrrolidine, or morpholine had been used to form the enamine.[80] On the other hand, Heubner and co-workers noted no difference in yields for cycloadditions between DMAD and enamines formed from morpholine or pyrrolidine.[81] Additionally, reported syntheses involving enamine cycloaddition with DMAD employed morpholine



116 **106a** **117**

Scheme 37

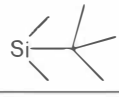
Entry	R	n	Compound
1		3	**116a**
2		1	**116b**

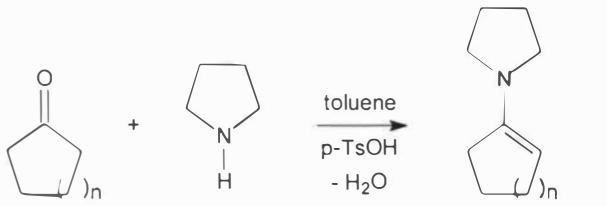
Table 4: Silyl Enol Ethers Used in Attempted Cycloadditions.

enamines.[83] Hirsch and Cross reported that morpholine enamines produced higher yields than pyrrolidine enamines in cycloadditions with DMAD to form eight membered rings, while pyrrolidine enamines formed seven membered rings more efficiently.[93] Based on these reports, and because the initial investigations were to involve formation of seven membered rings from five membered rings, enamines based on pyrrolidine were chosen as the preferred starting material.

Scheme 38 shows the synthesis of enamines. 1-Pyrrolidinylcyclopentene (**101a**, n=1) is easily and quickly formed by combining cyclopentanone (**118**), pyrrolidine (**119**), and a catalytic amount of *p*-toluenesulfonic acid in toluene. The water formed in the reaction was removed by azeotropic distillation, and collected by means of a Dean-Stark trap. The 1-pyrrolidinylcyclopentene (**101a**) was then collected by removal of the toluene by distillation, followed by *Kugelrohr* distillation of the enamine itself.

Because pyrrolidine enamines are very reactive, they are accordingly more likely to decompose. When exposed to air at room temperature, the decomposition can be followed over a span of a few minutes, as the material rapidly turns from colorless to a dark orange brown. Surprisingly, however, it was discovered that even when stored under argon in the freezer, the pyrrolidine enamine, while appearing colorless, had in fact decomposed over a period of two to three weeks. Accordingly, the enamine was always distilled immediately prior to use. **Figure 15** shows the variety of enamines prepared using the aforementioned procedure.

Scheme 39 shows the general reaction and intermediates in the cycloaddition of enamines with alkynyl phosphonates. Initially, the intention was to isolate the

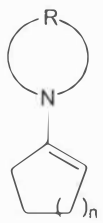


n=1,2

118 **119** **101a**: n = 1

b: n = 2

Scheme 38



101a: n = 1, R = $-(CH_2)_4-$

b: n = 2, R = $-(CH_2)_4-$

c: n = 1, R = $-(CH_2)_2O(CH_2)_2$

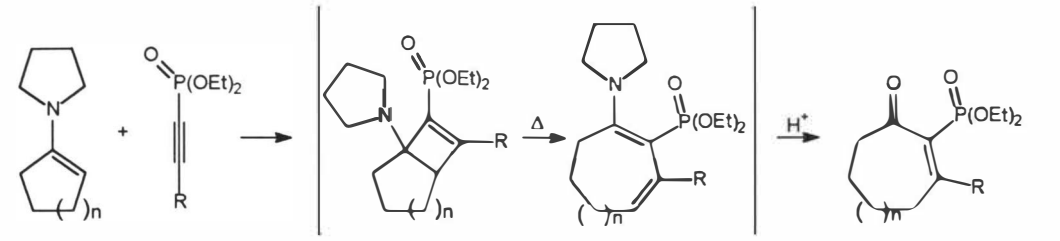
d: n = 2, R = $-(CH_2)_2O(CH_2)_2-$

Figure 15: Enamines Used for Cycloadditions

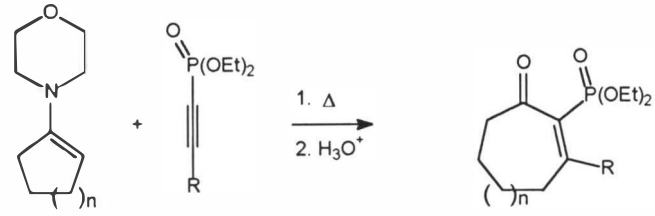
intermediates **120a** and **121a** resulting from enamine cycloaddition with alkynyl phosphonate **106a**. Following the procedure of Huebner and co-workers,[81] the reaction was to be carried out in ether and the temperature maintained below 35 °C. Isolation of the bicyclic intermediate resulting from the cycloaddition of enamines with propynoates and DMAD has been achieved under such conditions.[79-81]

Investigations into the cycloaddition with alkynyl phosphonates were then commenced using 1-pyrrolidinylcyclopentene (**101a**). In an attempt to isolate the bicyclic intermediate **120a**, analogous to those isolated by cycloaddition of enamines with DMAD and propynoates, the reactions was initially carried out at room temperature or below. In a typical procedure, the enamine was added to dry diethyl ether, and cooled to less than 10 °C in an ice-water bath. A solution of the phosphonate in diethyl ether was then added, and the solution was stirred under N_2 for 2 hours. No change in the color of the solution was noted, which was taken as an indication that the enamine was not undergoing any significant decomposition. Removal of solvent under reduced pressure (maintaining the temperature at or below 32 °C) gave a yellow oil. After ^{1}H NMR analysis, the sample was placed in an oil bath in order to effect ring expansion to give the medium sized ring.

This procedure most often resulted in recovery of unreacted phosphonate, and a product having two doublets of doublets, which each appeared as "triplets" δ = (7.26, J=14.7); (3.7, J=13.8). At first, it was believed that this second compound was the desired bicyclic intermediate **120a**. This assignment was based, in part, on the chemical shift which Huebner and co-workers reported for the vinyl proton of the bicyclic



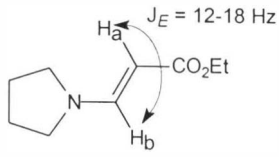
101a: n = 1 **106a**: R = H **120 a**: n = 1, R = H **121 a-e** **120 a**: n = 1, R = H
b: n = 2 **b**: R = $(CH_2)_2CH_3$ **b**: n = 1, R = $(CH_2)_2CH_3$ **b**: n = 1, R = $(CH_2)_2CH_3$
c: R = CH_2OCH_3 **c**: n = 1, R = CH_2OCH_3 **c**: n = 1, R = CH_2OCH_3
d: R = C_6H_5 **d**: n = 1, R = C_6H_5 **d**: n = 1, R = C_6H_5
e: n = 2, R = H **e**: n = 2, R = H



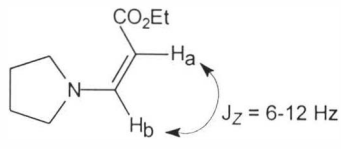
101 c: n = 1 **106 a-d** **122 a-e**
b: n = 2

Scheme 39

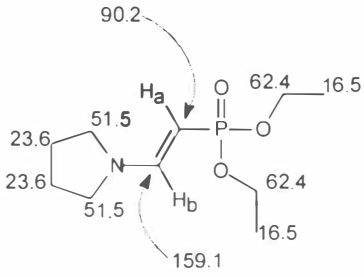
intermediate in the cycloaddition of ethyl propynoate.[81] However, in light of the fact that heating at over 110 °C for 4.5 hours failed to produce any change in the ^{1}H NMR spectrum of this substance, the assignment was called into question. Further analysis of the ^{1}H and ^{13}C NMR spectra, did, in fact show the initial assignment to be in error. In **Figure 16**, four structures are used to illustrate the process by which the assignment of structure **124** to the unknown product was accomplished. Based on the mass of the product ($^m/_z$ = 233 by GC/MS), and the literature reports of addition of amines to alkynyl phosphonates,[85a] the recovered product was believed to be enaminophosphonate **124**. The two isomeric structures **123a** and **123b** were used as a comparison to the analogous phosphonate in order to calculate the expected chemical shifts of the vinyl protons. The calculations of expected chemical shift were made using substituent constants determined by Pascual and co-workers.[94] For **123a** (the *E* isomer) values of δ_{Ha}= 4.93 ppm and δ_{Hb}= 7.12 ppm were calculated. The *Z* isomer **123b**, on the other hand, had calculated values of δ_{Ha} = 4.81 ppm and δ_{Hb} = 6.53 ppm. The observed values for the vinyl protons of the phosphonate substitued compound **124** were 3.88 ppm and 6.98 ppm. The proton with a chemical shift of 6.98 ppm must, in any case, be assigned as proton H_b of enaminophosphonate **124**. The observed value was closer to the calculated value for H_b of the *E* isomer, **123a**. Being further removed from the phosphonate, the chemical shift of H_b is likely to be more influenced by the amine substituent (for which the substituent constants provide an actual value) than the phosphonate (for which we approximated a value by substituting an ester in the calculation). Correspondingly, the α proton, being adjacent to the phosphonate (which



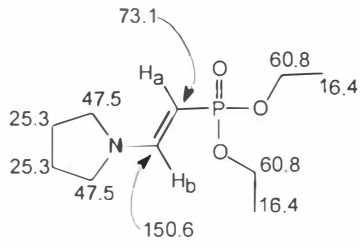
123a



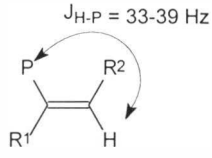
123b



124a



124b

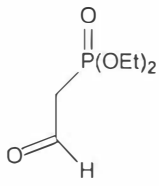


125

Figure 16: Structure Assignment for Enaminophosphonate **124**.

is less electron withdrawing than the ester) could be expected to appear further upfield than the calculated value due to increased shielding. Further evidence of the proposed *E* relationship is found in a comparison of the coupling constants expected for vinylogous systems and the observed values. While J_E is usually 12-18 Hz, J_Z is normally 6-12 Hz. As already noted, the vinyl protons appear as three lines with both coupling constants near 14 Hz which also tends to support the *E* structure. Finally, neither coupling constant is unusually large; a proton *trans* and *beta* to the phosphorus is virtually ruled out. Typical coupling values for $J_{H\text{-}P}$ across a double bond as shown in **125** (**Figure 16**) are on the order of 33-39 Hz.[43]

The ^{13}C chemical shifts predicted for the structure **124a** are compared with the experimentally obtained values **124b**.[95] The agreement of these values, along with the ^1H NMR and mass spectral data, gave considerable credence to the assignment of structure **124** to the product obtained. The enaminophosphonate was presumed to arise from Michael addition of the free amine (present as a result of decomposition of the enamine reagent) to the alkynyl phosphonate. To verify this proposed structure and origin, pyrrolidine was placed in a round bottomed flask, and one equivalent of alkynyl phosphonate **106a** was added under N_2. After stirring for a few minutes, the mixture was transferred to an NMR tube, and the ^1H spectrum was recorded. The product obtained from this reaction was identical in all respects to the enaminophosphonate **124** obtained in previous cycloaddition reactions, both by ^1H NMR and by GC/MS. Upon workup of the reaction mixture, dilute acid failed to effect hydrolysis of the enaminophosphonate, giving back instead compound **124**. Stronger conditions, *e.g.* strong acid with heating,



126

Figure 17: Hydrolysis Product of Enaminophosphonate **124**.

did hydrolyze the enaminophosphonate to give β-keto phosphonate **126** (**Figure 17**).

Having determined the structure of the enaminophosphonate byproduct **124**, the origin of the compound in the cycloaddition reactions (where concentrations of pyrrolidine should be minimal) became an item of interest. The question was whether it was forming in the cycloaddition procedure as a result of thermal decomposition of the enamine or reaction intermediates, or as a result of decomposition of the enamine at room temperature prior to combining the reagents. In order to study the formation of the enaminophosphonate **124**, the reaction was run in an NMR tube and the ^1H spectrum of the crude reaction mixture periodically measured. The enamine was added in portions to the phosphonate in C_6D_6 solution. The key peak which verified formation of the enaminophosphonate was the doublet of doublets at 7.28 ppm; this area of the spectrum was unencumbered by any other signals. Although this signal was not present after four minutes, the enaminophosphonate was present after fourteen minutes at room temperature, and continued to increase, as indicated by ^1H NMR spectra obtained over the next hour. No other product was evident at room temperature, and over time the concentration of the

enamine decreased, most likely due to gradual decomposition by moisture in the air. These results suggested that the reaction occured rapidly at room temperature to form the enaminophosphonate byproduct **124**. In addition, this indicated that the enaminophosphonate was not being formed as a result of the work-up nor decomposition of the desired product during solvent removal or heating.

The reaction conditions for cycloaddition were optimized using the "unsubstituted" alkynyl phosphonate **106a**. As already noted, in the initial cycloaddition attempts the enamine and alkynyl phosphonate were combined at room temperature (or below) in order to facilitate isolation of the bicyclic intermediate. In these reactions, the enamine was presumed to be reasonably pure as long as discoloration had not occurred. This proved not to be the case, and accordingly, many reactions were worked up only to discover that enaminophosphonate **124**, as well as highly complex mixtures were produced. Upon the realization that clear, colorless enamine (that had been stored in the freezer under argon) was **not**, in fact, "clean", the normal procedure became distillation of the enamine immediately prior to use.

Another factor which had not been anticipated was the highly hygroscopic nature of the alkynyl phosphonates. Even after precautions had been taken to ensure that the enamine was pure, reactions failed to produce the cycloadduct, and instead the enaminophosphonate byproduct **124** was isolated. When this occurred even after all glassware utilized had been flame dried, it was determined that the source of the moisture was the phosphonate itself. Two methods were effective in correcting the situation. The phosphonate could be distilled immediately prior to use, or dissolved in CH_2Cl_2 and dried

over a drying agent such as $MgSO_4$ or Na_2SO_4. These measures were adequate to reduce the formation of the enaminophosphonate **124** to no more than trace amounts.

In addition to reactions run at room temperature, a few limited attempts to carry out the addition of reagents at cold temperatures (-78 °C) confirmed that the failure to undergo cycloaddition was not due to thermal decomposition of the reagents or intermediates. These attempts invariably resulted in isolation of mixtures of the byproduct and starting materials.

It soon became apparent that even with dry reagents the desired cycloaddition reaction was not occurring at room temperature, and thus, efforts to isolate the bicyclic intermediate **120a** was abandoned. Since Darling and Subramanian[34] had utilized refluxing toluene as the solvent for cycloaddition of diethyl ethenylphosphonate **104** with enamines (**Scheme 30**), this seemed a reasonable initial approach for the alkynyl phosphonates. Consequently, enamine **101a** and alkynyl phosphonate **106a** werecombined in toluene in a round bottomed flask and heateed. However, after refluxing for 24 hours, reactions utilizing this procedure also produced primarily the undesired enaminophosphonate byproduct **124**. This was probably due to the presence of some water in the toluene, even though it had been distilled from calcium hydride and stored over molecular sieves. In addition to enaminophosphonate **124**, another product was detected in these reactions, but was not characterized at the time. This second compound featured two sets of peaks that appeared as doublets of doublets, one at 7.75 ppm and the other at 4.7 ppm, clearly different from the enaminophosphonate **124**. The enaminophosphonate predominated in the reaction mixture by 2.2:1 over the new product.

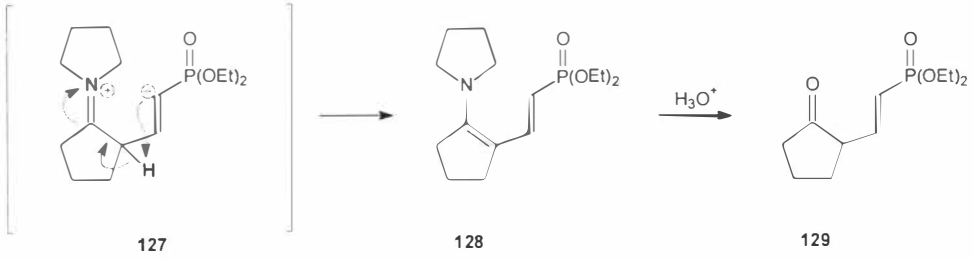
Purification was attempted on a silica preparative TLC plate, eluted with ethyl acetate/dichloromethane/methanol (15:15:1) in order to identify the components. However, the unknown compound was never located on the prep plate; this may have been due to decomposition on the plate or inadequate rinsing of the plate scrapings. Based on analysis of later reaction runs, it is believed that this compound was the ring expanded cycloadduct **121a** (**Scheme 39**). Attempts to purify cycloadduct **121a** prior to hydrolysis met with little success. Though the presence of **121a** was detected several times in ^{1}H NMR of crude reaction mixtures, it never survived column or thin layer chromatography. Distillation of cycloadduct **121a** unfortunately led to considerable destruction of the compound. A reaction mixture that was originally 64% **121a** by GC/MS (with some of the hydrolyzed product **122a** present as well), yielded an unidentified compound with $^m/_z$ 230 (a difference of 69 mass units from the cycloadduct). While amines are known to be susceptible to thermal deamination, two evidential points would seem to discount this as a possible explanation. First, and most significantly, loss of pyrrolidine would mean loss of 71 mass units. Secondly, the cycloadduct, an enamine prior to hydrolysis, would not be expected to undergo such an elimination process. As a result, **121a-e** were never isolated and characterized. Since adequate analysis was obtained for the hydrolyzed cycloadduct **122a**, the intermediacy of the bicyclic compound **120a** with subsequent thermal rearrangement to **121a** was inferred.

Although the presence of cycloadduct **121a** in the crude reaction mixture was an indication that the water-induced decomposition of the enamine **101a** was being reduced, thus allowing cycloaddition to occur, the predominance of enaminophosphonate **124** by

more than 2:1 in the reaction mixture showed that somehow, moisture was still entering the reaction system. In order to completely isolate the reagents from all sources of moisture, a cycloaddition reaction was performed in a sealed ampule, without solvent. A soft glass ampule, flame dried and cooled under a stream of flowing, dry argon, was charged with freshly distilled enamine, a trace of hydroquinone, a micro stir bar, and one equivalent of the dry phosphonate. The ampule was then sealed using a bunsen burner (while maintaining an argon blanket over the opening for as long as possible). The sealed ampule was placed in an oil bath at 100 °C. Unlike the reactions run in round bottomed flasks, there was little visible change in the color of the neat solution immediately after mixing in the sealed ampule. Even after more than 24 hours at 100 °C, the reaction mixture was only slightly yellow. This was in marked contrast to previous reactions carried out in round bottomed flasks, in which the reaction mixture ended up anywhere from dark gold to nearly black. The introduction of hydroquinone into the reaction mixture was based solely on the fact that this was specifically mentioned in the experimental details of at least two reports dealing with cycloadditions of enamines.[81,83a] Hydroquinone is a radical scavenger, and is easily oxidized to quinone. All other factors remaining constant, the introduction of hydroquinone seemed to have a positive effect on the outcome of these reactions.

GC/MS analysis of the crude reaction mixture showed the presence of a compound with a $^{m}/_{z}$ of 299, which corresponded to the cycloaddition product. ^{1}H NMR of the crude reaction mixture showed that three compounds were present in significant amounts, in a ratio of 3.4:3:1. Quite surprisingly, the major compound found in the crude reaction

mixture was the hydrolyzed cycloadduct **122a**. Given the lability of the enamine, and the reactiviy of the alkynyl phosphonate with the free amine, it is unlikely that the hydrolyzed cycloadduct was produced in the course of the reaction in the sealed tube. A more likely explaination would be spontaneous hydrolysis upon exposure of the contents of the vial to moist air, or introduction of traces of water upon addition of the NMR solvent (water was not evident in the crude NMR). The main evidence for the presence of the hydrolyzed, ring expanded product **122a** was the presence of a multiplet at 8.05 ppm. This corresponded well with both the expected chemical shift for the vinyl proton of the desired product, and with similar compounds formed by other methods.[96] The second major product was the non-hydrolyzed cycloadduct **121a**. The third product was assigned the structure **129** (**Scheme 40**), and is believed to arise from intermediate **127**. This

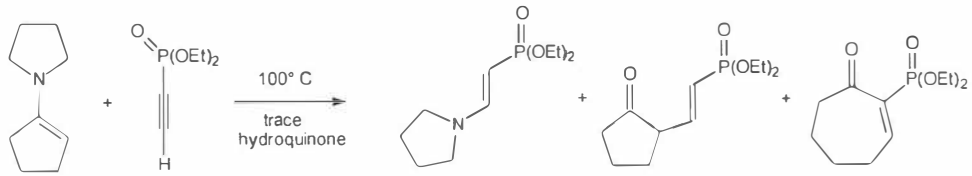


127 128 129

Scheme 40

intermediate was the result of the initial attack of the enamine on the alkynyl phosphonate. Additionally, intermediate **127** could have arisen by retro aldol-type reaction of the bicyclic intermediate **120a** (**Scheme 39**). Once formed, the zwitterionic intermediate **127** could either complete the cycloaddition to form intermediate **120a**,

undergo rearrangement to give **128** (which would undergo hydrolysis upon workup of the reaction mixture to form **129**), or be quenched by water present in the reaction mixture to give **129**.Hydrolysis of the reaction mixture with 5% aqueous acetic acid, followed by extraction into ether gave 2-diethylphosphonylcyclohept-2-ene-3-one (**122a**) in 25% isolated yield. The major products detected and identified in reaction mixtures are summarized in **Scheme 41**. Initially, the reactions were found to be **very** unreliable. Even when formation of the enaminophosphonate **124** was supressed, slight variations on reaction conditions led to widely varying results. Reactions run at 75 °C instead of 100 °C produced virtually none of the desired cycloadduct, but rather a 71% yield of the Michael adduct **129** was obtained. Even with extended reaction periods at 75 °C (*e.g.* 10 days), ^{1}H NMR of the crude reaction mixtures showed only trace amounts of the cycloadduct



101a **106a** **124** **129** **122a**

Scheme 41

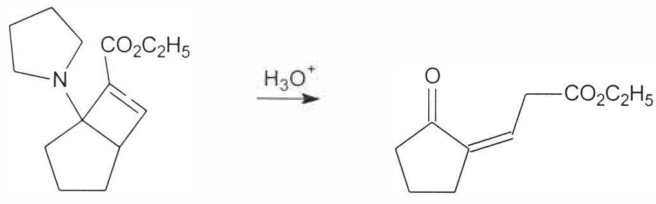
122a. Evidently, higher temperatures were required in order to force the intramolecular aldol-type reaction to proceed. No reaction run at less than 100 °C showed more than a small percentage of the cycloadduct, and due to the apparent retro-aldol reaction, long

reaction times appeared both to degrade the yield and increase the complexity of the reaction mixture considerably. As a result, 100 - 110 °C was found to be the optimum reaction temperature range.

Reaction at elevated temperature (*i.e.* 110-120 °C) seemed to produce significant amounts of product only when reaction times of 24 hours or less were used. Perhaps owing to the propensity of the cycloadduct to undergo retro-aldol reaction in addition to ring expansion, long reaction times generally led to isolation of primarily the Michael product.

Hydrolysis of the cycloadduct **121a** to give the desired, ring expanded α,β-unsaturated cyclic keto phosphonate **122a** was another aspect of the reaction process which required more careful consideration than had originally been anticipated. Although enamines are normally easy to hydrolyze, as previously noted, the enaminophosphonate **124** did **not** undergo hydrolysis under dilute acid conditions at room temperature. This is likely due to the fact that the enamine double bond is conjugated to the phosphonate. In fact, at least 50% acetic acid and heating were required to effect hydrolysis of **124** in a reasonable period of time (*i.e.* within an hour). In general, attempts to use strong mineral acids (*e.g.* hydrochloric acid) for hydrolysis tended to lead to the complete destruction of isolable product. Huebner and co-workers noted that the product isolated was dependent on the acid used to effect hydrolysis of the cycloadduct.[81] Specifically, they found in their cycloadditions of enamines with ethyl propynoate that, while the bicyclic cycloadduct **130** (**Scheme 42**) could be treated with dilute acetic acid to give the rearranged product **131**, no recoverable product could be isolated if HCl were used.

Ultimately, room temperature hydrolysis of cycloadducts **121a-e** was performed using a solution of 5% aqueous acetic acid in THF. While this method did not hydrolyze enaminophosphonate **124**, it did hydrolyze the ring expanded enamine **121**. Since **121** and **124** were easily separated by chromatography, the presence of unhydrolyzed enaminophosphonate **124** did not pose a problem.



130 **131**

Scheme 42

The cycloadducts **121** were thus formed in a "one pot" reaction. The neat enamine and phosphonate were combined in an ampule which was sealed and placed in an oil bath. After the reaction had been allowed to proceed for the desired amount of time, the neck of the ampule was broken, and a mixture of THF and 5% aqueous acetic acid was added. After stirring for 2 hours, the mixture was transferred to a separatory funnel for workup. The typical workup was accomplished by adding dichloromethane and washing the solution with saturated ammonium chloride. The aqueous portion was then extracted three times with dichloromethane, and the combined organic layers were dried over magnesium sulfate or sodium sulfate. The cycloaddition reactions and results obtained using the pyrrolidinyl enamines of cyclopentanone and cyclohexanone have been

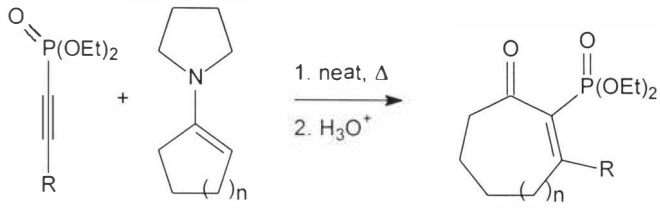
summarized in **Table 5**. The GC yields are reported, and, where available, the isolated yields are in parentheses.

For quite some time, it appeared that reactions using pyrrolidine enamines were giving reasonable yields of the eight membered cycloadduct **122e**. The vinyl proton of β-keto phosphonate **122e** was expected to appear in the 7-8 ppm range, as a doublet of triplets owing to spin-spin coupling with phosphorus and the allylic protons on the eight membered ring. This vinyl proton was expected to be easily distinguishable from the vinyl protons of the Michael adduct **129** or of the enaminophosphonate **124**, since in the latter two cases, the vinyl protons should appear as doublets of doublets. Analysis of early reactions of pyrrolidine enamines with alkynyl phosphonates produced a wide variation in results. Some reaction mixtures consisted entirely of enaminophosphonate addition product, while other reactions had a profusion of vinylogous protons, which made assignments to structures difficult. A doublet of triplets at 6.7 ppm was also detected. Isolation of this component and analysis by GC/MS showed that it had the desired $^{m}/_{z}$ of 260. Additionally, analysis by high-resolution mass spectrometry showed that, to within 1.1 milliDaltons, the compound matched the required chemical formula of $C_{12}H_{21}O_4P$. However, upon close examination, the NMR spectrum of the compound could not be fully reconciled with the structure **122e**. Other than the vinyl proton and the methylene protons of the ethoxy substituent, all of the protons in the ring expanded product **122e** were expected to be upfield of approximately 2.6 ppm. However, in the compound which had been identified as **122e**, a signal integrating to two protons appeared at 3.33 ppm. Simultaneously, reaction mixtures from formation of eight membered unsaturated

phosphonates *via* an alternative route were found to show two sets of doublets of triplets in some of their ^{1}H NMR spectra.[97] One set was the one already identified at 6.7 ppm. The other set appeared at about 7.05 ppm. In order to clear up the ambiguity between which set of triplets was the desired product, an independent route to **122e** was sought. Using an eight membered saturated β-keto phosphonate prepared by Wiemer's procedure,[98,99] a phenylselenation/oxidation/elimination scheme was utilized to produce the α,β unsaturated ketophosphonate **122e (Scheme 43)**.[100]

This unambiguous route to the unsaturated β-keto phosphonate established that the vinyl proton of interest occurred at 7.05 ppm. Heating the unsaturated phosphonates thus obtained failed to duplicate the doublet of triplets at 6.7 ppm. Analysis of the reactions carried out between the pyrrolidine enamine **101b** and alkynylphosphonate **106a** showed that the genuine α,β unsaturated eight membered β-keto phosphonate **122e**, with the doublet of triplets at 7.05 ppm, was present in trace amounts in some cases. The best yield for **122e** using 1-pyrrolidinylcyclohexene (**101b**) was 2.5% by ^{1}H NMR.

In all of the cycloadditions carried out, the utilization of the pyrrolidine enamines seemed to be accompanied by erratic results. For a given set of reagents, results would vary greatly from one day to another. This was mainly attributed to the unstable nature of the pyrrolidine based enamines. The primary cause of low yields in these reactions was formation of large amounts of the enaminophosphonate **124** or the β-keto phosphonate **126** (**Figure 17**) resulting from its hydrolysis. Use of crushed 4Å molecular sieves appeared to help sometimes, but not consistently. The prospects for relative success or failure of a given reaction run could be roughly judged based on the color of

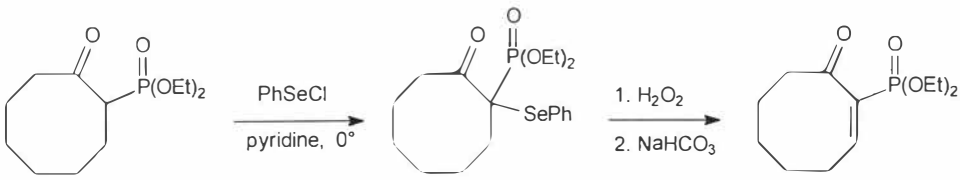


106a-d **101a,b** **122a-e**

Entry	n	R	% Yield[a]	Compound
1	1	-H	60 (25)[b]	**122a**
2	1	$-(CH_2)_2CH_3$	16	**122b**
3	1	$-CH_2OCH_3$	52 (7)[b]	**122c**
4	1	-Ph	20 (13)[b]	**122d**
5	2	-H	15 (2.5)[c]	**122e**

a: GC Yields b: Isolated Yields c: NMR Yield

Table 5: Cycloadditions of Enamines Derived From Pyrrolidine.



132 **133** **122e**

Scheme 43

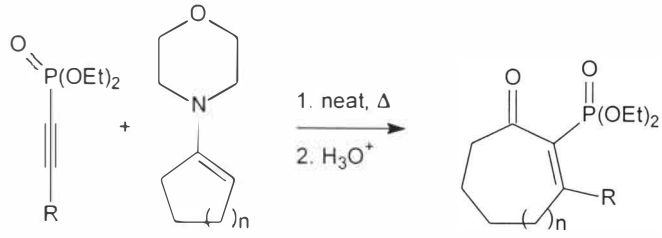
the reaction shortly after placing the sealed ampule in the oil bath. If only slight discoloration was observed, good success could be anticipated. If the reaction turned orange-brown, mediocre results were obtained. Reactions that turned very dark produced byproducts only, with no evidence of any cycloaddition or Michael addition occurring.

In light of these developments, and the fact that many of the measures and conditions neccessary to enhance the desired cycloaddition reaction had now been worked out, the cycloaddition reaction was carried out with enamines derived from morpholine rather than pyrrolidine. Earlier work by Brannock and co-workers had noted very different behavior between pyrrolidine and morpholine enamines of cyclopentanone and cyclohexanone.[80] It was found that morpholine enamines were more efficient than pyrrolidine enamines at formation of eight membered rings. Berchtold and co-workers reported that enamines formed from pyrrolidine and morpholine exhibited major differences in the yields of cycloadditions with DMAD.[82] In the same manner as before, the enamine and phosphonate reagents were combined, sealed in a vial, and stirred in an oil bath. The results were mixed. On the positive side, the presence of byproducts resulting from addition of the free amine to the phosphonate were dramatically reduced. In some cases, only traces of such products were detected. On the other hand, the reduced reactivity of the enamine itself rendered longer reaction times and higher temperatures necessary. **Table 6** summarizes the cycloadducts formed from morpholine enamines. Overall, reactions run with enamines based on morpholine followed the trend established by the groups of Berchtold and Hirsch,[82,93] in that cycloadditions to form seven membered rings were not as successful as was the formation of the eight membered ring.

The eight membered unsaturated β-keto phosphonate **122e** was obtained in 15% yield (GC) in reactions with pyrrolidinyl cyclohexene (**101b**). The GC yield of the same product was 31% starting with the morpholine enamine of cyclohexanone, **101d**. This was presumably due to the greater stability of the morpholine enamine, which can be stored for significant periods of time at room temperature with only slight decomposition. However, slightly higher reaction temperatures (110 °C as opposed to 100 °C) and longer reaction times (48 hours rather than 24 hours) were necessary to produce the desired eight membered unsaturated phosphonate **122e**.

The low yields reported in these reactions have been cause for some concern. The primary products that have been encountered and discussed thus far (enaminophosphonate **124**, Michael product **129**, in addition to the desired products) usually made up a small percentage of the reaction mixture. The major component in most of the cycloadditions has appeared to be dark colored material which does not elute off of columns or preparatory plates with normal solvents. When the adsorbent was washed with absolute ethanol or ethanol/acetic acid, a dark oil was isolated, which upon ^{1}H NMR analysis was found to have a few very broad absorbances, and contained no phosphonate group.

Photochemical cycloaddition was attempted in order to obtain the cycloadduct more cleanly and in higher yields. Photocycloaddition followed by ring expansion has been used as a method of generating medium sized rings.[101] Photochemical cycloadditions have been reported between enamines and dimethyl fumarate[102] as well as diphenylacetylene.[103] Using a Hanovia® lamp, the reagents were combined in dry, degassed hexanes, and irradiated 15-22 hours. In all cases, the only products that were



106a-d **101b,d** **122a-e**

Entry	n	R	% Yield[a]	Compound
1	1	-H	8	**122a**
2	1	$-(CH_2)_2CH_3$	5	**122b**
3	1	$-CH_2OCH_3$	4	**122c**
4	1	-Ph	2.5	**122d**
5	2	-H	31 (15)[b]	**122e**

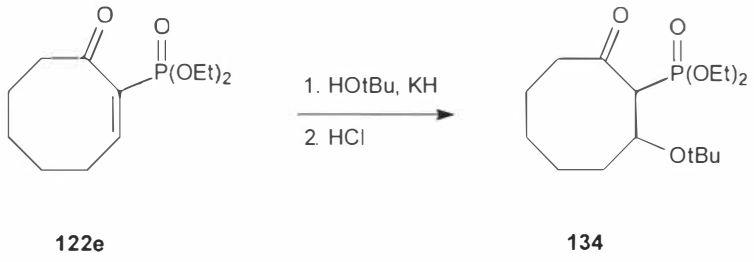
Notes a: GC Yields. b: Isolated Yield.

Table 6: Cycloadditions of Enamines Derived From Morpholine.

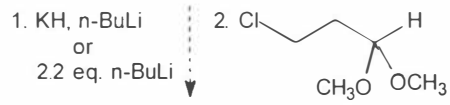
obtained were the enaminophosphonate **124** and the Michael product **129**. It became clear that the conjugate addition occurred too quickly for the two π systems to react in a concerted [2+2] cycloaddition.

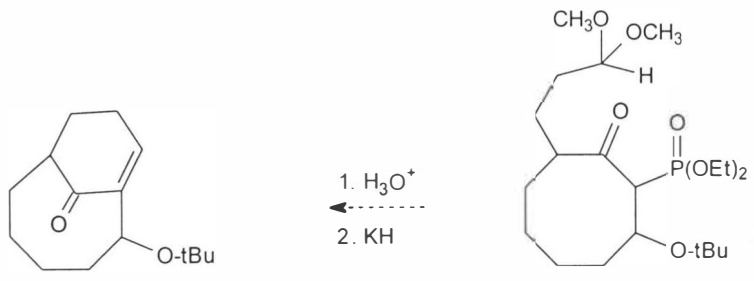
With a one-step pathway to the desired medium sized α,β-unsaturated β-keto phosphonates now in hand, demonstration of the utility of this compound in the formation of a bridged bicyclic stucture remains a future focus of this research. **Scheme 44** shows the steps completed towards utilization of the substituted β-keto phosphonates **122** in an intramolecular Horner-Wadsworth-Emmons reaction to generate the bicyclic system. Nucleophiles other than carbanions have been reported in Michael addition reactions.[104] β-keto phosphonate **122e** was reacted with potassium *tert*-butoxide to generate the substituted, saturated phosphonate **134**. Introduction of an oxygen at C-3 of **134** was of interest due to the substitution patterns of a number of natural products for which this method represents access to a portion of the basic carbon skeleton. The results were mixed. IR data seemed to indicate the presence of an ether, but the ^{1}H NMR and GC/MS spectra did not support this conclusion. A smaller nucleophile may be more effective for addition to the unsaturated phosphonate. After Michael addition to the cyclic phosphonate **122e**, the carbonyl-bearing side chain will be accomplished by formation of the dianion, by established procedures[105a] with some modifications, should proceed satisfactorily, since in related preliminary studies,[105b] when the alkylating agent was in good condition (purity, dryness) the alkylated product could be obtained in 4:1 ratio to the starting material.

This work has served to open a new pathway which could lead to substituted bicyclic systems which incorporate a bridgehead double bond. The method involves



122e **134**





136 **135**

Scheme 44

relatively few steps, is regiospecific, and provides useful intermediates in the synthesis of medically important natural products. Several marked differences between the activated alkynyl systems (propynoates and DMAD) and the alkynyl phosphonates were ascertained. Continuing facets of this research will deal with subjecting the alkylated β-keto phosphonate to the intramolecular HWE reaction in order to further demonstrate the utility of these substrates in construction of taxanes, kauranes, and other natural products of biological or medicinal interest.

Several meaningful contributions have resulted from this research. Direct comparison of the relative ability of esters and phosphonates to activate alkynes towards Michael addition can be made. Clearly, alkynyl phosphonates do activate triple bonds towards addition by nucleophiles such as enamines and some oxygen anions. Phosphonates do not activate as strongly as esters do, however. The tendency of morpholine enamines to more efficiently produce eight membered ring products as compared to pyrrolidine enamines was demonstrated. Other steps might be taken to increase the reliability and yield of these reactions (dry box, etc.), which could lead to improved yields. In the meantime, this route provides access to important building blocks in the synthesis of a number of biologically very important natural products. By providing eight membered rings which are comprised of α,β unsaturated carbonyl systems bearing a phosphonate substituent, functionalization at the 1, 2, 3, and 8 positions can be accomplished. Additionally, the application of the HWE reaction to this substrate will afford access to bridged bicyclic systems, and offers a potential route towards synthesis of compounds such as those shown in **Figure 1**.

Chapter 5:

Experimental

The following instruments and procedures were utilized in compiling structural and physical evidence with respect to the compounds synthesized in the course of this work. Melting points and boiling points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 1600 series FTIR and a MIDAC Collegian `FTIR, with absorbances expressed in wavenumbers (cm^{-1}). GC analysis was performed on a Shimadzu GC 14a instrument equipped with a 15 meter x 0.32mm glass capillary column, with a 3μ thick adsorbent of methyl silicone (5% phenyl substituted) and a flame ionization detector. ^{1}H NMR spectra were recorded on a 300 MHz General Electric QE 300 FT-NMR; ^{13}C NMR were recorded at 75.6 MHz. Unless otherwise noted samples were run in deuterochloroform as solvent with tetramethylsilane as the internal standard set to 0.00 ppm. Coupling constants (J) have been expressed in terms of Hertz (Hz). Combustion analyses were performed by Galbraith Laboratories, Inc. Knoxville, Tennessee. High resolution mass spectrometry was performed by the Southern California Mass Spectrometry Facility at the University of California, Riverside. Low resolution mass

spectrometry was performed on a Hewlett-Packard 5988A GC/MS system. Preparative thin-layer chromatography was performed on 20 cm x 20 cm precoated glass supported plates, with a 1.5 mm layer of either alumina or silica gel adsorbent. Visualization was normally by ultraviolet light, but on occasion a solution of ceric ammonium nitrate was sprayed onto an unprotected strip of the plate followed by heating. Column chromatography was performed on E.M. Science silica gel 60 (230 - 400 mesh) or on Baker alumina adsorbent (Brockman activity 1 to 3).

Chemical reagents were obtained from Aldrich Chemical Co., J. T. Baker Chemical Co., Merck and Co., Fluka, Inc., and TCI, Inc.

Prior to usage, all glassware was dried in an oven at 120 °C. All reactions were magnetically stirred using teflon coated stirring bars. Unless otherwise noted, all reactions were carried out under a positive pressure of N_2 or Ar. THF and diethyl ether used for reactions was maintained dry by benzophenone-sodium ketyl in a recycling still. DMSO for reactions was dried by stirring over BaO overnight, filtered, and fractionally distilled and stored over molecular sieves.

1-Triphenylphosphoranylideneacetaldehyde (**53a**):

Methyltriphenylphosphonium bromide (4.99g, 13.98 mmol) was stirred in suspension in dry diethyl ether (50 mL) and cooled to 0 °C. Phenyllithium (7.8 mL, 1.8

M, 14.04 mmol) was added to the solution. The now bright yellow solution was added by inverse addition to a solution of ethyl formate (1.4 mL, 17.3 mmol) in diethyl ether (50 mL) and stirred for 30 min. The solution was then transferred to a separatory funnel, extracted into 10% HCl (3 x 75 mL), and then the aqueous layer was neutralized by addition of 10% NaOH solution. The neutral aqueous portion was extracted into benzene, and the solvent removed under reduced pressure to give **53a** (1.69g, 39.7%) mp 185 - 188 °C (Lit. 185 - 188 °C)[106] **Note**: The ^{1}H NMR of the product, as synthesized, always contained four sets of proton signals (apart from the aryl protons). Each set was comprised of a pair of doublet of doublets in a 1:1 ratio, of similar chemical shift but different coupling. When their integration was combined, each pair together was proportional to 15 aryl protons. Based on the $J_{H\text{-}P}$ values, this is evidently a result of atropsisomerism of the π system; the PCCO system can either be in the s-cis or s-trans configuration.[43] ^{1}H NMR δ 9.0 (dd, J = 38.2, 3.5 Hz, 1H), 8.23 (dd, J = 10.8, 3.5 Hz, 1H), 7.45 - 7.75 (m, 30 H), 4.1 (dd, J = 19.2, 10.8 Hz, 1H), 3.7 (dd, 24.5, 3.5 Hz, 1H).

2-(Triphenylphosphoranylidene)propanaldehyde **53c**:

(Ethyl)triphenylphosphonium bromide (2.03g, 5.48 mmol) was suspended in dry diethyl ether (15 mL) and cooled to 0 °C. Phenyllithium (3 mL, 1.8M, 5.4 mmol) was added to the mixture while stirring. The solution was stirred an additional 20 min, and then was transferred **slowly** *via* cannula to a flask containing ethyl formate (0.55 mL, 6.8 mmol) in dry diethyl ether (50 mL). After a few minutes, the organic layer was extracted into 10% HCl. The aqueous layer was then neutralized with 10% NaOH, followed by

extraction into benzene. Removal of the excess solvent was accomplished under reduced pressure on a rotary evaporator to give **53c** (499 mg, 29%). mp 209 - 211 °C (Lit. 219 - 221 °C)[106] ^{1}H NMR δ 8.15 (d, J = 5.7 Hz, 1H), 7.4 - 7.7 (m, 15 H), 1.9 (d, J = 13.4 Hz, 3H). IR: 1545, 1438, 1362, 1321, 1162, 1104, 962, 759, 715, 696 cm^{-1}.

(1-Triphenylphosphoranylidene)3,3-dimethyl-2-butanone (**53f**):

Phenyllithium (2.8 mL, 1.8M, 5.46 mmol) was added to a solution of methyltriphenylphosphonium iodide (1.995 g, 4.94 mmol) in dry diethyl ether (50 mL). This solution was transferred *via* cannula to a solution of ethyl 2,2-dimethylpropionate (0.83 mL, 5.46 mmol). After the addition was complete, the reaction was heated to 30 °C overnight. After extraction into 10% HCl, the aqueous layer was neutralized with 10% NaOH and extracted into benzene. The solution was dried over K_2CO_3 and the solvent removed under reduced pressure on a rotary evaporator to give **53f** (300 mg, 20% based on 178 mg recovered ester). ^{1}H NMR δ 7.3 - 7.7 (m, 15H), 3.8 (d, J = 28.5 Hz, 1H), 1.2 (s, 9H). IR: 1738, 1462, 1438, 1173, 1120, 754, 722, 695 cm^{-1}.

General procedure for β-alkoxy vinyltriphenylphosphonium salts (**54a-c**):

The β-ketoylide was placed in a round bottomed flask, and a large excess of bromoethane was added (10-13 mL bromoethane for each gram of ketoylide). The solution was stirred at room temperature for 24 h, at which time the excess bromoethane was removed at reduced pressure on a rotary evaporator. The product was recrystallized by adding ethyl acetate, followed by just enough dichloromethane to effect dissolution,

then adding hexanes until faint turbidity persisted. Under these conditions, the *Z* isomer predominated (except for **54c**, for which the *E* isomer predominated in all cases). If bromoethane was added to just dissolve the ketoylide and the solution was maintained at 35 °C, the *E* isomer predominated 3.5:1.

2-(Ethoxyethenyl)triphenylphosphonium bromide (**54a**):

Following the general procedure, freshly prepared (triphenylphosphoranylidene) acetaldehyde (656 mg, 2.16 mmol) was dissolved in bromoethane (13 mL). Removal of the solvent gave **54a** (836 mg, 94%; *Z*:*E* 14:1). mp: 116-117 °C. IR: 1606, 1438, 1109, 750, 723, 691 cm^{-1}. ^1H NMR (mixture *Z* and *E*) δ 8.35 (dd, J=7.3, 33.4 Hz, 1H), 7.85-7.6 (m, 30H), 6.7 (dt, J=12.6, 31.7 Hz, 2H), 5.75 (dd J=17.3, 7.3 Hz, 1H), 4.55 (q, J=7.7 Hz, 2H), 4.2 (q, J=7.7 Hz, 2H), 1.4 (t, 7.7 Hz, 3H), 0.95 (t, J=7.7 Hz, 3H).

2-(Ethoxypropenyl)triphenylphosphonium bromide(**54b**):

Following the general procedure, (triphenylphosphoranylidene)-2-propanone (518 mg, 1.63 mmol) was stirred in bromoethane (6 mL) at room temperature for 64 h. Removal of the solvent gave **54b** (657 mg, 94%; *Z*:*E* 30:1). mp: 169.6-171.1 °C IR: 1598, 1437, 1107, 750, 720, 693 cm^{-1}. ^1H NMR: δ 7.8-7.6 (m, 30H), 5.65 (d, J=18.3 Hz, 2H), 4.05 (q, J=7.7 Hz, 2H), 3.5 (q, J=7.7 Hz, 2 H), 2.6 (s, 6H), 1.2 (t, J=7.7 Hz, 3H), 0.7 (t, J=7.7 Hz, 3H).

(3-Ethoxypropenyl)triphenylphosphonium bromide(**54c**):

Following the general procedure, (2-triphenylphosphoranylidene) propanaldehyde (171 mg, 0.54 mmol) was stirred in bromoethane (4 mL) and dichloromethane (2 mL, to complete dissolution of all solids) for 44 h. Removal of the solvent gave **54c** (181 mg, 79%; *Z*:*E* 1:20). mp: 203.3 °C (dec). IR: 1627, 1440, 1216, 1110, 761, 719, 690 cm^{-1}. ^1H NMR (mixture) δ 8.25 (d, J=30 Hz, 1H), 7.9-7.6 (m, 30H),6.7 (d, J=10.6 Hz, 1 H), 4.1 (q, J=7.1 Hz, 2 H), 4.25 (q, J=7.5 Hz, 2 H), 1.95 (d, J=13.4 Hz, 3 H), 1.88 (d, J=13.8 Hz, 3 H), 1.35 (t, J=7.5 Hz, 3 H), 0.77 (t, J=7.1 Hz, 3 H).

(2-Acetoxypropenyl)triphenylphosphonium chloride(**54d**):

1-Triphenylphosphoranylidene-2-propanone (251 mg, 0.789 mmol) was stirred in dry benzene under N_2. Acetyl chloride (66 μL, 0.928 mmol) was added, and the solution allowed to stir for 1 h. The solvent was removed under reduced pressure on a rotary evaporator to give hygroscopic crystals of **54d** (218 mg, 70%). The product could be recrystallized from dry acetone, and kept in a vial sealed with parafilm and stored in the freezer. IR: 1714, 1613, 1438, 1361, 1110, 997, 748, 718, 690. ^1H NMR: δ 7.95-7.55 (m,15 H), 6.08 (d, J=16.7 Hz, 1 H), 2.69 (s, 3 H), 1.42 (s, 3 H).

Attempted acetylation of (triphenylphosphoranylidene)acetaldehyde **53a**:

Method A: (Triphenylphosphoranylidene)acetaldehyde (52 mg, 0.172 mmol) was stirred at room temperature for 24 h in acetyl chloride (1 mL, 14 mmol) which had been distilled from K_2CO_3. The excess acetyl chloride was removed under reduced pressure on a rotary evaporator. The resulting solid was dissolved in CH_2Cl_2 and washed with

saturated $NaHCO_3$. Unchanged starting material **53a** was recovered. Even when the same reaction was carried out at 100 °C for 17 h, starting material was recovered.

Method B: LiBr (13 mg, 0.150 mmol) was added with stirring to a solution of ylide **53a** (46 mg, 0.150 mmol) in CH_2Cl_2 (1 mL), followed by addition of acetyl chloride (11 μL, 0.155 mmol). The reaction was stirred at room temperature for 40 h, then transferred to a separatory funnel, washed with saturated $NaHCO_3$, dried over K_2CO_3, and the remaining solvent removed under reduced pressure on a rotary evaporator. ^1H NMR of the crude reaction mixture revealed unreacted starting material.

Method C: Acetyl chloride (1 mL, 14.1 mmol) was stirred over anhydrous K_2CO_3 for 3 h. To this suspension, ylide **53a** (41 mg, 0.135 mmol) was added, and the mixture stirred for 168 h. Removal of the remaining acetyl chloride on a rotary evaporator gave a solid which was dissolved in CH_2Cl_2 (25 mL). The resulting solution was washed with $NaHCO_3$, and dried over K_2CO_3. The ^1H NMR of the resulting material contained only aryl protons and a broad singlet at 2.0 ppm (area ratio 6.66:1).

Method D: Acetyl chloride (excess) was stirred with anhydrous $MgSO_4$, and ylide **53a** (35 mg, 0.116 mmol) was added and allowed to stir for 24 h. After removal of the excess acetyl chloride on a rotary evaporator, the ^1H NMR spectrum of the resulting material was found to have three doublets of doublets (7.1, 6.0, and 4.8 ppm), but no peak integrated properly for the methyl group.

Method E: Acetyl chloride (2 mL, 28.1 mmol) was stirred under N_2 in a sealed tube with anhydrous $CaCl_2$ for 5 min. Ylide **53a** (41 mg, 0.134) was added, and the tube was sealed and stirred at room temperature for 52 h. The mixture was then transferred

to a round bottomed flask using CH_2Cl_2, and the excess acetyl chloride and solvent removed on a rotary evaporator. CH_2Cl_2 was added to the resulting solid. The solution was washed with 10% HCl, dried over $CaCl_2$, and the solvent removed under reduced pressure on a rotary evaporator. The ^1H NMR was a poorly resolved complex mixture, with no peaks assignable to the desired product.

Method F: Ylide **53a** (47 mg, 0.156 mmol) was dissolved in CH_2Cl_2 (1 mL). LiBr (14 mg, 0.156 mmol) was added, and the solution was stirred while acetic anhydride (15 μL, 0.156 mmol) was added. The mixture was stirred at room temperature for 46 h. CH_2Cl_2 was added, and the organic layer was washed with saturated $NaHCO_3$, dried over K_2CO_3, and the solvent was removed under reduced pressure on a rotary evaporator. ^1H NMR showed that the unchanged starting material was recovered.

Attempted cyclopropanation of **54a** with **67a**:

Pentanes (2 mL) was added to a 60% suspension of NaH in mineral oil, stirred, and the solvent (containing mineral oil) was pipetted off. The process was repeated two more times, and the residual solvent was then removed under reduced pressure on a vacuum pump to give a dry powder (8 mg, 0.32 mmol) to which dry DMSO (1 mL) was then added. The mixture foamed, but became clear in a few minutes. After 10 min, trimethylsulfoxonium iodide (37 mg , 0.17 mmol) was added to form anion **67a**. β-alkoxy vinylphosphonium salt **54a** (47 mg, 0.11 mmol) dissolved in dry DMSO (2 mL) was added. The reaction was allowed to stir for 60 h at room temperature. The mixture was then poured into a separatory funnel, and extracted into CH_2Cl_2 (3 x 25 mL). The

combined organic layers were washed with saturated $NaHCO_3$, then brine, and then dried over K_2CO_3. The product observed by ^1H NMR was phosphine oxide **68a**. In an attempt to identify conditions under which cyclopropanation could be accomplished using this reagent, modifications on this procedure included using reaction temperatures between -78 °C and 100 °C. Ratios of vinylphosphonium salt to dimsyl anion were altered (from excess dimsyl to excess vinylphosphonium salt). Reaction times were varied between 20 h and 240 h. In all cases the only products detected were starting materials and phosphine oxide **68a**. In addition, trimethylsulfoxonium chloride was used to generate the dimsyl anion, with the reaction having the same outcome as that noted above.

Attempted cyclopropanation of **54a** with **67b**:

Trimethylsulfonium iodide (26 mg, 0.127 mmol) was dissolved in dry CH_2Cl_2, and cooled to -78 °C. n-Butyllithium (1.34M, 0.134 mmol) was added, and the mixture was stirred for 1.5 h. β-Alkoxy vinylphosphonium salt **54a** was added (50 mg, 0.121 mmol), and the reaction was allowed to warm to room temperature and stirred for 2 d. The mixture was transferred to a separatory funnel, washed with 10% $NaHCO_3$ (2 x 25 mL), and dried over K_2CO_3. The solvent was removed under reduced pressure on a rotary evaporator, and the ^1H NMR of the crude reaction mixture showed only starting material.

Attempted cyclopropanation of **54a** with **67c**:

β-Alkoxy vinylphosphonium salt **54a** (205 mg, 0.496 mmol) was added to a

solution of ethyl(dimethylsulfuranylidene)acetate **67c** (82 mg, 0.55 mmol) dissolved in CH_2Cl_2 (6 mL). The mixture was then heated to reflux. After 48 h the mixture was transferred to a separatory funnel and quenched with brine, extracted into CH_2Cl_2 (3 x 20 mL) and dried over K_2CO_3. The ^1H NMR of the highly complex mixture had no fewer than six triplets between 0.8 and 1.5 ppm. Preparatory TLC was performed on silica gel (eluted with 50% hexanes/ 35% CH_2Cl_2/ 15% methanol) to give four major bands. ^1H NMR analysis of the compounds thus isolated showed that none of them could be assigned the structure of the desired product, as none showed spectra consistent with incorporation of the phosphonium salt, the ethoxy group, and the ethyl ester in one compound.

Attempted cyclopropanation of **54a** with dichlorocarbene:

Vinylphosphonium salt **54a** (102 mg, 0.246 mmol) was dissolved in CH_2Cl_2 (2 mL). Benzyltriethylammonium chloride (5 mg, 0.03 mmol, 10 mol %) was added, followed by 50% NaOH (2 mL). The mixture was stirred vigorously for 7 h at room temperature. Upon transfer to a separatory funnel, CH_2Cl_2 was added, the mixture was washed twice with water and twice with brine, then the organic layer was dried, and the solvent was removed on a rotary evaporator. The ^1H NMR spectrum of the reaction product showed it to be pure diphenyl phosphine oxide **68a**.

Attempted Simmons-Smith cyclopropanation of **54a**:

A variety of cyclopropanation procedures based on the use of activated zinc

complexes are collected here, in addition to the traditional Simmons-Smith procedure using zinc, a copper salt, and diiodomethane.

Uncatalyzed Simmons-Smith cyclopropanation: Zinc (42 mg, 0.63 mmol) and copper chloride (75 mg, 0.76 mmol) were added to dry diethyl ether (2 mL) and the mixture was then heated to reflux under dry N_2. After 30 min, β-alkoxy vinylposphonium salt **54a** (109 mg, 0.26 mmol; *Z*:*E* = 1.3:1) was added, followed by CH_2I_2 (25μL, 0.31 mmol). After 24 h, the solution was filtered in order to remove the grey-green ZnCu couple, and the collected couple was washed with CH_2Cl_2. The ether and CH_2Cl_2 solutions were combined in a separatory funnel, washed with water and saturated $NaHCO_3$, dried, and concentrated on a rotary evaporator. ^1H NMR of the resulting material showed it to be starting material (*Z*:*E* = 1:1.6)

Simmons-Smith activated by addition of catalytic acetyl chloride: To Zinc dust (25 mg, 0.379 mmol) in a round bottomed flask was added copper iodide (7 mg, 0.066 mmol), dioxane (1 mL), CH_2I_2 (10 μL, 0.124 mmol) and acetyl chloride (2 μL, 0.281 mmol). Over the next few minutes, the zinc turned from light grey to dark grey, and some evolution of gas was noted. β-Alkoxy vinylphosphonium salt **54a** (50 mg, 0.120 mmol; *Z*:*E* = 10:1) was added. One additional mL of dioxane was added, followed by another aliquot of CH_2I_2 (10 μL, 0.124 mmol, total 0.248 mmol). The reaction mixture was then placed in an oil bath at 60 °C for 2.5 h. The solids were removed by filtration and washed with saturated NH_4Cl. The resulting aqueous solution was extracted into CH_2Cl_2,

washed with 10% $NaHCO_3$, and dried over K_2CO_3. The solvent was removed under reduced pressure on a rotary evaporator. The ^1H NMR spectrum of the collected residue revealed a 1:1 ratio of *Z:E* starting material (**54a**).

Zinc/ultrasound/CH_2I_2: To Zinc powder (53 mg, 0.815 mmol) in a screw-top tube was added, under flowing nitrogen, diglyme (1 mL). The tube was sealed and lowered into an oil bath (within an ultrasonic cleaning bath) at 67 °C, and sonicated for 1 h. The tube was removed from the oil bath, opened, and under flowing nitrogen, vinylphosphonium salt **54a** (50 mg, 0.120 mmol; *Z:E* > 10:1) was added, followed by CH_2I_2 (20 μL, 0.248 mmol) and the tube re-sealed. Upon addition of the diiodomethane, the solution turned yellow. The color dissipated over the next few minutes. After 2 h, saturated NH_4Cl was added, and the mixture was filtered and extracted into CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with brine, and treated with a crystal of $Na_2S_2O_3$ to discharge the color of iodine which developed during the workup. The solution was dried over K_2CO_3, and the solvent was removed under reduced pressure. ^1H NMR of the material thus recovered showed a 1.2:1 ratio of *Z:E* starting material (**54a**).

ZnCu/CH_2I_2/acetyl chloride/ ultrasound: In a screw-top tube, zinc powder (24 mg, 0.373 mmol) was added to dioxane (1 mL) followed by CuCl (12 mg, 0.120 mmol), the tube was blown with N_2, sealed, and the mixture was sonicated for 5 min. The tube was opened and CH_2I_2 (10 μL, 0.124 mmol) was added under flowing nitrogen, followed by a catalytic amount of acetyl chloride (4 μL , 0.056 mmol) and the tube was re-sealed.

This mixture was sonicated at 80 °C for 5 min, after which time vinylphosphonium salt **54a** (48 mg, 0.116 mmol; *Z:E* > 10:1) was added, followed by an additional aliquot of CH_2I_2 (10 μL, total added = 20 μL, or 0.248 mmol). The solution turned gold upon addition of the phosphonium salt. After blowing the reaction tube with nitrogen, it was re-sealed, and tube was placed in the ultrasonic bath at 80 °C. After 2 h 20 min, the solution had turned milky white, and the bath temperature was 98 °C. Saturated NH_4Cl was added, the mixture was filtered through a Büchner funnel, and the collected residue washed with CH_2Cl_2. The ammonium chloride washes were extracted 5 times into CH_2Cl_2, and the combined organic extracts dried over K_2CO_3. The solvent was removed under reduced pressure on a rotary evaporator. ^1H NMR of the resultant yellow oil showed starting material only (*Z:E* = 2.8:1).

<u>Et_2Zn/ CH_2I_2</u>: Et_2Zn in hexanes (0.33 mL, 1M; 0.33 mmol) was added to a solution of vinylphosphonium salt **54a** (68 mg, 0.16 mmol; *Z:E* = 7:1) in dioxane (1 mL), followed by addition of CH_2I_2 (26 μL, 0.33 mmol). The reaction flask was placed in an oil bath at 100 °C for 26 h. The solution was diluted with CH_2Cl_2, washed 2 times with water, once with saturated $NaHCO_3$, and dried over K_2CO_3. ^1H NMR of the material thus obtained showed only unreacted starting material (*Z:E* = 1:2). The same procedure followed in diglyme produced the same results, returning starting material only.

<u>Attempted cyclopropanation of **54a** with difluorocarbene</u>:

Difluorocarbene was formed *in situ* by combining triphenylphosphine (32 mg,

0.120 mmol) in triglyme (0.2 mL) with CF_2Br_2 (11 μL, 0.120 mmol). The mixture was stirred under N_2 for 30 min. The vinylphosphonium salt **54a** (49 mg, 0.119 mmol; *Z*:*E* > 10:1) was added, followed immediately by anhydrous KF (28 mg, 0.485 mmol). The reaction was stirred at room temperature for 24 h, then heated to 100 °C for 266 h. The triglyme was distilled off on a *Kugelrohr*, and the residue was dissolved in CH_2Cl_2, washed with saturated NH_4Cl, dried over K_2CO_3, and concentrated under reduced pressure on a rotary evaporator. The ^1H NMR of the solids obtained revealed phenyl protons and triglyme, with a total absence of protons from the ethoxy group.

Equilibration of (*Z*)-β-alkoxy vinylphosphonium salt **54a** with $(CH_3CH_2)_3N$:

Vinylphosphonium salt **54a** (66 mg, 0.158 mmol; *Z*:*E* = 13:1) was stirred at room temperature in dry CH_2Cl_2 (2 mL) and triethylamine (0.1 mL) for 48 h. The material produced, analyzed by ^1H NMR, was determined to have a *Z*:*E* ratio of 1:7.

Attempted cyclopropanation of β-alkoxy vinylphosphonium salt **54b** with **67a**:

Pentanes (2 mL) was added to a 60% suspension of NaH in mineral oil, stirred, and the solvent (containing mineral oil) was pipetted off. The process was repeated two more times, and the residual solvent was then removed under reduced pressure on a vacuum pump to give a dry powder (29 mg, 1.2 mmol), to which DMSO (5 mL) was added. The solution foamed, but after a few minutes became clear. Trimethylsulfoxonium iodide (236 mg, 1.1 mmol) was added, and the solution was heated to 87 °C in a round bottomed flask for 50 min. The β-alkoxy vinylphosphonium salt **54b**

(198 mg, 0.46 mmol) was added, and the solution was stirred at 87 °C for 24 h. The dark gold colored solution was transferred to a separatory funnel and extracted into CH_2Cl_2, then was washed successively with saturated $NaHCO_3$ and brine. The organic layer was dried over K_2CO_3, and the solvent removed under reduced pressure on the rotary evaporator. The ^1H NMR revealed one product only, diphenylphosphine oxide **68b**.

Attempted cyclopropanation of **54b** with difluorocarbene:

Following the same general procedure used for the attempted cyclopropanation of **54a** with difluorocarbene, triphenylphosphine (30 mg, 0.116 mmol) and CF_2Br_2 (21 μL, 0.230 mmol) were stirred together in triglyme (0.2 mL) for several minutes. Vinylphosphonium salt **54b** (48 mg, 0.112 mmol) and KF (28 mg, 0.485 mmol) were added, and the solution was stirred at room temperature for 100 h. After removal of the solvent on a *Kugelrohr*, the remaining solids were dissolved in CH_2Cl_2, washed with saturated NH_4Cl, and dried over K_2CO_3. The ^1H NMR indicated only unchanged starting material was recovered.

Attempted cycloaddition of **54b** with dichloroketene:

Vinylphosphonium salt **54b** (49 mg, 0.116 mmol) was placed in a two necked round bottomed flask along with dry ether (1.8 mL) and ZnCu couple (~2 mg). Trichloroacetyl chloride (17μL, 0.152 mmol) was added to this mixture over the span of a few minutes. After four hours, the solids were removed by filtration, and the collected ether solution washed with saturated NH_4Cl. The ether solution was dried over $MgSO_4$,

and the solvent was removed on a rotary evaporator. The IR spectrum of the product obtained a medium strength peak at 1759cm^{-1}. Since cyclobutanones would give an absorption at 1800 cm^{-1}, lack of a peak at this position was taken as an indication that the cycloaddition did not take place.

Reaction of **54b** with sodium ethoxide:

Absolute ethanol (15 μL, 0.257 mmol) was added to Na° (3 mg, 0.117 mmol) in THF (0.2 mL) at 0 °C. After a few minutes, β-alkoxy vinylphosphonium salt **54b** (47 mg, 0.109 mmol) was added, and the reaction was allowed to warm to room temperature. The solids were filtered from the mixture, and found to be unreacted starting material by ^{1}H NMR. The filtrate was concentrated on a rotary evaporator. The ^{1}H NMR of the filtrate revealed some unreacted starting vinylphosphonium salt, as well as other components. The expected product should have had a doublet near 3.5 ppm (due to the ylide proton) coupled to phosphorus. No such signal was present. In fact, the phosphine oxide **68b** was present as the second major compound other than unreacted starting material (**54b**:**68b** = 2:1).

Attempted rearrangement of O-alkylated **54** to C-alkylated **94b**:

β-Alkoxy vinylphosphonium salt **54**, (R = CH_2CH_2Br, R^1 = H, R^2 = CH_3) prepared beforehand was subjected to a number of conditions in order to find an optimal set of parameters by which rearrangement of the vinylphosphonium salt could be accomplished. A number of solvents were utilized: chloroform, toluene, acetonitrile, carbon

tetrachloride, DMSO, HMPA, and acetone. Reaction temperatures were between 55 °C and 160 °C. In addition to the two characteristic methylene protons of the O-alkylated vinylphosphonium salt (starting material), two new pairs of methylene protons were evident in crude ^{1}H NMR spectra of the products. The starting material, formed under room temperature conditions, has the following pertinent peaks: δ 5.65 (d, J = 19.1 Hz, 1H), 4.58 (m, 2H), 2.95 (m, 2H). The second compound, formed from the first compound upon heating in 1,2-dibromoethane overnight, has the following peaks: δ 5.72 (d, J = 13.4 Hz, 1H), 5.0 (m, 2H), 3.8 (m, 2H). This may be the *E* isomer of the β-alkoxy vinylphosphonium salt. The third compound that was detected may be the C-alkylated material, based on the lack of a signal for a vinyl proton to the structure, it having instead two identifiable multiplets: δ 4.48 (m, 2H), 3.14 (m, 2H). The reaction conditions which seemed to maximize the magnitude of the ^{1}H NMR signal of the third compound were evidently around 100 °C, 48 h or more, in a polar solvent (chloroform, 1,2-dibromoethane, etc.). After 72 h at 100 °C, the ratio of O-alkylated compound to C-alkylated compound was 3.7:1, but the C-alkylated compound was only 13% by ^{1}H NMR.

Attempted cyclopropanation of **54c** with **67a**:

Pentanes (2 mL) was added to a 60% suspension of NaH in mineral oil, stirred, and the solvent (containing mineral oil) was pipetted off. The process was repeated two more times, and the residual solvent was then removed under reduced pressure on a vacuum pump to give a dry powder (4 mg, 0.175 mmol), to which dry DMSO (5 mL),

and trimethylsulfoxonium iodide (31 mg, 0.141 mmol) were added, and the reaction allowed to stir for 15 min. β-alkoxy vinylphosphonium salt **54c** (55 mg, 0.128 mmol) was added as a powder. The mixture was stirred for 1 h at room temperature, then transferred to an oil bath at 40 °C for 40 h. The reaction was quenched with water, extracted into CH_2Cl_2 (3 x 20 mL), and the organic layer was washed with 10% $NaHCO_3$ (2 x 20 mL). After the solution was dried over K_2CO_3, the solvent was removed on a rotary evaporator. The ^1H NMR analysis of the reaction products confirmed formation of the diphenylphosphine oxide **68c**: δ 7.8 - 7.4 (m, 10 H), 6.75 (d, J = 11.5 Hz, 1H), 4.0 (q, J = 7.0 Hz, 2H), 1.7 (d, J = 15.4 Hz, 3H), 1.3 (t, J = 7.0 Hz, 3H).

Attempted cyclopropanation of β-alkoxy vinylphosphonium salt **54c** with **67c**:

Sulfonium ylide **67c** (29 mg, 0.193 mmol), dissolved in CH_2Cl_2, was added to a solution of vinylphosphonium salt **54c** (40 mg, 0.094 mmol) in CH_2Cl_2. The reaction mixture was stirred at room temperature for 18 h, then heated to reflux (40 °C) for 42 h. The ^1H NMR of the material thus obtained showed predominantly unreacted starting material.

Attempted cyclopropanation of (2-acetoxypropenyl)triphenylphosphonium chloride **54d** with **67a**:

Pentanes (2 mL) was added to a 60% suspension of NaH in mineral oil, stirred, and the solvent (containing mineral oil) was pipetted off. The process was repeated two more times, and the residual solvent was then removed under reduced pressure on a

vacuum pump to give a dry powder (6 mg, 0.245 mmol), to which dry DMSO (2 mL) was added, followed by trimethylsulfoxonium iodide (47 mg, 0.211 mmol). Vinyl phosphonium salt **54d** (86 mg, 0.216 mmol) was dissolved in dry DMSO (2 mL) and added to the solution. The reaction was stirred at room temperature for 36 h. The ^{1}H NMR of the product shows very clean β-keto phosphonium salt, **74**. ^{1}H NMR: δ 7.6 - 8.0 (m, 15 H), 5.85 (d, J = 11.4 Hz, 2H), 2.6 (d, J = 3.8 Hz, 3H).

Attempted duplication of the reported[30a,b] reaction to form **57** from **54a**:

NaOEt (40 mg, 0.588 mmol) was added in four portions to a cold solution (0 °C) of vinylphosphonium salt **54a** (51 mg, 0.123 mmol) in THF (10 mL). The mixture was stirred for 5 min, then the ice bath was removed and the solution allowed to warm to room temperature. The solution was filtered and the remaining solvent removed on a rotary evaporator. The recovered material was shown by ^{1}H NMR analysis of the crude reaction mixture to be diphenylphosphine oxide **68a**.

Attempted synthesis of diphenylfuran **65** from **54a** and benzoin:

A mixture of vinylphosphonium salt **54a** (51 mg, 0.123 mmol), NaH 60% suspension in mineral oil (5 mg, 0.12 mmol), and benzoin (20 mg 0.096 mmol) was stirred in dry 1,2-dimethoxyethane (5 mL) at room temperature for 86 h. The solution was filtered, and the collected residue and filtrate analyzed by ^{1}H NMR. The residue was found to be unreacted starting material. The filtrate contained both starting material and diphenylphosphine oxide **68a**.

Ethyl(dimethylsulfuranylidene)acetate (**67c**[52]):

Methyl sulfide (4 mL, 54 mmol) was added to a stirred solution of ethyl bromoacetate (6 mL, 54 mmol) in acetone (20 mL). After 14 h, a large amount of crystals had formed in the flask. The mixture was filtered, and dried under vacuum to give $(CH_3)_2S^+CH_2CO_2CH_2CH_3$ Br^- (8.6 g, 69.5%). A portion of the resulting carbethoxymethyl dimethylsulfonium bromide (2.07 g, 9.05 mmol) was dissolved in $CHCl_3$ (10 mL) and cooled to 0 °C. A mixture of saturated K_2CO_3 (5 mL) and 12N NaOH (0.8 mL) was added while stirring vigorously. The bath temperature was raised to 20 °C for 15 min. The NaBr formed was removed by filtration, the chloroform layer separated, and the aqueous layer was extracted into chloroform (2 x 50 mL). The organic layers were combined, dried over K_2CO_3, and the solvent removed under reduced pressure to give a light yellow oil (1.23 g, 92%). ^{1}H NMR δ 4.0 (q, J = 7.7 Hz, 2H), 2.9 (s, 1H), 2.75 (s, 6H), 1.2 (t, J = 7.7 Hz, 3H).

1-Diphenylphosphinyl-2-ethoxyethene (**68a**):

Pentanes (2 mL) was added to a 60% suspension of NaH in mineral oil, stirred, and the solvent (containing mineral oil) was pipetted off. The process was repeated two more times, and the residual solvent was then removed under reduced pressure on a vacuum pump to give a dry powder (10 mg, 0.40mmol) which was placed in 2 mL DMSO. The mixture began to foam, but became clear after a few minutes. After about 10 min, β-alkoxy vinylphosphonium salt **54a** (163 mg, 0.40 mmol) was added, and the

reaction was stirred at room temperature for 12.5 h. The reaction was quenched with water, extracted into CH_2Cl_2, and washed with brine. The solution was dried over K_2CO_3, and the solvent removed on a rotary evaporator to give **68a** (101 mg, 94%). mp: 132 °C IR: 1605, 1437, 1340, 1177, 1096, 758, 720, 703 cm^{-1}. ^1H NMR δ 7.6 - 7.8 (m, 4 H), 7.4 - 7.6 (m, 6 H), 7.0 (dd, J=13.5, 10.9 Hz, I H), 5.3 (dd, J=14.5, 13.5 Hz, I H), 4.0 (q,J=7.0 Hz, 2 H), 1.3 (t, J=7.0 Hz, 3 H). ^{13}C NMR: 162 (d, J=15.1 Hz), 133.9 (d, J=121 Hz), 131.6, 131.2, 128.4, 93 (d, J=114.9 Hz), 66.4, 14.5. Analysis calc'd for $C_{16}H_{17}O_2P$: C, 70.58; H, 6.29. Found: C, 70.84; H, 6.35.

Attempted cyclopropanation of diphenylphosphine oxide **68a** with **67a**:

Diphenylphosphine oxide **68a** (39 mg, 0.141 mmol) was added to a solution of the dimsyl anion formed by combining trimethylsulfoxonium iodide (49 mg, 0.22 mmol), NaH (5 mg, 0.221 mmol), and dry DMSO. The reaction was carried out at temperatures from ambient to 150 °C, with reaction times up to 90 h. In all cases, the product isolated after workup was shown by ^1H NMR to be unchanged diphenylphosphine oxide **68a**.

Attempted cyclopropanation of diphenylphosphine oxide **68a** with SmI_2/CH_2I_2:

Diphenylphosphine oxide **68a** (68 mg, 0.249 mmol) was dissolved in dry THF (15 mL). SmI_2 in THF (2.5 mL, 0.1 M, 0.25 mmol) was added slowly. The colorless solution initially dissipated the blue-green color of the samarium iodide immediately, but upon continued addition, the solution turned white, then blue-green. The solution was stirred for 15 min (at which time the blue-green color was still present), and CH_2I_2 (20

μL, 0.248 mmol) was added. The solution became pale yellow over a few minutes, and was stirred at room temperature for 16 h. The reaction was quenched by addition of water, and extracted into ether (2 x 20 mL) and CH_2Cl_2 (2 x 20 mL). Only unchanged diphenylphosphine oxide was recovered from the reaction mixture, as determined by ^1H NMR.

Formation of 1-diphenylphosphinyl-2-ethoxypropene **68b**:

Pentanes (2 mL) was added to a 60% suspension of NaH in mineral oil, stirred, and the solvent (containing mineral oil) was pipetted off. The process was repeated two more times, and the residual solvent was then removed under reduced pressure on a vacuum pump to give a dry powder (15 mg, 0.621 mmol). Dry DMSO (2 mL) was added and the mixture was allowed to stir for 10 min, until foam had subsided. To this solution, β-alkoxy vinylphosphonium salt **54b** (130 mg, 0.304 mmol) was added, and the reaction was allowed to stir for 24 h. The reaction was quenched by addition of water, and extracted successively into CH_2Cl_2 and ether. The organic washes were combined, dried over K_2CO_3, and the solvents removed on a rotary evaporator. mp 147 °C. IR: 1605, 1437, 1383, 1321, 1192, 1117, 1069, 786, 746, 720, 696 cm^{-1}. ^1H NMR δ 7.7 - 7.8 (m, 4 H), 7.4 - 7.55 (m, 6 H), 4.9 (d, J = 15.3 Hz, 1H), 3.9 (q, J = 6.9 Hz, 2H), 2.1 (s, 3H), 1.35 (t, J = 6.9 Hz, 3H). Analysis calcd for $C_{17}H_{19}O_2P$: C, 71.3; H, 6.7. Found: C, 71.56; H, 6.86.

Attempted reduction of **68b** with SmI_2/HMPA:

A flame-dried round bottomed flask was allowed to cool under flowing nitrogen. Once cool, phosphine oxide **68b** (56 mg, 0.130 mmol) was added, followed by freshly distilled HMPA (130 μL, 0.747 mmol) and SmI_2 (2.9 mL, 0.1M in THF, 0.286 mmol). Hexanes were added to the resulting cloudy tan mixture, which was then filtered through a pad of florisil. The florisil pad was then washed with THF and hexanes and the filtrate collected. The florisil pad was next washed with CH_2Cl_2, and a bright yellow filtrate collected. Finally, the florisil pad was washed with methanol, to give a dark gold solution. The solvents were removed on a rotary evaporator from each fraction collected. Only the CH_2Cl_2 wash contained material of interest. The ^1H NMR of the yellow crystalline product revealed unreacted starting material only.

Attmpted reduction of **68b** with lithium aluminum hydride/cerium trichloride:

$CeCl_3 \bullet 7\ H_2O$ was dried in a vacuum oven at 130 °C for 3 h. In a round bottomed flask, lithium aluminum hydride (9 mg, 0.248 mmol) was combined with $CeCl_3$ (45 mg, 0.182 mmol). The flask was then charged with dry THF (20 mL), and phosphine oxide **68b** (51 mg, 0.119 mmol). The reaction was then heated on an oil bath for 45 min. The reaction was quenched by addition of water, extracted into CH_2Cl_2, and dried over $MgSO_4$. After removal of the solvent on a rotary evaporator, the product was examined by ^1H NMR and/or IR. If the reaction was allowed to proceed at 40 °C for 45 min, only phosphine oxide **68b** was recovered after workup. If the reaction was run 24 h at 80 °C, however, starting material plus an unknown compound showing a doublet at 2.62 ppm was detected.

Attempted reduction of **68b** with trichlorosilane:

Diphenylphosphine oxide **68b** (56 mg, 0.131 mmol) was dissolved in benzene (6 mL). Trichlorosilane (40 μL, 0.396 mmol) was then added. The solution changed color immediately, from red-brown to light gold. After 2.5 h at room temperature, the reaction was quenched with water, extracted into CH_2Cl_2 and dried over $CaCl_2$. Removal of the solvent under reduced pressure on a rotary evaporator gave acetonyl diphenylphosphine oxide, **73b** as the only detected product. IR: 1709, 1438, 1359, 1224, 1182, 1122, 750, 734, 720, 697 cm^{-1}. ^1H NMR δ 7.6-7.4 (m, 10 H), 3.65 (d, J=15.2 Hz, 2 H), 2.3 (s, 3 H).

2-Diphenylphosphinyl-1-ethoxypropene (**68c**):

Pentanes (2 mL) was added to a 60% suspension of NaH in mineral oil, stirred, and the solvent (containing mineral oil) was pipetted off. The process was repeated two more times, and the residual solvent was then removed under reduced pressure on a vacuum pump to give NaH (6 mg, 0.258 mmol). DMSO (4 mL) was added, and after the solution turned clear, β-alkoxy vinylphosphonium salt **54c** (72 mg, 0.169 mmol) was added and the reaction was stirred at room temperature for 24 h. The reaction was quenched by addition of water, extracted into CH_2Cl_2, dried over $MgSO_4$, and the solvent removed under reduced pressure on a rotary evaporator to give diphenylphosphine oxide **68c**. mp 192 °C (dec) IR: 1636, 1437, 1208, 1115, 749, 720, 696 cm^{-1}. ^1H NMR δ 7.6 - 7.8 (m, 4 H), 7.4 - 7.6 (m, 6 H), 6.75 (d, J=11.5 Hz, 1 H), 4.0 (q, J=7.0 Hz, 2 H), 1.7 (d, J=15.4 Hz, 3 H), 1.3 (t, J=7.0 Hz, 3 H). Calcd for $C_{17}H_{19}O_2P$: C, 71.3; H, 6.7.

Found: C, 66.32; H, 5.94. Even though satisfactory analysis was not obtained, ^{1}H NMR, and the IR spectrum taken together clearly point to the diphenylphosphine oxide **68c** as the sole product of the reaction.

Attempted cyclopropanation of vinyl phosphonium bromide (**71**) with methoxycarbene:

Vinylphosphonium bromide (**71**) (1.106g, 3 mmol) was placed in a round bottomed flask, and distilled diglyme (15 mL) was added. An equalizing addition funnel was fitted atop the flask, and diglyme (1 mL) and tetramethylpiperidine (169 μL, 1 mmol) were added to the funnel. Chloromethylmethyl ether (76 μL, 1 mmol) was added to the solution of vinylphosphonium bromide in the flask. n-Butyllithium (0.68 mL, 1.48M, 1 mmol) was added to the mixture in the addition funnel in order to generate the yellow-gold solution of lithium tetramethylpiperidide (LiTMP). The LiTMP solution was added in three portions, with no visible changes to the reaction mixture. After 10 d, the reaction was quenched by addition of water and extracted into CH_2Cl_2. The ^{1}H NMR of the crude reaction mixture showed starting material only. In addition to the LiTMP, lithium dicyclohexylamide was also used, with identical results, isolation of starting material only.

C-alkylation of (formylmethyl)triphenylphosphonium bromide with CH_3I:

PhLi (0.2 mL, 1.8M, 0.36 mmol) was added to phosphonium salt **92**, R = H (104 mg, 0.306 mmol) in dry THF (3 mL) at 40 °C and the solution turned dark red. Immediately upon addition of CH_3I (21 μL, 0.327 mmol) the solution lightened, and a precipitate formed. After 22 h, the reaction was removed from heat, diluted with water,

extracted into CH_2Cl_2, and dried over $MgSO_4$. ^1H NMR of the crude reaction mixture showed a doublet at 1.9 ppm characteristic of a methyl group on the α carbon. δ 11.5 (bs, 1H), 7.8 - 8.0 (m, 16 H), 1.9 (d, J = 11 Hz, 3H). Purification of the mixture by radial chromatography on silica gel (eluted with 45% CH_2Cl_2, 45% Et_2O, 10% MeOH) gave **94a** (8 mg, 8%). As proof of structure, treatment of this compound with K_2CO_3 gave material identical to 2-triphenylphosphoranylidene propanaldehyde **53c** by ^1H NMR.

Attempted C-alkylation of (formylmethyl)triphenylphosphonium bromide (**92**, R = H) with alkyl halides:

A number of alkyl halides were used in various reactions in order to attempt alkylation on the α carbon of phosphonium salts **92** (where R = H, CH_3). For the most part, these reactions involved attempts to form the ylide *in situ*, while at the same time providing some degree of complexation of the carbonyl oxygen in order to promote C-alkylation over O-alkylation. The procedures used are outlined below.

Attempted C-alkylation of **92** (R = H) with ICH_2Cl: (Formylmethyl)triphenylphosphonium chloride (98 mg, 0.288 mmol) was stirred in dry THF (4 mL) and heated to 45 °C. As PhLi (0.14 mL, 1.8M, 0.252 mmol) was added, the solution turned brown. Upon addition of ICH_2Cl (31 μL, 0.426 mmol), the solution lightened rapidly. The reaction was stirred for 26 h, then removed from heat, quenched with saturated NH_4Cl, extracted into CH_2Cl_2, and dried over $MgSO_4$. The solvent was removed under reduced pressure on a rotary evaporator. ^1H NMR of the product usually revealed only phenyl protons, although on

one occasion the product which was detected was the ylide **93a** resulting from deprotonation of phosphonium salt **92** (R = H).

Attempted C-alkylation of **92** (R = H) with dibromoethane: (Formylmethyl) triphenylphosphonium chloride (70 mg, 0.206 mmol) was suspended in diglyme (10 mL). PhLi (0.11 mL, 1.8 M, 0.198 mmol) was added dropwise while the mixture was stirred. Dibromoethane (18 μL, 0.209 mmol) was added dropwise. The reaction was then stirred at room temperature for 22 h. In addition to the O-alkylated product, a product detected in the ^{1}H NMR had some multiplets (6.7 - 7.1 ppm) but no protons associated with the methylene protons.

Attempted C-alkylation of acetonyltriphenylphosphonium chloride (**92**, R = CH_3) with CH_3I: PhLi (0.20 mL, 1.8M, 0.36 mmol) was added to a suspension of acetonyltriphenylphosphonium chloride (103 mg, 0.291) in dry THF (5 mL), and the solution immediately turned dark red. CH_3I (20 μL, 0.321 mmol) was added, and the solution immediately became pale gold and cloudy. After 75 h, the reaction was quenched by addition of deionized water, the solution was extracted into CH_2Cl_2 and dried over $MgSO_4$. ^{1}H NMR of the crude mixture showed only the ylide **53b**, a result of deprotonation of the phosphonium salt starting material.

Attempted C-alkylation of acetonyltriphenylphosphonium chloride (**92**, R = CH_3) with $ClCH_2I$: PhLi (0.15 mL, 1.8M, 0.270 mmol) was added to a suspension of

acetonyltriphenylphosphonium chloride (107 mg, 0.302 mmol) in dry benzene (4 mL). The solids dissolved, and the solution turned bright yellow. $ClCH_2I$ (34 μL, 0.467 mmol) was added, and the color dissipated somewhat over the next few minutes. After 26 h at room temperature, the mixture was washed with saturated NH_4Cl, extracted into CH_2Cl_2, and dried over $MgSO_4$. The solvent was removed under reduced pressure on a rotary evaporator. ^1H NMR of the crude product showed the ylide resulting from deprotonation of the phosphonium salt as the only product.

Attempted C-alkylation of acetonyltriphenylphosphonium chloride (**92**, R=CH_3) with 1-bromo-2-chloroethane: PhLi (0.15 mL, 1.8 M, 0.270 mmol) was added to a suspension of acetonyltriphenylphosphonium chloride (103 mg, 0.290 mmol). The solution turned bright yellow immediately, then gradually paled over a period of minutes. $ClCH_2CH_2Br$ (48 μL, 0.577 mmol) was added, and the solution stirred for 5 h. The solvent was removed from the crude mixture on a rotary evaporator, to give the ylide, **93b** as the only product detected by ^1H NMR.

Attempted C-alkylation of acetonyltriphenylphosphonium chloride **92** (R = CH_3) with $BrCH_2CH_2OCH_3$: PhLi (0.15 mL, 1.8M, 0.270 mmol) and 2-bromoethyl methyl ether (57 μL, 0.606 mmol) were added, in rapid succession, to a suspension of acetonyltriphenylphosphonium chloride (107 mg, 0.302 mmol) in dry toluene (4 mL). After 5 h, the solvent was removed under vacuum, and a ^1H NMR of the crude product

run. Predominantly, the ylide was recovered.

Attempted C-alkylation of (triphenylphosphoranylidene)acetaldehyde (**93a**) with $ClCH_2OCH_3$:

Chloromethyl methyl ether (26 μL, 0.343 mmol) was added to a solution of ketoylide **93a** (51 mg, 0.169 mmol) in dry THF (2.0 mL). After 1 h, crystals had formed on the side of the reaction flask. Other than aryl protons and a large doublet at 2.0 ppm, the ^1H NMR was lacking any peak for a methoxy group.

O-alkylation of 1-triphenylphosphoranylidene-2-propanone (**93b**) with $BrCH_2CH_2Br$:

Ylide **93b** (497 mg, 1.560 mmol) was stirred in 1,2-dibromoethane (4 mL) at room temperature for 48 h. The product crystallized out of solution but was collected by removing the remaining solvent and recrystalizing the solids thus recovered from ethyl acetate/methylene chloride/hexanes to give the O-alkylated vinylphosphonium salt **86** (R = CH_2CH_2Br, $R^1 = CH_3$) (677 mg, 86%). IR: 1615, 1436, 1336, 1185, 1109, 719, 690, 586, 512 cm^{-1}. ^1H NMR δ 7.6 - 7.8 (m, 15 H), 5.5 (d, J = 17.4 Hz, 1H), 4.58 (m,2H), 2.95 (m, 2H), 2.7 (s, 3H).

C-alkylation of 1-triphenylphosphoranylidene-2-propanone (**93b**) with CH_3I:

Methyl iodide (0.1 mL, 1.61 mmol) was added to ketoylide **93b** (105 mg, 0.330 mmol) in benzene (0.5 mL). The reaction was stirred at room temperature for 14 h. The light yellow crystals which had formed on the sides of the reaction flask were washed

with benzene and dried under vacuum. Preparatory TLC on silica gel (eluted with 80% ethyl acetate, 20% ethanol (95%)) gave pure C-alkylated product, **94a** (9 mg, 6%) δ 7.9 - 8.0 (m, 6H), 7.6 - 7.8 (m, 9 H), 7.2 (dq, J = 9.9, 7.5 Hz, 1H), 2.61 (d, J = 1.2 Hz, 3H), 1.7 (dd, J = 18.3, 7.5 Hz, 3H).

Attempted C-alkylation of 1-triphenylphosphoranylidene-2-propanone (**93b**) with alkyl halides:

Ketoylide **93b** was treated with a variety of alkyl halides in an attempt to produce C-alkylated rather than O-alkylated products. For the most part, these represented attempts to isolate, starting from the ylide, the C-alkylated product. An alternate approach was to isolate the O-alkylated material, and effect rearrangement to the C-alkylated material. This was only attempted on one compound (**86**, R = CH_2CH_2Br, R^1 = CH_3), but a wide range of conditions were studied.

Attempted C-alkylation of **93b** with $ClCH_2OCH_3$: Chloromethyl methyl ether (26 μL, 0.344 mmol) was added to a solution of ketoylide **93b** (55 mg, 0.173 mmol) in dry THF (2 mL). The reaction was placed in an oil bath at 50 °C, and crystals began to form after 10 min. After 35 min, the mixture began to turn pink, and the reaction was stopped by removing the remaining solvent under reduced pressure. The ^1H NMR of the crude product showed only unreacted starting material and the O-alkylated compound (1.4:1).

Attempted C-alkylation of **93b** with $BrCH_2OCH_3$: Bromomethyl methyl ether (20 μL, 0.245 mmol) was added to a solution of ketoylide **93b** (47 mg, 0.147 mmol) in ethyl

acetate (5 mL). The addition was carried out at 0 °C, and the reaction was allowed to warm to room temperature. After 19 h, crystals had formed on the sides of the flask. The mother liquor was pipetted off of the crystals, concentrated on a rotary evaporator, and the ^{1}H NMR of both components were run. The spectrum taken of the crystals showed them to be the phosphonium salt, **92** R = CH_3. The ^{1}H NMR of the mother liquor was found to be comprised of phenyl protons only.

Attempted C-alkylation of **93b** with CH_2I_2: Ketoylide **93b** (298 mg, 0.937 mmols) was suspended in freshly distilled diiodomethane (1 mL, 12.4 mmol). The milky white mixture was stirred at room temperature for 40 min, then was transferred to an oil bath at 80 °C. The solids appeared to dissolve, and the solution turned bright yellow. After a total reaction time of 4 h, a ^{1}H NMR of the crude reaction mixture revealed a 2:1 mixture of the keto salt **92b** as opposed to the ketoylide **93b**.

Attempted C-alkylation of **93b** with $ClCH_2I$: Chloro iodomethane (57 μL, 0.783 mmol) was added to a solution of ketoylide **93b** (48 mg, 0.152 mmol) in benzene (2 mL) and the reaction was heated for 24 h at 75 °C, followed by 3 d at room temperature. The ^{1}H NMR of the material collected showed only the keto salt **92b** was present.

Attempted C-alkylation of **93b** with $BrCH_2CH_2Br$: 1,2-Dibromoethane (62 μL, 0.719 mmol) was added to a stirred solution of ketoylide **93b** (115 mg, 0.36 mmol) in CCl_4 (1 mL) and the tube sealed. The mixture was stirred at room temperature for 5.5 h, then

placed in an oil bath at 70 °C for 12 h. White crystals on the side of the tube were determined by ^{1}H NMR to be the unreacted ylide **93b**. Other minor products were detected, including the vinylphosphonium salt (*Z* and *E* isomers, ≈1:1).

Attempted C-alkylation of **93b** with $BrCH_2CH_2Cl$: Ketoylide **93b** (109 mg, 0.342 mmol) was added to a solution of LiBr (48 mg, 0.554 mmol) in dry THF (5 mL). After stirring at room temperature for 30 min, 1-bromo-2-chloroethane (31 μL, 0.372 mmol) was added and the mixture allowed to stir for 24 h. The ^{1}H NMR of the crude product revealed unreacted starting material, ketoylide **93b**.

Attempted C-alkylation of **93b** with $BrCH_2CH_2OCH_3$: 2-Bromoethyl methyl ether (35 μL, 0.372 mmol) was added to a solution of ketoylide **93b** (104 mg, 0.328 mmol) in dry CH_2Cl_2 (3 mL), and the reaction was allowed to stir for 2 d. The solvent and unreacted 2-bromoethyl methyl ether were removed under reduced pressure on a rotary evaporator. The ^{1}H NMR of the resulting solids revealed only unchanged starting material.

Attempted C-alkylation of **93g** with $ClCH_2OCH_3$:

Chloromethyl methyl ether (20 μL, 0.265 mmol) was added to a solution of ketoylide **93g** (48 mg, 0.134 mmol) in dry THF (2 mL). The reaction was heated to 50 °C for 45 min, then the solvent was removed under reduced pressure, and the ^{1}H NMR of the resulting solid taken. The product exhibited no vinyl protons of any magnitude,

indicating no O-alkylation had taken place. The only peaks were in the aryl region, and a large singlet at 1.2 ppm, indicating no addition of the chloromethyl methyl ether had occurred.

Diethyl ethynylphosphonate (**106a**):

Method A: Diethyl chlorophosphite (0.5 mL, 3.46 mmol) was stirred in dry diethyl ether (20 mL) and cooled to 0 °C under N_2. Ethynyl magnesium bromide (7.0 mL, 0.5M, 3.5 mmols) was added **very slowly**, with stirring. Upon complete addition, the greyish solution was allowed to warm to room temperature. Within 5-10 min, the color began to darken, and by 45 min after the addition, the solution was a dark red/black. The reaction mixture was quenched with aqueous NH_4Cl, extracted into ether, dried over $MgSO_4$, and analyzed by ^1H NMR. Integration of the alkynyl proton at 2.95 ppm gave, by comparison with the integration of the ethyl groups, a yield of 12% **106a**.

Method B: Chloroethynyl trimethylsilane (1.14 g, 8.6 mmol) was placed in a round bottomed flask. Freshly distilled triethylphosphite (1.74 g, 10.5 mmol) was added, the flask was purged with dry N_2, and the reaction refluxed for 18.5 h. The resulting solution of alkynyl phosphonate **112** was combined with 10% aq Na_2CO_3, and the mixture was stirred for 15 min, then the product was extracted into ether. The combined ether extracts were washed with saturated brine and dried over $MgSO_4$. The solvent was removed at reduced pressure on a rotary evaporator. The resulting oil was purified by radial chromatography, 60% ethyl acetate/hexanes eluent to give alkynyl phosphonate

106a (0.731g, 52 %) .

Method C: Trimethylsilyl ethyne (2.57g, 26.2 mmol) was dissolved in dry diethyl ether (50 mL) and cooled to -78 °C. n-Butyllithium (18 mL, 1.6 M, 28.8 mmol) was added, and the solution was allowed to stir for 1 h. Diethyl chlorophosphate (4.95 g, 28.7 mmol) was dissolved in 100 mL dry diethyl ether and cooled to 0 °C. Over a period of 1 h, the trimethylsilylethynyl lithium solution was added *via* cannula. The reaction turned a dark rose color over the course of the addition. After another hour, the reaction was quenched by adding saturated NH_4Cl and extracted into diethyl ether. The ether extracts containing alkynyl phosphonate **112** were combined, shaken together with 10% Na_2CO_3, and dried over Na_2SO_4. The solvent was removed under reduced pressure on a rotary evaporator. The resulting oil was purified by column chromatography on silica gel, eluted with 30% ethyl acetate/hexanes to give **106a** (2.53 g, 60%). bp 120 °C (35mm Hg), d = 1.055 $^{g}/_{mL}$ IR: 3169, 2987, 2064, 1267, 1028, 979, 780 cm^{-1}. ^1H NMR δ 3.9 - 4.1 (m, 4H), 2.95 (d, J=13.4 Hz, 1 H), 1.39 (t,J=7.3 Hz, 6 H).

1-Diethylphosphoryl-1-pentyne (**106b**):

Mg° (180 mg, 7.4 mmol) was placed in a round bottomed flask and heated under dry, flowing N_2. Once cool, dry diethyl ether (2 mL) was added, followed by ethyl bromide (0.55 mL, 7.4 mmol) and the reaction rate was controlled by cooling on an ice bath. The mixture was allowed to stir for 2 h, then added *via* cannula to a solution of 1-pentyne (493 mg, 7.2 mmol) in ether (20 mL). Diethyl chlorophosphite (1.3 g, 7.5 mmol) was dissolved in ether (10 mL) and cooled to 0 °C, and the solution of the alkynyl

magnesium bromide was added slowly. The reaction was allowed to warm to room temperature overnight. The solution was quenched with saturated NH_4Cl, and the aqueous phase extracted into ether. The combined ether layers were dried over $MgSO_4$, and the solvent removed under reduced pressure on a rotary evaporator. Distillation of the product (90 °C, 0.1 mm Hg) gave phosphonate **106b** (333 mg, 23%), d = 1.054 $^{g}/_{mL}$ IR: 2982, 2205, 1263, 1028, 975, 799, 760 cm^{-1}. ^1H NMR δ 4.0 - 4.2 (m, 4 H), 2.34 (dt, J=7.03, 4.4 Hz, 2 H), 1.63 (sextuplet, J=7.2 Hz, 2 H), 1.37 (t, J=7.1 Hz, 6 H), 1.03 (t, J=7.3 Hz, 3 H). GC/MS: $^{m}/_{z}$ = 203, 176, 148, 131.

General procedure for substituted alkynyl phosphonates(**106c-d**):

The terminal alkyne was dissolved in dry diethyl ether and cooled to -78 °C under N_2. n-Butyllithium (1.1 eq) was added, and the solution stirred for an additional 20 min. The cold bath was then removed, and the solution allowed to warm to room temperature for 45 min. The solution of the alkynyl lithium was then added *via* cannula to a stirred, ice-cold (0 °C) solution of freshly distilled diethyl chlorophosphate (1.1 eq) in dry diethyl ether. After 2 h, the reaction was quenched by addition of saturated NH_4Cl, followed by extraction into diethyl ether. The extracts were dried over $MgSO_4$, solvent removed under reduced pressure on a rotary evaporator, and purified by distillation or column chromatography.

1-Diethylphosphoryl-3-methoxypropyne (**106c**):

Following the general procedure for the formation of alkynyl phosphonates,

methylpropargyl ether (1.05 g, 14.9 mmol), n-butyllithium (10.25 mL, 1.6M, 16.4 mmol) and diethyl chlorophosphite (2.82 g, 16.4 mmol) were combined in dry ether. After 24 h, the reaction was worked up as described in the general procedure. Distillation of the oil collected gave **106c** (2.1 g, 68%). bp = 80 °C (0.1 mm Hg), d = 1.125 $^{g}/_{mL}$ IR: 2987, 2204, 1726, 1446, 1394, 1379, 1266, 1106, 1020, 799, 772 cm^{-1}. ^{1}H NMR δ 4.24 (d, J=3.7 Hz, 2 H), 4.1 - 4.22 (m, 4 H), 3.42 (s, 3 H), 1.39 (dt, J=7.0, 0.5 Hz, 6 H).

1-Diethylphosphoryl-2-phenylethyne (**106d**):

Following the general procedure described for the formation of alkynyl phosphonates, phenylacetylene (1.02 g, 9.9 mmol), n-butyllithium (6.8 mL, 1.6M, 10.9 mmol) and freshly distilled diethyl chlorophosphate (1.89 g, 10.9 mmol) were combined. After 3h 40 min, the reaction was quenched, and purified by distillation to give **106d** (1.77 g, 75%). bp = 180 °C, 0.1 mm Hg, d = 1.087 $^{g}/_{mL}$ IR: 2187, 1264, 1024, 978, 857, 760 cm^{-1}. ^{1}H NMR δ 7.55 - 7.6 (m, 2 H), 7.35 - 7.5 (m, 3 H), 4.2 - 4.3 (m, 4 H), 1.42 (t, J=7.1 Hz, 6 H).

Chloroethynyltrimethylsilane (**111**):

Method A: Dry THF (14 mL) was cooled to 0 °C. Methyllithium (20.0 mL, 1.4 M, 28 mmol) was added, followed by dropwise addition of a solution of *trans* dichloroethylene (1.0 mL ,13.0 mmol) in ether (3 mL). After the addition was completed, (0.5 h) the reaction was allowed to warm to room temperature for 1 h 15 min. The reaction mixture was then cooled to -78 °C and $(CH_3)_3SiCl$ (3.4 mL 26.8 mmol) in ether

(3.5 mL) and THF (3.5 mL), was added dropwise, and the reaction allowed to warm to room temperature overnight. The product was purified by distillation, to give **111**[89] (1.14 g, 66%).

Method B: Li° (1.0 g, 144 mmol) was stirred in dry THF (20 mL) at -78 °C. Tetrachloroethylene (2.1 mL, 21 mmol) was added, and the temperature was maintained at -78 °C for 31 h. The resultant thick, grey slurry was added *via* cannula to a stirred solution of $(CH_3)_3SiCl$ (6.8 g, 63 mmol) in dry THF (20 mL) that had been cooled to -78 °C, and allowed to warm to room temperature overnight. The resulting solution was fractionally distilled to give **111**[89] (1.07 g, 38%).

Trimethylsilylethyne (**115**[89]):

Method A: Li° (0.4 g, 58 mmol) was stirred in dry THF (20 mL) and cooled to -78 °C. Trichloroethylene (2.60 mL 0.029 mole) was added, followed by trimethylsilyl chloride (10.0 mL, 0.079 mole). The necessity of repeated distillations in order to purify the product led to isolation in low yield (<50%).

Method B: Li° (0.4 g, 57.6 mmol) was stirred in dry Bu_2O (25 mL). CH_3I (9.0 g, 63 mmol) was added, and the solution was stirred at room temperature for 2 d. After cooling to 0 °C , *E*-1,2-dichloroethene (2.8 g, 29 mmol) in Bu_2O 7 mL) was added over a 1.5 h time period, and the solution was warmed to room temperature. Upon distillation of the resultant liquid, negligible product was collected.

Method C: Zinc dust (3.9 g, 0.06 mole) was placed in HMPA (20 mL) freshly distilled from CaH_2. Chlorotrimethylsilane (4.9g, 0.045 mole) was added under N_2.

Finally, trichloroethene (3.3g, 0.025 mole) was added, and the mixture was stirred at room temperature for 3 d. After that time, the flask was placed in an oil bath at 90 °C, and the distillate collected. Trimethylsilylethyne (**115**) was collected over the next 6 h (1.64g, 67%).

Attempted photocycloaddition of enamine **101a** with alkynyl phosphonate **106a**

Enamine **101a** (46 μL, 0.319 mmol) and alkynyl phosphonate **106a** (50 μL, 0.325 mmol) were combined under flowing argon in an oven-dried photoreaction tube, the tube was evacuated, and the mixture irradiated using a Hanovia® lamp for 24 h. The mixture was then heated on an oil bath at 100 °C for 30 min. The reaction mixture was then hydrolyzed by stirring 2 h with THF (2 mL), p-toluenesulfonic acid monohydrate (17 mg), and H_2O (0.1 mL), after which GC analysis indicated that hydrolysis was complete. The mixture was then washed once with 10% $NaHCO_3$, following which the aqueous phase was extracted with THF (3 x 25 mL), and the organic layers were then washed once with saturated NaCl. ^1H NMR of the resulting oil showed only the presence of enaminophosphonate **124** and the Michael adduct **129**.

Attempted photocycloaddition of enamine **101c** and alkynyl phosphonate **106a**:

Hexanes (6 mL, distilled from CaH_2 and $LiAlH_4$) in a flame dried photoreaction tube, was degassed three times by the freeze-thaw method, two 4Å sieves were added, and two further freeze-thaw cycles were performed. Alkynyl phosphonate **106a** (50 μL, 0.325 mmol) was added, followed by enamine **101c** (75 μL, 0.470 mmol), and the tube

was purged with argon and sealed. After irradiation for 22 h, a hexanes-insoluble film had developed on the inside of the reaction tube, and the solution was cloudy. The reaction mixture was transferred to a round bottomed flask by aid of dissolution in CH_2Cl_2, and the solvents were removed under reduced pressure on a rotary evaporator. The resulting light yellow oil was placed on an oil bath at 100 °C for 2 h, and hydrolyzed by addition of THF (5 mL), H_2O (0.25 mL), and p-toluenesulfonic acid monohydrate (32 mg) and allowed to stir for 3 d. GC analysis of the material thus obtained revealed only enaminophosphonate **124** and Michael product **129**.

2-Diethylphosphorylcyclohept-2-ene-1-one (**122a**):

The freshly distilled pyrrolidine enamine **101a** (30 μL, 0.208 mmol) was placed in an ampule with a micro stir bar under flowing argon. Diethyl ethynyl phosphonate **106a** (32 μL, 0.208 mmol) was added, the ampule was sealed and placed in an oil bath at 100 °C. After an initial change to a light yellow color, no further degradation was noted. After 27 h, the seal was broken, and the crude sample analyzed by GC and NMR. The reaction mixture was then transferred to a round bottomed flask and 5 mL 5% acetic acid was added and stirred at high speed for 6 h. The product was extracted into diethyl ether, dried over $MgSO_4$, and the excess solvent removed under reduced pressure on a rotary evaporator. The ^1H NMR of the resultant light yellow oil revealed the presence of an unusual multiplet at 8.05 ppm, near the expected chemical shift for the vinyl proton of the desired product. This mixture was combined with the product of a separate reaction, and together purified by preparative TLC, eluted with 3:1 ethyl acetate/hexanes

(plus 3% methanol). The combined isolated yield was 25%. Formation of the same product using the morpholine based enamine resulted in a product yield of 8% by GC. IR: 1665, 1613, 1444, 1393, 1356, 1256, 1055, 1027, 967, 798 cm^{-1}. ^1H NMR δ 8.05 (m,1 H), 4.3 - 4.0 (m, 4H), 2.99 (t, J=7.5 Hz, 2 H), 2.13 (m, 2 H), 1.95 - 1.7 (m, 4H), 1.36 (t, J=7.15 Hz, 6 H). Calcd for $C_{11}H_{19}O_4P$: C, 53.65; H, 7.78. Found: C, 53.95; H 8.00.

2-Diethylphosphoryl-3-propylcyclohept-2-ene-1-one (**122b**):

The phosphonate **106b** (0.1 mL, 0.516 mmol) and freshly distilled pyrrolidine enamine **101a** (0.07 mL, 0.538 mmol) were combined in dry toluene (0.5 mL, stored over sodium metal), along with a micro stir bar, and a 3Å sieve in a small ampule. The ampule was sealed, wrapped in aluminum foil and stirred at room temperature for 25 h before being placed in an oil bath at 112 °C. After 42 h, the ampule was removed from the oil bath. The very light yellow solution was diluted with diethyl ether, and extracted into 5% HCl. The organic layers were then dried and the solvent was removed under reduced pressure on a rotary evaporator. The best GC yield for **122b** obtained using the pyrrolidine enamine was 16%. Using the same procedure, but with morpholine enamine **101d**, the optimum GC yield was 5%. IR: 3488, 2965, 2205 (residual alkynylphosphonate), 1708, 1639, 1565, 1459, 1415, 1393, 1261, 1167, 1028, 975, 796, 762, 629 cm^{-1}. ^1H NMR δ 4.1 - 4.21 (m, 4 H), 2.8 (bs, 1 H), 2.55 (bs, 1H), 2.35 (m, 4H), 1.95 (dt, J= Hz, 1 H), 1.8-1.6 (m, 5 H), 1.4 (t, J= Hz, 6 H), 1.05 (t, J= Hz, 3 H). ^{13}C NMR δ 207.2, 158.4, 103, 39.8, 34.3, 32.6, 27.0, 21.1, 20.1, 16.1, 13.4.

2-Diethylphosphonyl-3-methoxymethylcyclohept-2-ene-1-one (**122c**):

Freshly distilled pyrrolidine enamine **101a** (76 μL, 0.530 mmol) was placed in a flame-dried, argon-purged ampule along with a crushed 4Å molecular sieve. The phosphonate **106c** (150 μL, 0.79 mmol) was added, the ampule was immediately sealed and placed in an oil bath at 80 °C for 63 h. The reaction mixture was hydrolyzed by addition of THF (0.7 mL), H_2O (0.1 mL), and p-TsOH• H_2O and stirred for 24 h. The reaction was quenched with a mixture of saturated NH_4Cl and saturated $NaHCO_3$, then extracted into CH_2Cl_2 (5 x 20 mL). The reaction mixture was purified first by column chromatography on alumina (eluted with 20% ethyl acetate / heptane). Some unreacted phosphonate was recovered (12 mg), but the product (**122c**) was not completely purified. Further purification on an alumina preparative TLC plate eluted with 100% ethyl acetate gave pure **122c** (11 mg, 7%). The same procedure applied to the morpholine enamine **101d** was found to give a GC yield of 18%. IR: 1710, 1632, 1446, 1393, 1251, 1218, 1100, 1053, 1025, 962, 792 cm^{-1}. ^1H NMR δ 4.12 (m, 4H), 3.35 (s, 3H), 2.7 (m, 2H), 2.4 (m, 2H), 2.0 (m, 2H), 1.3 (m, 10H). MS: 290, 275, 258, 244, 229, 201(base peak).

2-Diethylphosphonyl-3-phenylcyclohept-2-ene-1-one (**122d**):

Alkynyl phosphonate **106d** (155 μL, 0.723 mmol) was placed in a flame-dried, argon-purged ampule, and a trace of hydroquinone was added. Freshly distilled pyrrolidinyl enamine **101a** was added (210 μL, 1.457 mmol), the ampule was sealed, and placed in an oil bath at 95 °C. After 63 h, the mixture was transferred to a round bottom flask, and ethanolic acetic acid (5 mL, 3% AcOH in 95% ethanol) was introduced for the

hydrolysis of the product. GC/MS indicated that hydrolysis was complete after 2 h. The solution was transferred to a separatory funnel containing water, and extracted into ether (3 x 35 mL), and the combined ether fractions were washed with 5% $NaHCO_3$. Purification was performed on an alumina column, eluted with 100 % ethyl acetate. Further purification of the fractions from the column which contained the product was performed on an alumina preparatory TLC plate, eluted with 38% ethyl acetate, 60% hexanes, and 2% MeOH, to give **122d** (31 mg, 13%). ^{1}H NMR δ 7.4 (m, 5H), 3.9 (m, 4H), 2.55 (m, 2H), 2.3 (t, J = 7 Hz, 2H), 1.75 (m, 2H), 1.25 (t, J = 7 Hz, 2H), 1.0 (t, J = 7 Hz, 6H). ^{13}C NMR δ 207, 142, 136, 128, 127, 64, 61, 41, 33, 32, 29, 20, 16. MS: $^m/_z$ 322, 276, 248, 210, 185(base peak).

2-Diethylphosphonyl cyclooct-2-ene-1-one (**122e**):

Alkynyl phosphonate **106b** (910 mg, 5.61 mmol) was placed in an oven-dried ampule, along with a 3Å molecular sieve and a few crystals of hydroquinone. Freshly distilled enamine **101b** (963 mg, 5.76 mmol) was added, and the ampule was sealed and stirred at room temperature for 4 d. The reaction was then heated for 15 d at 110 °C, after which time it was hydrolyzed by addition of THF and a few mL of 50% AcOH. After 27 d, the mixture was extracted into CH_2Cl_2 (3 x 25 mL), the aqueous layer was saturated with NaCl, and re-extracted with CH_2Cl_2 (4 x 30 mL). Removal of the solvent on a rotary evaporator gave a syrup which appeared to have the product present in a small amount, based on ^{1}H NMR. A number of purification schemes were attempted on this compound, including reversed phase column chromatography. Ultimately, by combination

of techniques, a fraction containing mostly product (but not pure) was isolated using silica column chromatography, eluted with 3:1 CH_2Cl_2 : ethyl acetate. IR: 2936, 1710, 1670, 1449, 1387, 1254, 1029, 969, 796 cm^{-1}. ^1H NMR δ 7.06 (dt, J=26.75, 4.38 Hz, 1 H), 4.14 (m, 4 H), 2.53 (m, 2 H), 2.43 (m, 2 H), 1.90 (m, 2 H), 1.65 (m, 4 H), 1.35 (t, J=7 Hz, 6 H).

2-Diethylphosphonylcyclooct-2-ene-1-one (**122e**) *via* phenylselenenylation:

PhSeCl (283 mg, 1.48 mmol) was dissolved in dry CH_2Cl_2 (10 mL) at 0 °C. Pyridine (120 μL 1.48 mmol) was added, and the solution allowed to stir for 15 min. To this mixture was added a solution of β-keto phosphonate **140** (192 mg, 0.733 mmol) in CH_2Cl_2 (2 mL). After 0.5 h, the ice bath was removed, and the solution stirred overnight. After 24 h, another aliquot of PhSeCl (190 mg, 1 mmol) and pyridine (100 μL, 1.23 mmol) was added, and the solution stirred for another 5 h. The solution was washed with 10% HCl, and returned to the flask, and 0.2 mL H_2O_2 was added. Another 0.6 mL H_2O_2 was added in three increments. The resulting solution was washed with $NaHCO_3$ and dried over $MgSO_4$. After removal of the solvent on a rotary evaporator, the product recovered consisted of 174 mg material, of which 50% was the desired unsaturated phosphonate **122e**, based on the ^1H NMR signal.

Unknown compound with dt at 6.7 ppm:

Phosphonate **106a** (910 mg, 5.61 mmol) was placed in a dry ampule with a stir bar, a 3Å sieve, and a trace of hydroquinone. Freshly distilled enamine **101b** (963 mg,

5.76 mmol) was added, and the ampule was sealed. After stirring at room temperature for 24 h, the ampule was placed in an oil bath at 110 °C for 15 d. After cooling, the seal was broken, and the sample was transferred to a round bottomed flask by dissolution in THF. Acetic acid (4 mL, 50%) was added, and the mixture was allowed to stir under N_2 for 27 d. The product was extracted into a mixture of CH_2Cl_2/ethyl acetate (6:1, 3 x 20 mL), the aqueous portion was then saturated with NaCl, and further extraced (4 x 20 mL), and finally extracted with ethyl acetate (1 x 25 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure on a rotary evaporator. The resulting yellow-gold oil was initially identified as **122e**, based on GC/MS data. In fact, high-resolution mass spectral analysis of a sample of this reaction product provided the following results: calc'd mass for $C_{12}H_{21}O_4P$ = 260.117748. Obtained: 260.116600. However, the ^{1}H NMR contained a signal at 3.33 ppm, integrating for two protons, which could not be attributed to the known structure, nor was the signal present in **122e** produced by phenylselenenylation/oxidation/elimination of 2-(diethylphosphonyl)cyclooctanone. ^{1}H NMR: δ 6.7 (dt, J = 25.6, 7 Hz, 1H), 4.15 - 4.0 (m, 4H), 3.33 (dd, J = 7, 4.7 Hz, 2H), 2.5 (m, 2H), 2.4 - 2.3 (m, 2H), 1.9 - 1.8 (m, 2H), 1.8 - 1.7 (m, 2H), 1.32 (t, J = 7 Hz, 6H).

(2-pyrrolidinyl)vinyl diethylphosphonate (**124**):

Pyrrolidine (14 μL, 0.168 mmol) was placed in around bottomed flask. Alkynyl phosphonate **106a** (25 μL, 0.163 mmol) was added, and the mixture became noticeably warm. After 24 h, $CDCl_3$ was added, and a ^{1}H NMR spectrum was obtained. IR: 3432,

1615, 1551, 1448, 1393, 1333, 1211, 1029, 958, 884, 790 cm^{-1}. ^1H NMR δ 7.3 (dd, J = 13.5, 13.5 Hz, 1H), 4.1 - 4.0 (m, 4H), 3.7 (dd, J = 13.5, 13.5 Hz, 1H), 3.25 (bs, 4H), 1.95 (bs, 4H), 1.35 (t, J = 7 Hz, 6H). ^{13}C NMR: δ 150 (d, J = 18 Hz), 73 (d, J = 212 Hz), 61, 48, 25, 16. GC/MS: $^m/_z$ = 233 (M+), 204 (M-CH_2CH_3), 188 (M-OCH_2CH_3), 96 (M-137, loss of phosphonate).

2-(Vinyldiethylphosphonyl)cyclopentanone (**129**):

Following the general procedure for cycloadditions of pyrrolidine enamines with alkynyl phosphonates, enamine **101a** was distilled and placed in an ampule (30 μL, 0.208 mmol), along with a trace of hydroquinone, and alkynyl phosphonate **106a** (32 μL, 0.208 mmol) was added. The tube was sealed and placed in an oil bath at 78 °C. After 24 hours, ^1H NMR of the crude reaction mixture revealed only traces of the desired product, along with two sets of unexplained vinyl resonances: one pair integrating 1:1 at 7.7 ppm (dd, J = 21.1, 16.1 Hz) and 4.6 ppm (dd, J = 20.7, 16.1 Hz) and the second pair integrating 1:1 at 6.7 ppm (ddd, J = 52.1, 13.1, 10.3 Hz) and 5.55 ppm (dd, J = 18.8, 13.1 Hz). The crude mixture was hydrolyzed with acetic acid in diethyl ether (0.25 mL, 1M) and water (0.5 mL) for 36 h, and the resulting solution was neutralized with 10% NaOH followed by extraction into diethyl ether. The ether extract contained trace quantities of the desired product, **122a**, already described. The aqueous portion of the reaction mixture was still highly colored. The water was removed and the resulting solids washed with CH_2Cl_2 to give **129** as a mixture of the described compound and enaminophosphonate **124** (62 mg, 71%). The assignement of the ^1H NMR is based on reasonable assignment of

the observed peaks to the structure given, consistent with mass spectral data observed on the product. ^{1}H NMR: δ 6.67 (ddd, J = 52.1, 13.1, 10.3 Hz, 1H), 5.6 (dd, J = 188, 13.1 Hz, 1H), 4.15 - 4.0 (m, 4H), 3.5 - 3.6 (m, 1H), 2.6 (bs, 2H), 1.7 (bs, 4H).

Conjugate addition of *tert*-butoxide to α,β-unsaturated β-keto phosphonate **122e**

KH in mineral oil was washed by stirring in a few mL hexanes, pipetting off the supernatant solvent, and repeating the process two more times. The residual hexanes were then evaporated off under dry, flowing N_2 to give dry powder (8 mg, 0.218 mmol). Dry THF was added (0.5 mL), followed by *t*-butanol (20 μL), and the mixture was stirred at room temperature for 1.5 h. After cooling to -45 °C, α,β-unsaturated β-keto phosphonate **122e** was added (15 mg, 0.059 mmol), and the solution turned yellow. The mixture was allowed to warm to room temperature overnight, and quenched by addition of HCl (0.2 mL, 1N), during which process the yellow color of the solution dissipated. Evidence of Michael addition was found in the IR spectrum of the product, which exhibited peaks consistent with a product with high enolic content, as well as peaks equating to ether linkages. IR: 3343, 2938, 1699, 1608, 1445, 1250, 1170, 1167, 1031, 970, 794 cm^{-1}.

References

References

1. The following reports pertain to the structure and/or activity of the named compounds:
   a. Taxol: Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325-2327.
   b. Taxotere: Bissery, M.-C.; Guènard, D.; Guèritte-Voegelein, F.; Lavelle, F. *Cancer Res.* **1991**, *51*, 4845-4852.
   c. Cephalomannine: Miller, R. W.; Powell, R. G.; Smith, C. R., Jr. *J. Org. Chem.* **1981**, *46*, 1469-1474.
   d. Foetidin: Pinar, M.; Rico, M.; Pascual, C.; Fernàndez, B. *Phytochemistry*, **1983**, *22*, 2775-2777.
   e. Rabdohakusin: Kubo, I.; Matsumoto, T.; Asaka, Y.; Kubota, T.; Naoki, H.; Fludzinski, P.; Kende, A. S. *Chem. Lett.* **1984**, *9*, 1613-1616.
   f. Taxusin: Miyazaki, M.; Shimizu, K.; Mishima, H.; Kurabayashi, M. *Chem. Pharm. Bull.* **1968**, *16*, 546-548.
   g. Taxinine: Shiro, M.; Koyama, H.; *J. Chem. Soc. (B)* **1971**, *6*, 1342-1346.

2. Andreu, J. M.; Diaz, J. F.; Gil, R.; de Pereda, J. M.; de Lacoba, M. G.; Peyrot, V.; Briand, C.; Towns-Andrews, E.; Bordas, J. *J. Biol. Chem.* **1994**, *269*, 31785-31792.

3. Incidence and survival figures are from: Jones, H. W. III In *Early Detection of Ovarian Carcinoma with Transvaginal Sonography*; Fleischer, A. C., Jones, H. W. III, Eds.; Raven, New York, 1993; p. 3.

4. Burkhart, C. A.; Berman, J. W.; Swindell, C. S.; Horwitz, S. B. *Cancer Res.* **1994**, *54*, 5779-5782.

5. Ojima, I.; Fenoglio, I.; Park, Y.; Sun, C.-M.; Appendino, G.; Pera, P.; Bernacki, R. *J. Org. Chem.* **1994**, *59*, 515-517.

6. DeTar, D. F.; Luthra, N. P. *J. Am. Chem. Soc.* **1980**, *102*, 4505-4512.

7. Hesse, M., In *Ring Enlargement in Organic Chemistry*, VCH, New York, 1991, p 2.

8. Wharton, P. S. *J. Org. Chem.* **1965**, *30*, 3254-3257.

9. Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 3493-3494.

10. Janardhanam, S.; Shanmugam, P.; Rajagopalan, K. *Synth. Commun.* **1993**, *23*, 311-323.

11. Jefford, C. W.; Gunsher, J.; Hill, D. T.; Brun, P.; Le Gras, J.; Waegell, B. *Org. Synth.* **1971**, *51*, 60-65.

12. a) Reissig, H.-U.; Hirsch, E. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 813-814. b) Reissig, H.-U. *Tetrahedron Lett.* **1981**, *22*, 2981-2984.

13. Franck-Neumann, M.; Miesch, M.; Kempf, H. *Synthesis* **1989**, 820-824.

14. Shea, K. J. *Tetrahedron* **1980**, *36*, 1683-1715.

15. Bredt, J.; Thouet, H.; Scheitz, J. *Ann.* **1924**, *437*, 1.

16. Wiseman, J. R. *J. Am. Chem. Soc.* **1967**, *89*, 5966-5968.

17. Warren, S. in *Organic Synthesis: the Disconnection Approach.* Wiley Interscience, New York, 1982, Chapter 1.

18. A few examples will suffice to show the variety of techniques available:

    a. Photocycloaddition: Ikeda, M.; Ohno, K.; Takahashi, M.; Himma, K.-i.; Uchino, T.; Tamura, Y. *Heterocycles* **1983**, *20*, 1005-1008.
    b. Substitution: Fischli, A.; Branca, Q.; Daly, J. *Helv. Chim. Acta* **1976**, *59*, 2443-2461.
    c. Aldol reaction: Felix, D.; Schreiber, J.; Ohloff, G.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 2896-2912.
    d. Diels-Alder reaction: Fujiwara, T.; Ohsaka, T.; Inoue, T.; Takeda, T. *Tetrahedron Lett.* **1988**, *29*, 6283-6286.

19. a) Wittig, G.; Geissler, G. *Liebigs Ann. Chem.* **1953**, *580*, 44-57. b) Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318-1330.

20. For reviews on the Wittig reaction, see: a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863-927. b) Murphy, P. J.; Brennan, J. *Chem. Soc. Rev.* **1988**, *17*, 1-30.

21. Gosney, I.; Rowley, A. G. in *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press, New York, 1979; pp 17-153.

22. Vedejs, E.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1973**, *95*, 5778-5780.

23. Wittig, G. *Science* **1980**, *210*, 600-604.

24. a) Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61-63. b) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733-1738.

25. Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73-253.

26. Becker, K. *Tetrahedron* **1980**, *36*, 1717-1745.

27. Chatterjee, S. *J. Chem. Soc., Chem. Commun.* **1979**, 620-621.

28. Han, Q.; Wiemer, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 7692-7697.

29. Zanger, M.; VanderWerf, C. A.; McEwen, W. E. *J. Am. Chem. Soc.* **1959**, *81*, 3806-3807.

30. a) Bestmann, H. J.; Roth, K.; Ettlinger, M. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 687. b) Bestmann, H. J.; Roth, K.; Ettlinger, M. *Chem. Ber.* **1982**, *115*, 161-171. c) Swan, J. M.; Wright, S. H. B. *Aust. J. Chem.* **1971**, *24*, 777-783.

31. Blomberg, C.; Hartog, F. A. *Synthesis* **1977**, 18-30.

32. Neomeyanov [sic], N. A.; Berman, S. T.; Reutov, O. A. *B. Acad. Sci.* **1975**, *24*, 2737. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1975**, 2845. **Note:** The Principle Investigator's name is misspelled in the English translation. For other work by this group, Nesmeyanov is the correct name.

33. Shevchuk, M. I.; Volynskaya, E. M.; Dombrovskii, A. V. *J. Gen. Che. R.* **1970**, *40*, 45-53.

34. Darling, S. D.; Subramanian, N. *Tetrahedron Lett.* **1975**, *38*, 3279-3282.

35. a) Grimm, E. L.; Reissig, H.-U. *J. Org. Chem.* **1985**, *50*, 242-244. b) Kunkel, E.; Reichelt, I.; Reissig, H.-U. *Liebigs Ann. Chem.* **1984**, 512-530. c) Reichelt, I.; Reissig, H.-U. *Liebigs Ann. Chem.* **1984**, 531-551. d) Kunkel, E.; Reichelt, I.; Reissig, H.-U. *Liebigs Ann. Chem.* **1984**, 802-819. e) Reichelt, I.; Reissig, H.-U. *Liebigs Ann. Chem.* **1984**, 820-827. f) Reichelt, I.; Reissig, H.-U. *Chem. Ber.* **1983**, *116*, 3895-3914.

36. Benkert, E.; Hesse, M. *Helv. Chim. Acta* **1987**, *70*, 2166-2186.

37. Bhat, V.; Cookson, R. *J. Chem. Soc., Chem. Commun.* **1981**, 1123-1124.

38. Tanaka, M.; Suemune, H.; Sakai, K. *Tetrahedron Lett.* **1988**, *29*, 1733-1736.

39. Milenkov, B.; Süsse, M.; Hesse, M. *Helv. Chim. Acta* **1985**, *68*, 2115-2118.

40. Christau, H. J.; Plénat, F. in *The Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; John Wiley & Sons: New York, 1994; Vol 3, p 149.

41. Some references for general methods of cyclopropanation of alkenes are given below:

a. Carbenes: 1) Doering, W. v. E.; Hoffman, A. K. *J. Am. Chem. Soc.* **1954**, *76*, 6162-6165. 2) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256-4264.
b. Ylides: Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353-1364.
c. Metal carbene complexes: 1) Wulff, W. D.; Yang, D. C.; Murray, C. K. *Pure & Appl. Chem.* **1988**, *60*, 137-144. 2) Murray, C. K.; Yang, D. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1990**, *112*, 5660-5662.
d. Diazomethanes: See reference 12a.

42. Ruder, S. M.; Norwood, B. K. *Tetrahedron Lett.* **1992**, *33*, 861-864.

43. Snyder, J. P.; Bestmann, H. J. *Tetrahedron Lett.* **1970**, *38*, 3317-3320.

44. Cristau, H. J.; Bottaro, D.; Plénat, F.; Pietrasanta, F.; Christol, H. *Phosphorus Sulfur* **1982**, *14*, 63-71.

45. Cristau, H. J.; Bottaro, D.; Plénat, F.; Pietrasanta, F.; Christol, H. *Phosphorus Sulfur* **1982**, *14*, 73-80.

46. Linderman, R. J.; Meyers, A. I. *Tetrahedron Lett.* **1983**, *24*, 3043-3046.

47. Khandker, M. N. I.; Ahmad, A.; Hossain, M.G. *Indian J. Chem.* **1987**, *26B*, 773-775.

48. Garst, M. E.; Spencer, T. A. *J. Org. Chem.* **1974**, *39*, 584-585.

49. Keogh, P. T.; Grayson, M. J. *J. Org. Chem.* **1964**, *29*, 631-635.

50. Schweizer, E. E.; Bach, R. D. *J. Org. Chem.* **1964**, *29*, 1746-1751.

51. Trost, B. M.; Melvin, L. S., Jr. *Sulfur Ylides, Emerging Intermediates*; Academic: New York, 1975; p 43.

52. Hammerschmidt, F.; Zbiral, E. *Liebigs Ann. Chem.* **1977**, 1026-1038.

53. Payne, G. B. *J. Org. Chem.* **1967**, *32*, 3351-3355.

54. Moss, R. A. in *Carbenes*; Jones, M., Jr.; Moss, R. A., Eds.; John Wiley & Sons: New York, 1973; Vol. 1, Chapter 2.

55. Kirmse, W. in *Carbene Chemistry*; Academic: New York, 1964; p 1.

56. Ibid, p 163.

57. Ibid, p 204.

58. Moss, R. A., *op. cit.* p 160.

59. Ryu, H. H.; Aya, T.; Otani, S.; Murai, S.; Sonoda, N. *J. Organomet. Chem.* **1987**, *321*, 279-290.

60. Friedrich, E. C.; Lewis, E. J. *J. Org. Chem.* **1990**, *55*, 2491-2494.

61. Lie Ken Jie, M. S. F.; Lam, W. L. K. *J. Am. Oil Chem.* **1988**, *65*, 118-121.

62. Liebowitz, S. M.; Johnson, H. J. *Synth. Commun.* **1986**, *16*, 1255-1259.

63. Christol, H.; Cristau, H. J.; Soleiman, M. *Bull. Soc. Chim. Fr.* **1976**, 161-166.

64. Cristau, H. J.; Plenat, F. *op. cit.* p 112.

65. Nace, H. R.; Monagle, J. J. *J. Org. Chem.* **1959**, *24*, 1792 - 1793.

66. Imamoto, T.; Takiyama, N. *Tetrahedron Lett.* **1987**, *28*, 1307-1308.

67. a) Handa, Y.; Inanaga, J.; Yamaguchi, M. *J. Chem. Soc., Chem. Commun.* **1989**, 298-299. b) Zhang, Y.; Lin, R. *Syn. Comm.* **1987**, *17*, 329-332.

68. S. M. Ruder, unpublished results.

69. Ruder, S. M. *Tetrahedron Lett.* **1992**, *33*, 2621-2624.

70. Burton, D. J.; Naae, D. G. *J. Am. Chem. Soc.* **1973**, *95*, 8467-8468.

71. a) Formation of the LiTMP: Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 582-584. An accompanying article (ibid, pp. 581-582) discusses some synthetic applications of the base. b) LiTMP in preparing methoxycarbenes: Olofson, R. A.; Lotts, K. D.; Barber, G. N. *Tetrahedron Lett.* **1976**, *42*, 3779-3782.

72. Imamoto, T.; Takeyama, T.; Kusumoto, T. *Chem. Lett.* **1985**, 1491-1492.

73. a) Horner, L.; Balzer, W. D. *Tetrahedron Lett.* **1965**, 1157-1162. b) Marsi, K. *J. Org. Chem.* **1974**, *39*, 265-267.

74. Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 3173-3179.

75. Barbier, P. *C. R. Acad. Sci. Paris* **1899**, *128*, 110.

76. Sato, Y.; Ogawa, M.; Kojima, H.; Takeuchi, M.; Shirai, H. *Yakugaku Zasshi* **1974**, *94*, 75-79; *Chem. Abstr.* **1974**, *80*, 108088a.

77. Chopard, P. A.; Hudson, R. F.; Klopman, G. *J. Chem. Soc.* **1965**, 1379-1386.

78. Ding, M. X. Master's Thesis, Virginia Commonwealth University, December, 1994.

79. Clark, R. D.; Untch, K. G. *J. Org. Chem.* **1979**, 44, 248-253.

80. Brannock, K. C.; Burpitt, R. D.; Goodlett, V. W.; Thweatt, J. G. *J. Org. Chem.* **1964**, *29*, 818-823.

81. Huebner, C. F.; Dorfman, L.; Robison, M. M.; Donoghue, E.; Pierson, W. G.; Strachan, P. *J. Org. Chem.* **1963**, *28*, 3134-3140.

82. Berchtold, G. A.; Uhlig, G. F. *J. Org. Chem.* **1963**, *28*, 1459-1462.

83. a) Fex, T.; Froborg, J.; Magnusson, G.; Thorèn, S. *J. Org. Chem.* **1976**, *41*, 3518-3520. b) Froborg, J.; Magnusson, G. *J. Am. Chem. Soc.* **1978**, 100, 6728-6733.

84. Ruder, S. M.; Kulkarni, V. R. *J. Chem. Soc., Chem. Commun.* **1994**, 2119-2120.

85. a) Chattha, M. S.; Aguiar, A. M. *Tetrahedron Lett.* **1971**, 1419-1420. b) Minami, T.; Nishimura, K.; Hirao, I.; Suganuma, H.; Agawa, T. *J. Org. Chem.*, **1982**, *47*, 2360-2363. c) Darling, S. D.; Muralidharan, F. N.; Muralidharan, V. B. *Tetrahedron Lett.* **1979**, 2757-2760. d) Minami, T.; Suganuma, H.; Agawa, T. *Chem. Lett.* **1978**, 285-288.

86. a) For a reaction of alkynyl phosphonates with enamines, see: Darling, S. D.; Subramanian, N. *Abs. Pap. Am. Chem. Soc.* **19(#98)**; also: Subramanian, N. Ph.D. Dissertation, University of Ohio, December, 1975.

87. Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207-222.

88. a) Chattha, M. S.; Aguiar, A. M. *J. Org. Chem.* **1971**, *36*, 2719. b) Burt, D. W.; Simpson, P. *J. Chem. Soc. (C)* **1969**, 2273-2276. c) Acheson, R. M.; Ansell, P. J.; Murray, J. R. *J. Chem. Res.* **1986**, (M) 3001-3019.

89. West, R.; Quass, L. C. *J. Organomet. Chem.* **1969**, *18*, 55-67.

90. Viehe, H. G. *Chem. Ber.* **1959**, *92*, 3064-3075.

91. Bakassian, G.; Bazouin, A. Fr. Patent 2 079 814, 1970; Gr. Patent 2 106 702, 1971; *Chem. Abstr.* **1971**, *75*, 129933j.

92. Unpublished results of research conducted by Craig Hodge, undergraduate research exchange student from Great Britain, whose help is here gratefully acknowledged.

93. Hirsch, J. A.; Cross, F. J. *J. Org. Chem.* **1971**, *36*, 955-960.

94. Pascual, J. M.; Simon, W. *Helv. Chim. Acta* **1966**, *49*, 164-168.

95. ^{13}C NMR chemical shifts as predicted by the ChemWindow ^{13}C shift module by Softshell International, Inc., Grand Junction, CO.

96. Ruder and Kulkarni, unpublished results.

97. Additional work by Craig Hodge.

98. British undergraduate Clare Higgins and REU summer student Melissa Maderia prepared cyclic β-keto phosphonates according to the procedures published by Wiemer and co-workers. Their help and support is much appreciated.

99. Formation of cyclic β-keto phosphonates: Lee, K.; Wiemer, D. F. *J. Org. Chem.* **1991**, *56*, 5556-5560. Five and six membered cyclic β-keto phosphonates: Calogeropoulou, T.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1897**, *52*, 4185-4190.

100. a) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Org. Chem.* **1974**, *39*, 2133-2135.
b) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434-5447.

101. Inouye, Y.; Shirai, M.; Michino, T.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 324-326.

102. Lewis, F. D.; Ho, T-I.; DeVoe, R. J. *J. Org. Chem.* **1980**, *45*, 5283-5286.

103. Miyamoto, N.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1257-1260.

104. Oxygen nucleophiles in Michael additions: Duffy, J. L.; Kurth, J. A.; Kurth, M. J. *Tetrahedron Lett.* **1993**, *34*, 1259-1260. Sulfur nucleophiles in Michael additions: McIntosh, J. M.; Steevensz, R. S. *Can. J. Chem.* **1977**, *55*, 2442-2449.

105. Grieco, P. A.; Pogonowski, C. S. *Synthesis*, **1973**, 425-426. British undergraduate student Clare Higgins for her evaluation and optimization of the conditions for this reaction on our own substrates.

106. Aldrich Catalog of Fine Chemicals, 1994/95 edition.

Appendix 1

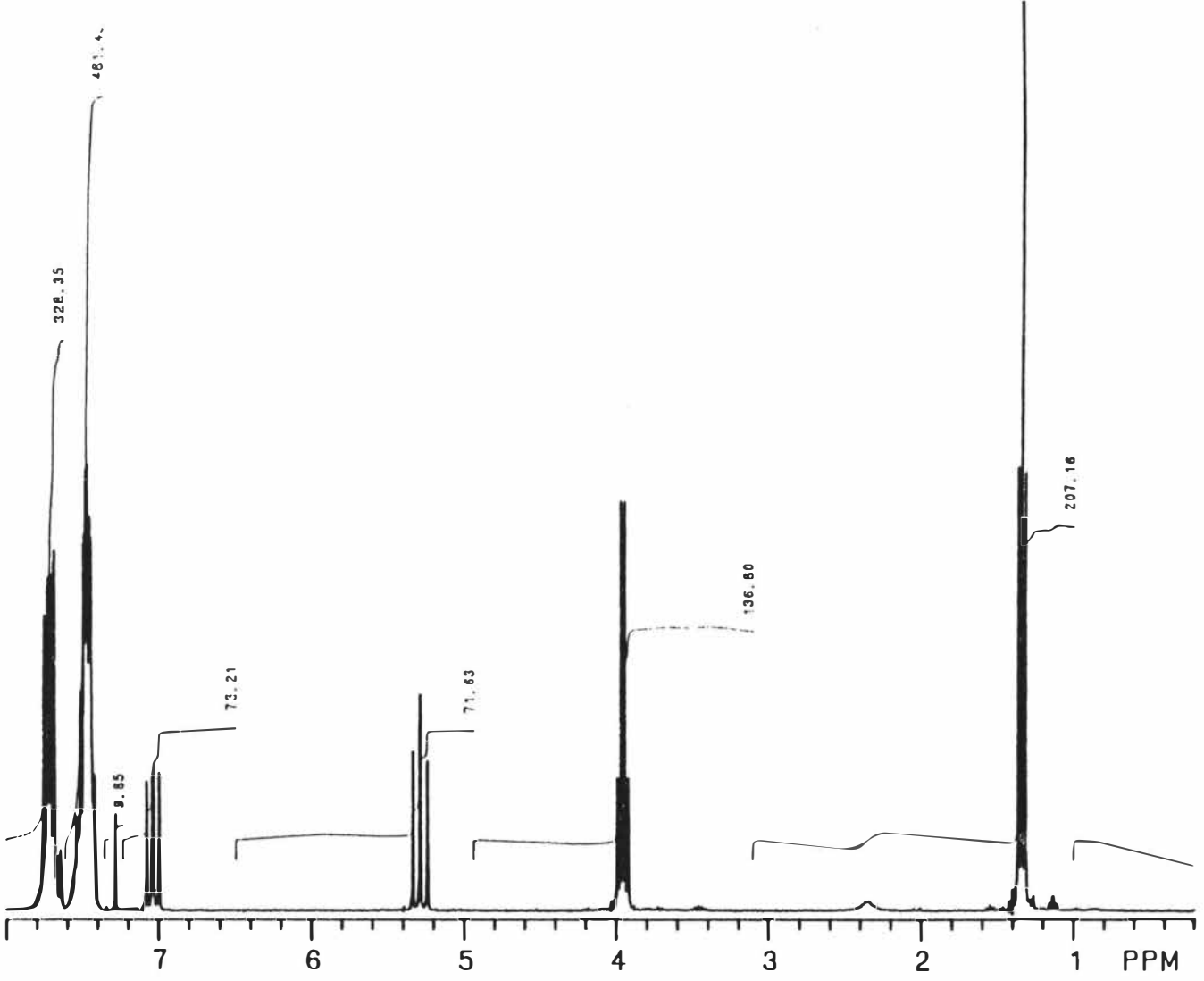


Figure 18: ^{1}H NMR Spectrum of Diphenylphosphine Oxide **68a**.

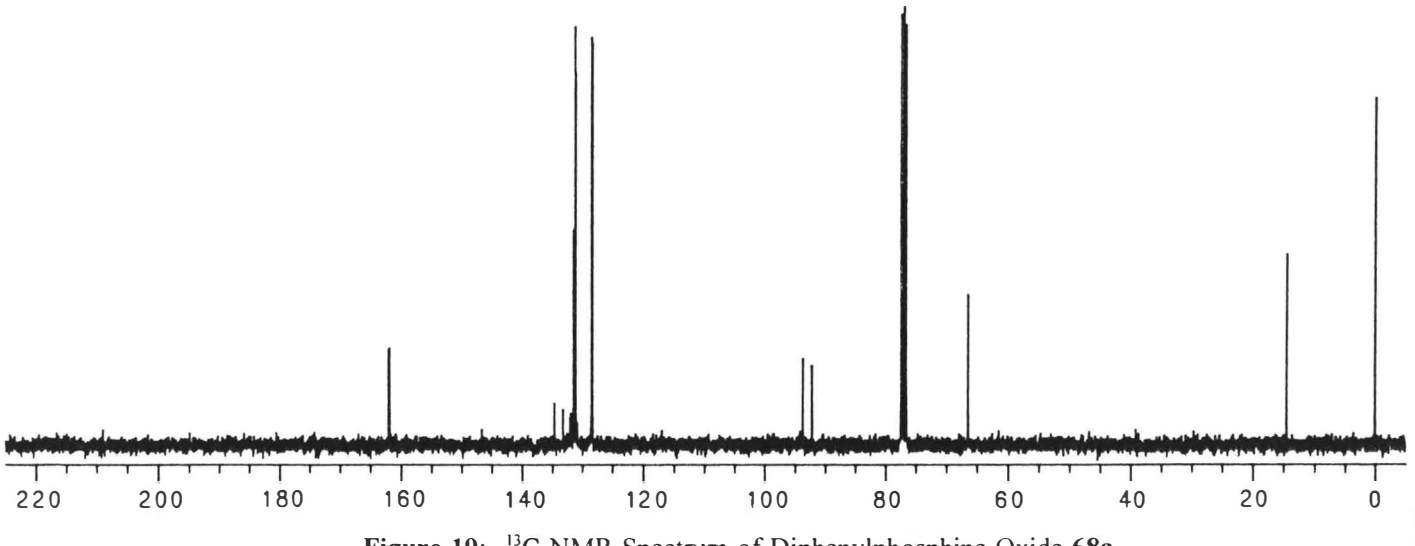


Figure 19: ^{13}C NMR Spectrum of Diphenylphosphine Oxide **68a**.

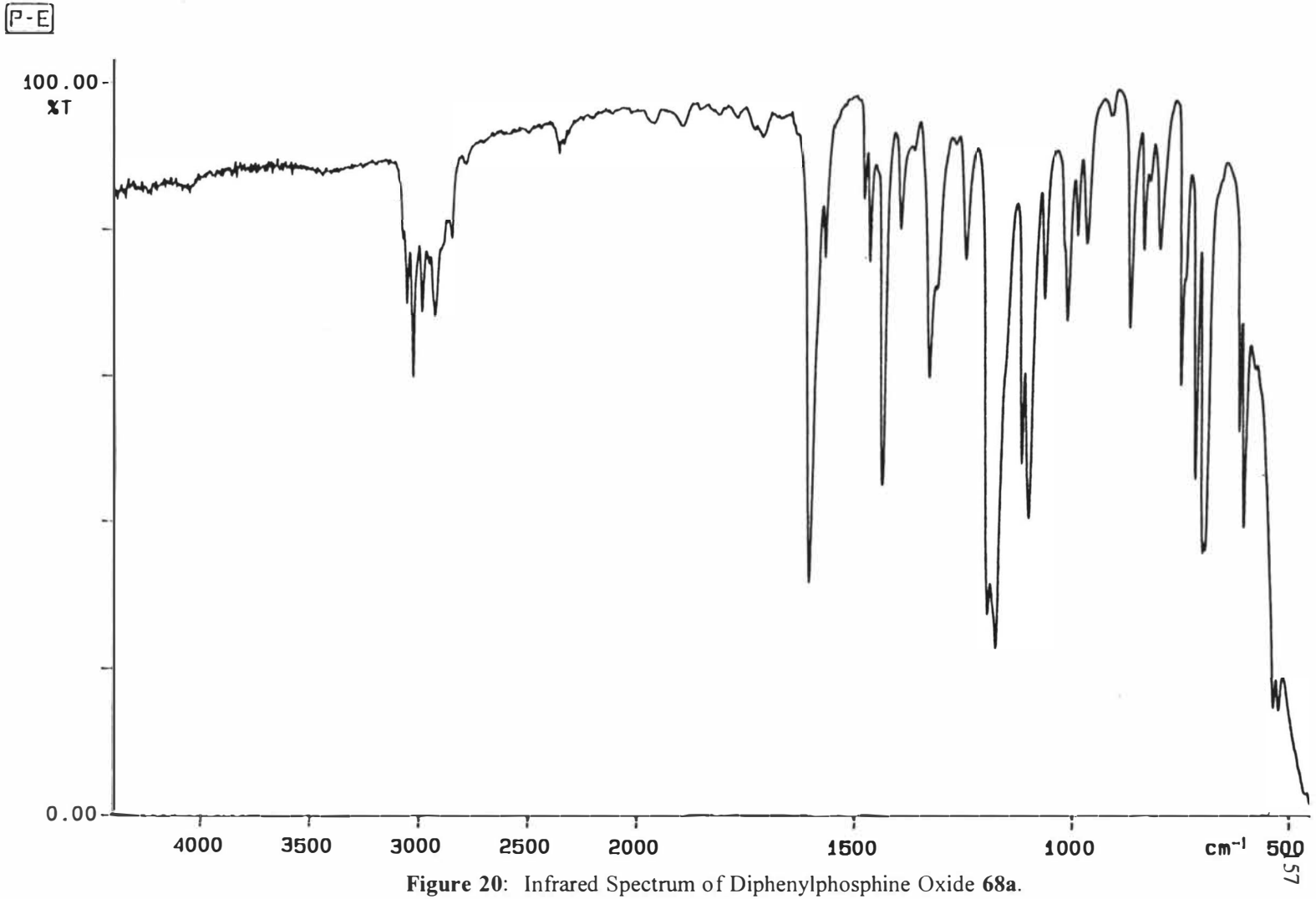


Figure 20: Infrared Spectrum of Diphenylphosphine Oxide **68a**.

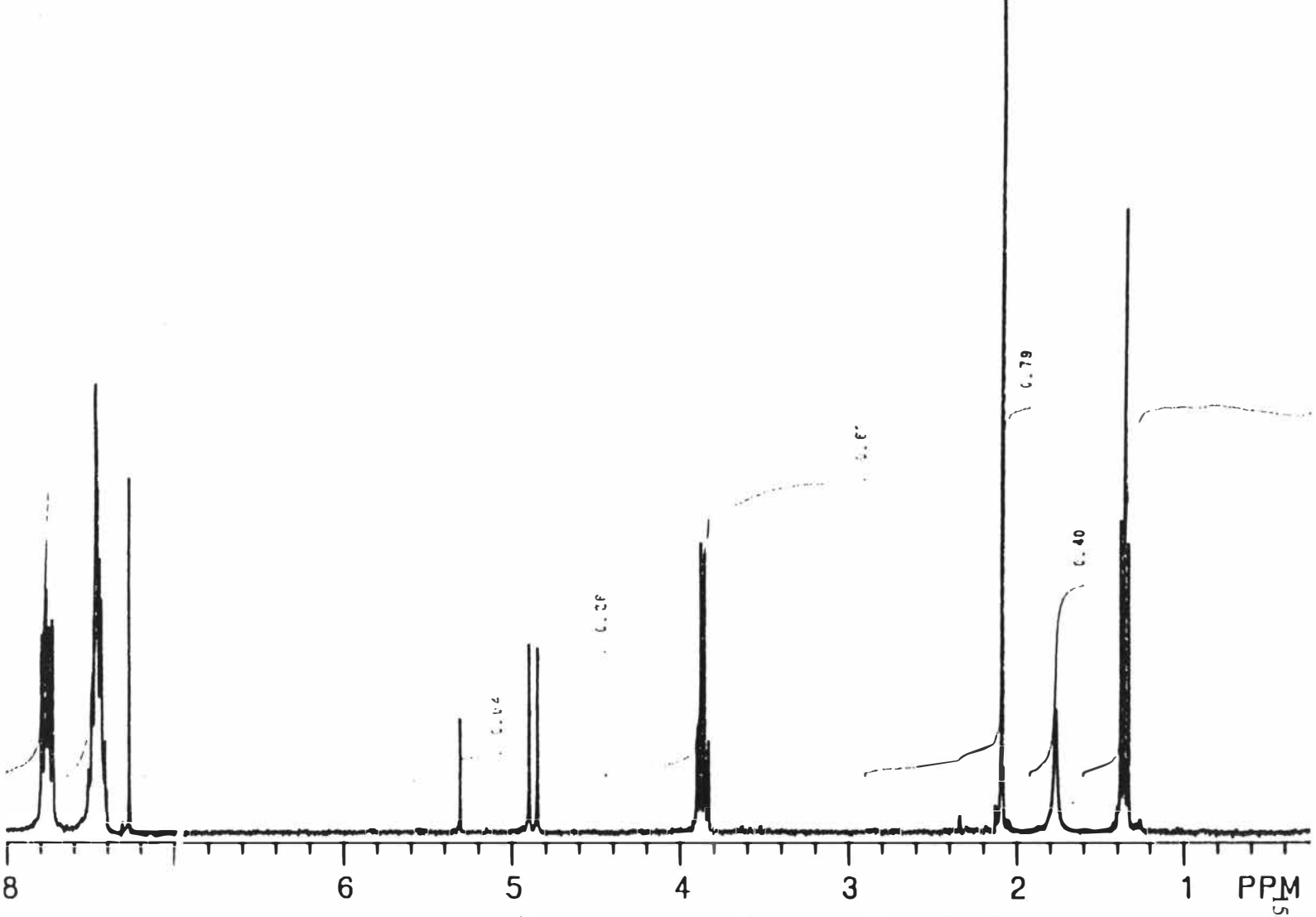


Figure 21: ^{1}H NMR Spectrum of Diphenylphosphine Oxide **68b**.

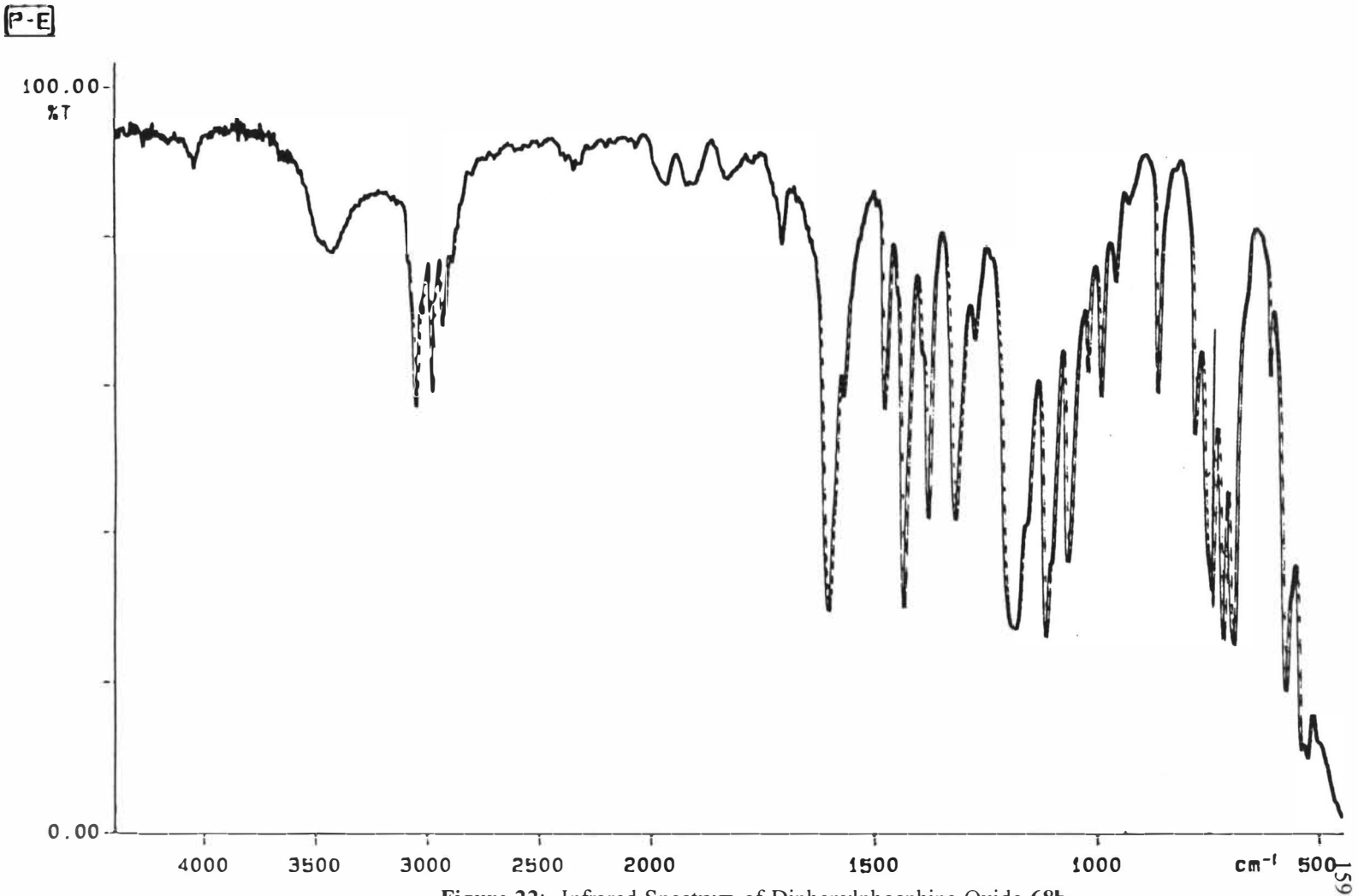


Figure 22: Infrared Spectrum of Diphenylphosphine Oxide **68b**.

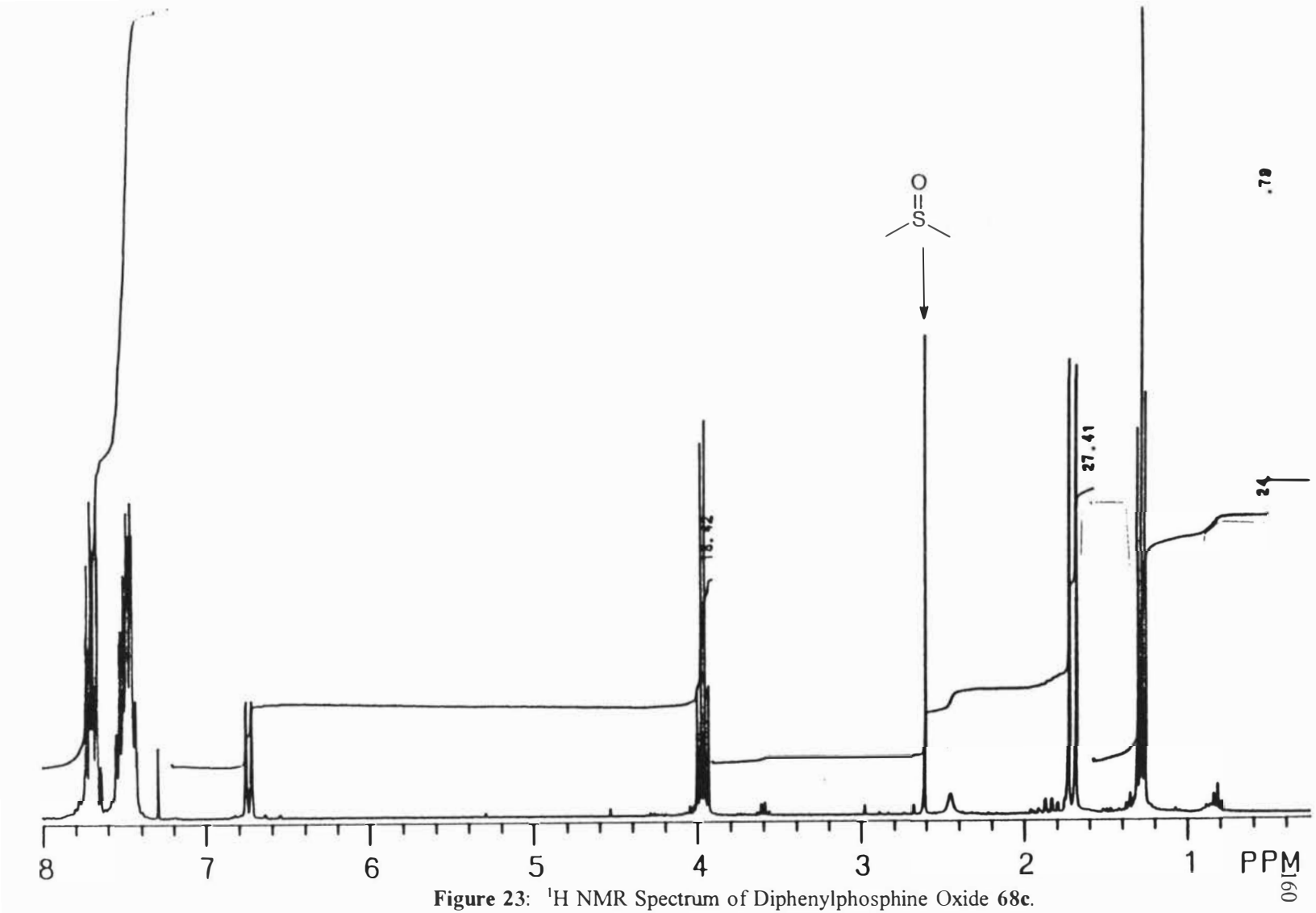


Figure 23: ^{1}H NMR Spectrum of Diphenylphosphine Oxide **68c**.

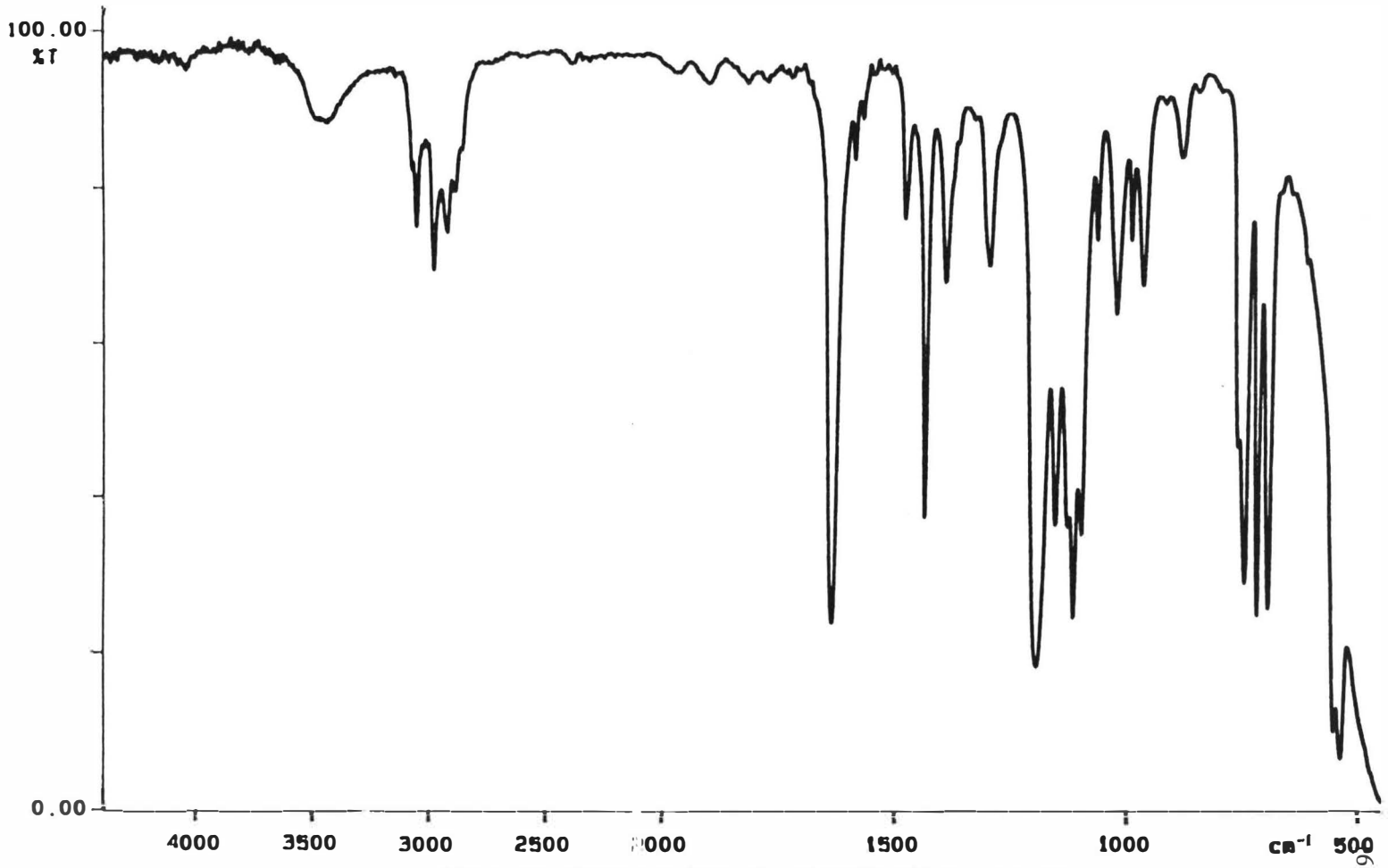


Figure 24: Infrared Spectrum of Diphenylhosphine Oxide **68c**.

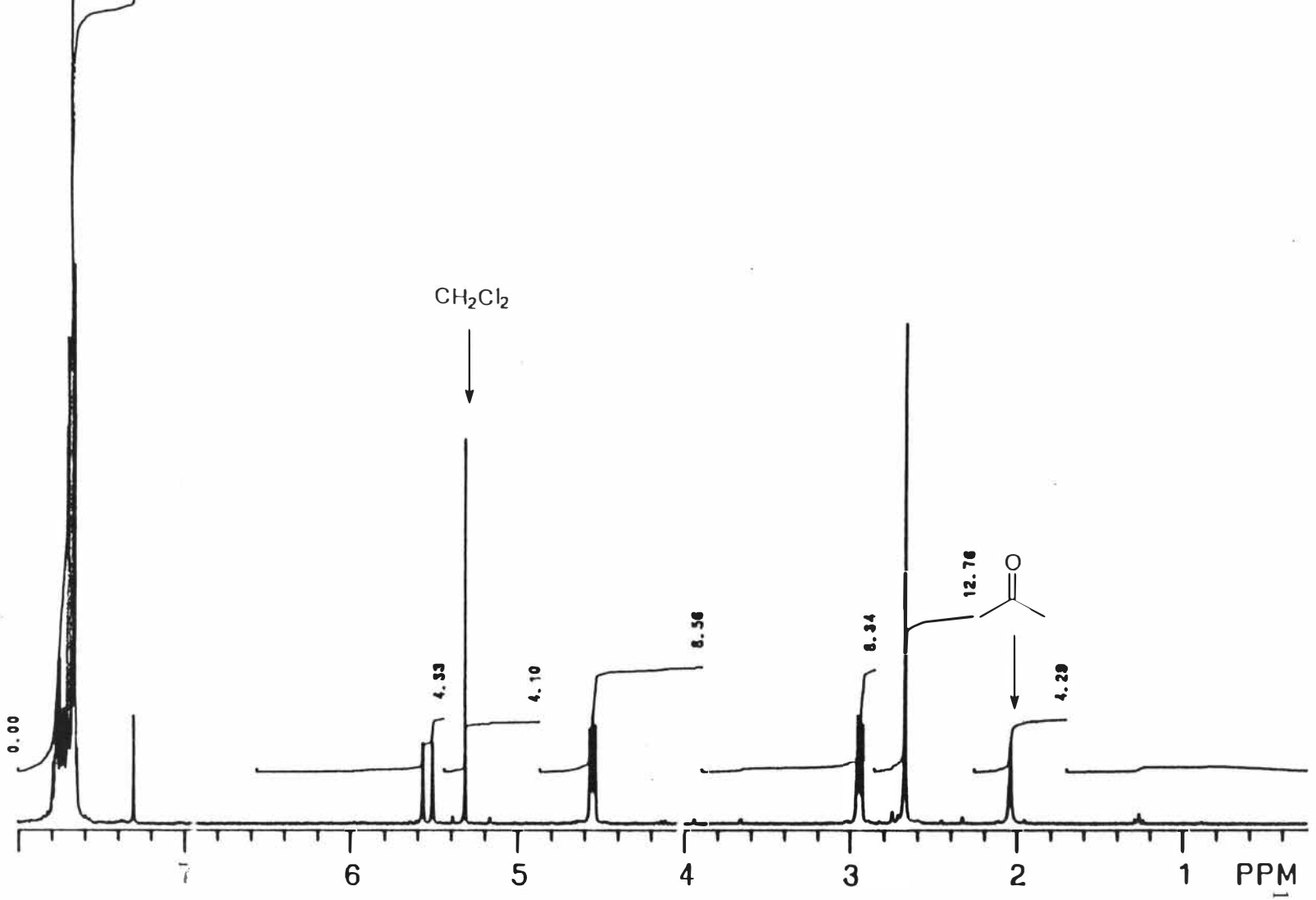


Figure 25: ^{1}H NMR Spectrum of 1-Triphenylphosphinyl-2-(2'-bromo)ethoxypropene (**86**, R = CH_2CH_2Br, R^1 = CH_3).

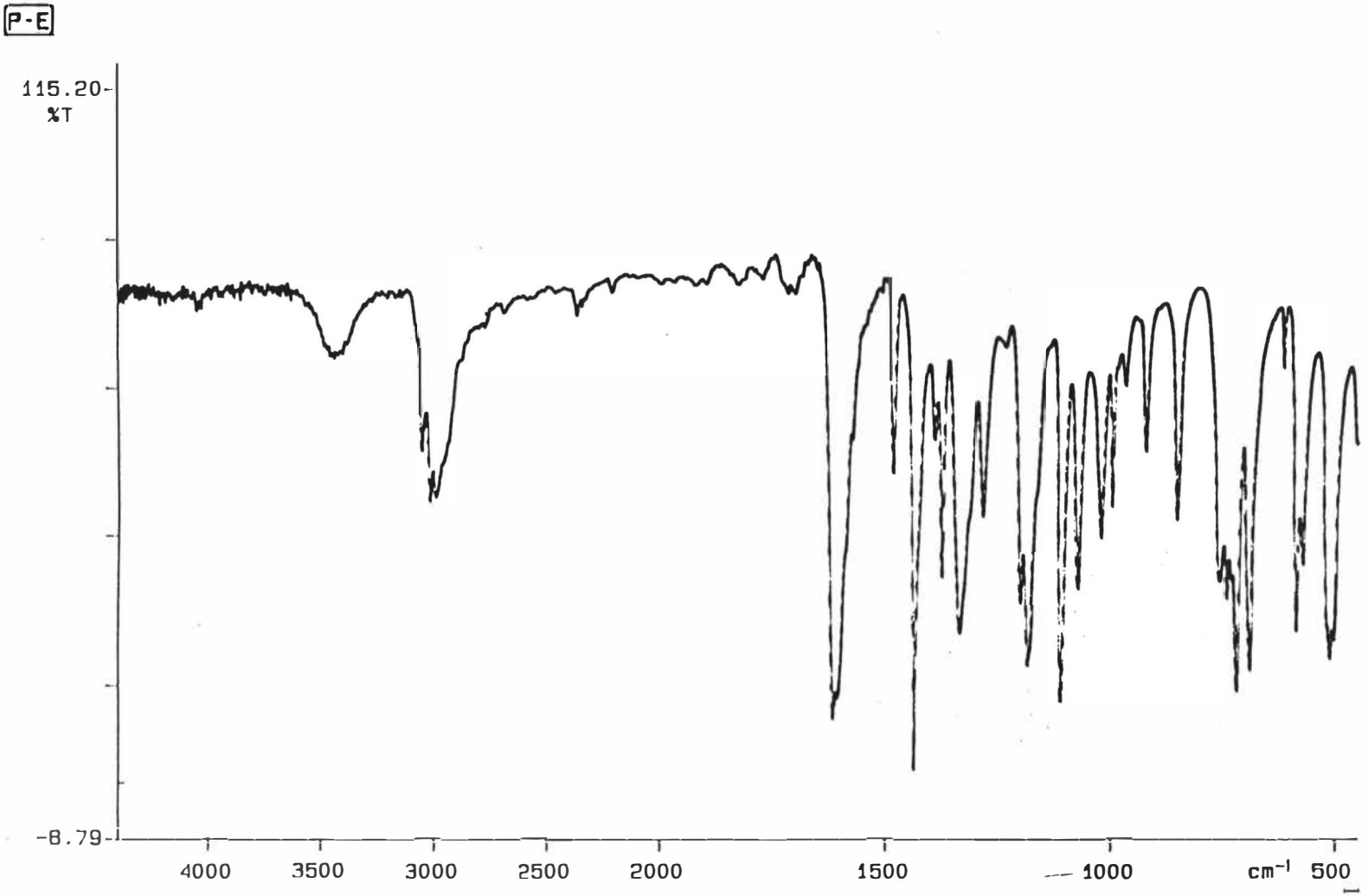


Figure 26: Infrared Spectrum of **86** (R = CH_2CH_2Br, R^1CH_3).

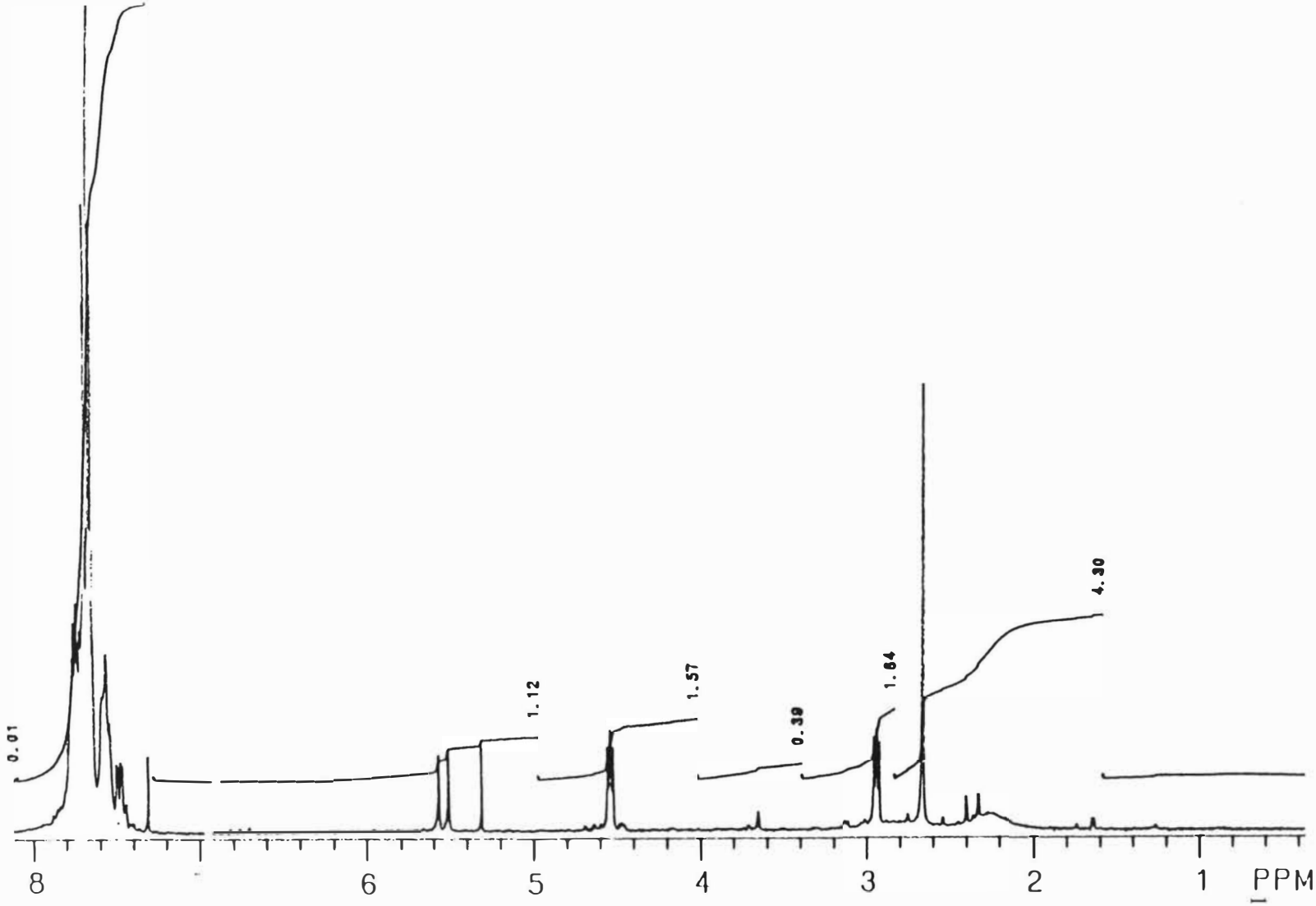


Figure 27: ^{1}H NMR Spectrum of **86** (R = CH_2CH_2Br, R^1 = CH_3) 12% Rearranged to **87**.

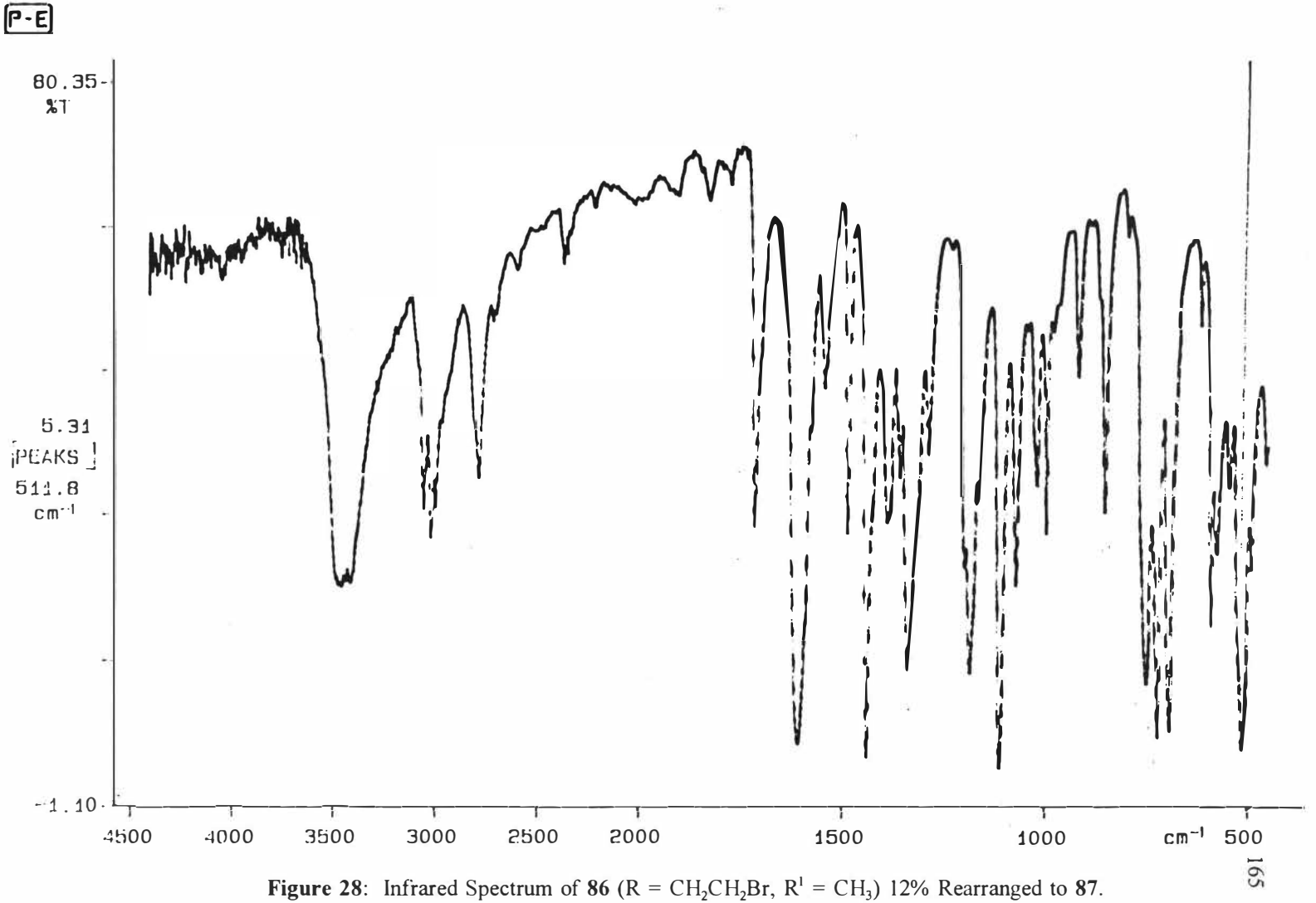


Figure 28: Infrared Spectrum of **86** (R = CH_2CH_2Br, R^1 = CH_3) 12% Rearranged to **87**.

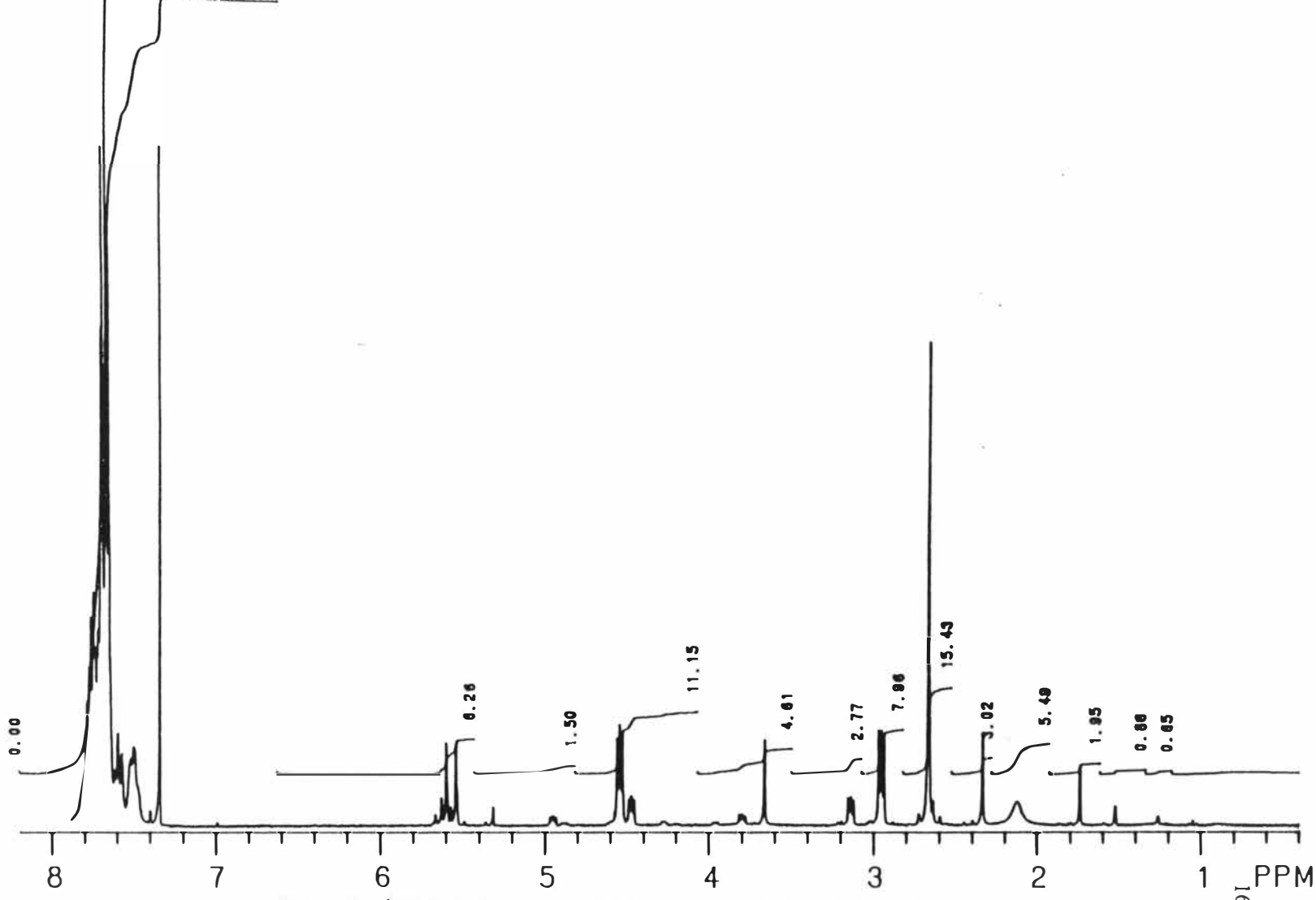


Figure 29: ^{1}H NMR Spectrum of **86** (R = CH_2CH_2Br, R^1 = CH_3) 38% Rearranged to **87**.

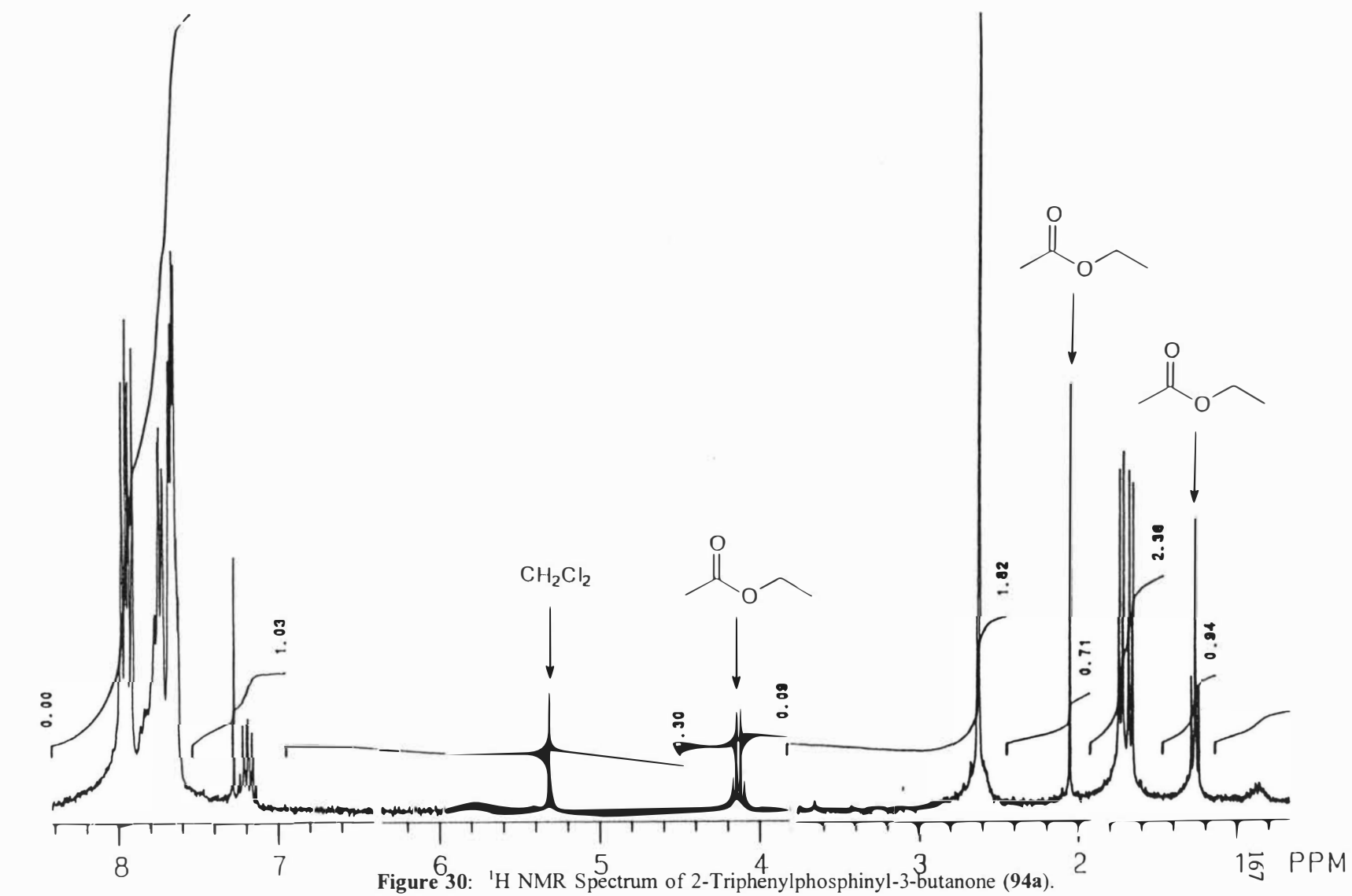


Figure 30: ^{1}H NMR Spectrum of 2-Triphenylphosphinyl-3-butanone (**94a**).

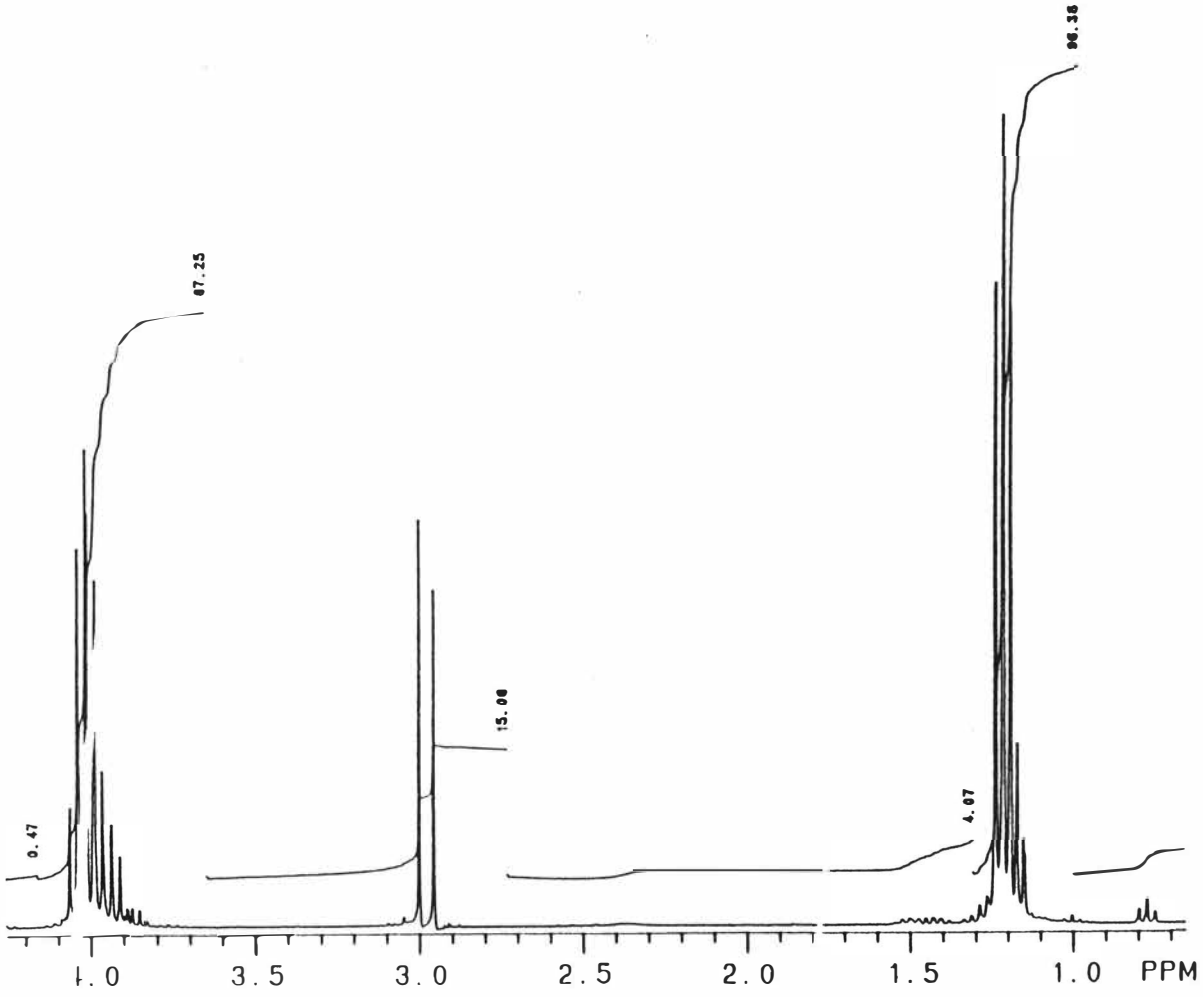


Figure 31: ^{1}H NMR Spectrum of Diethyl Ethynylphosphonate (**106a**).

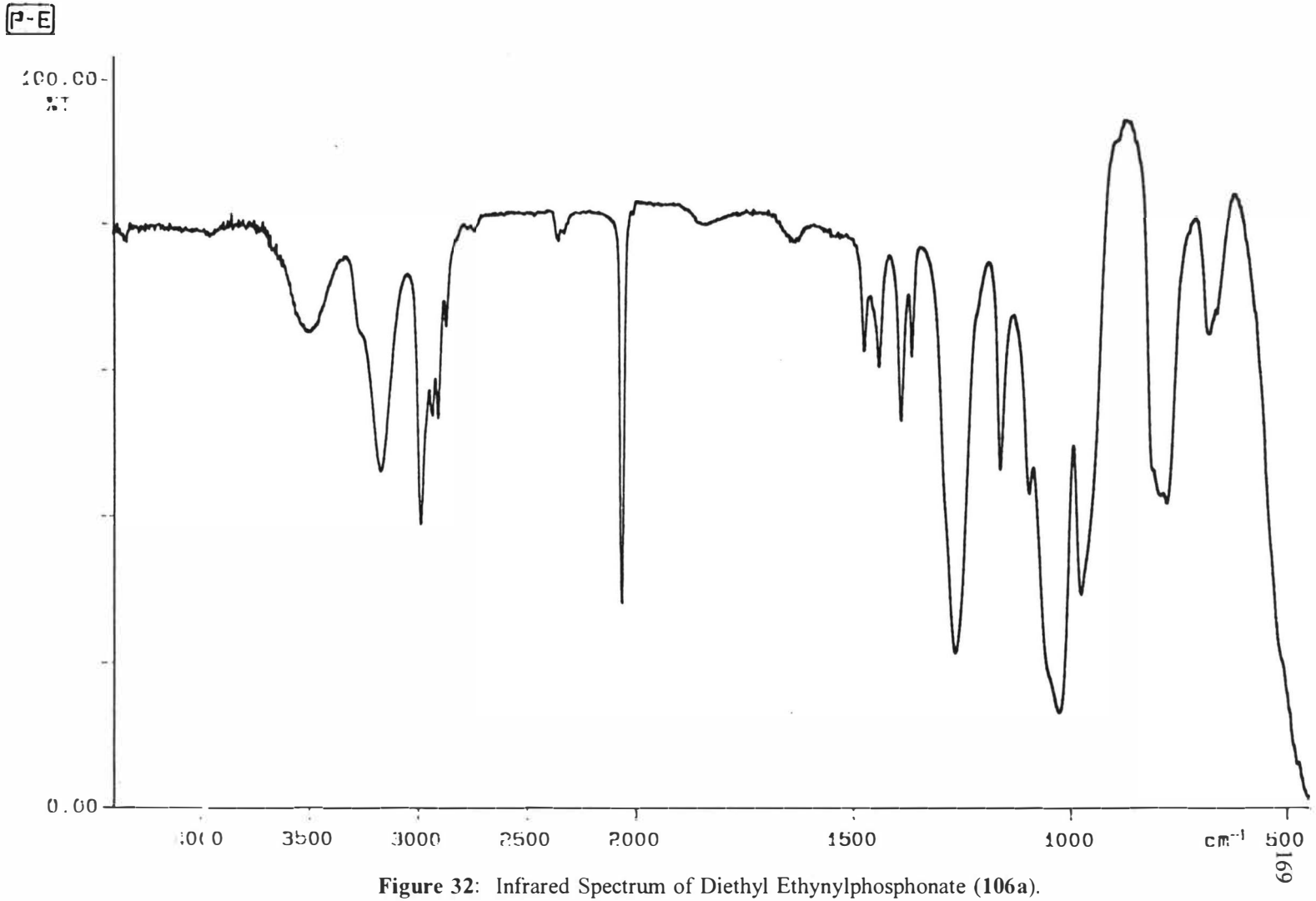


Figure 32: Infrared Spectrum of Diethyl Ethynylphosphonate (**106a**).

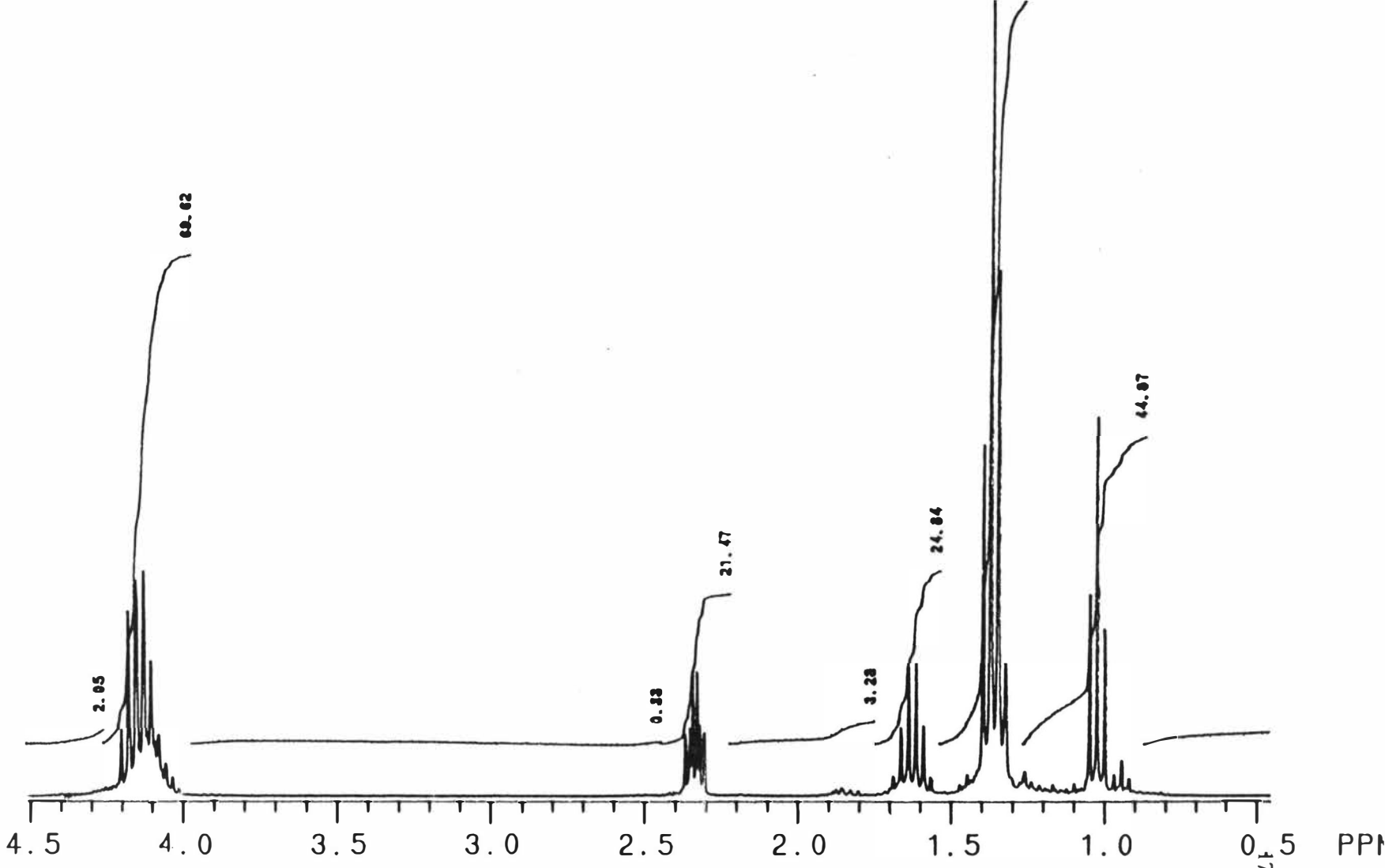


Figure 33: ^{1}H NMR Spectrum of Diethyl Pentynylphosphonate (**106b**).

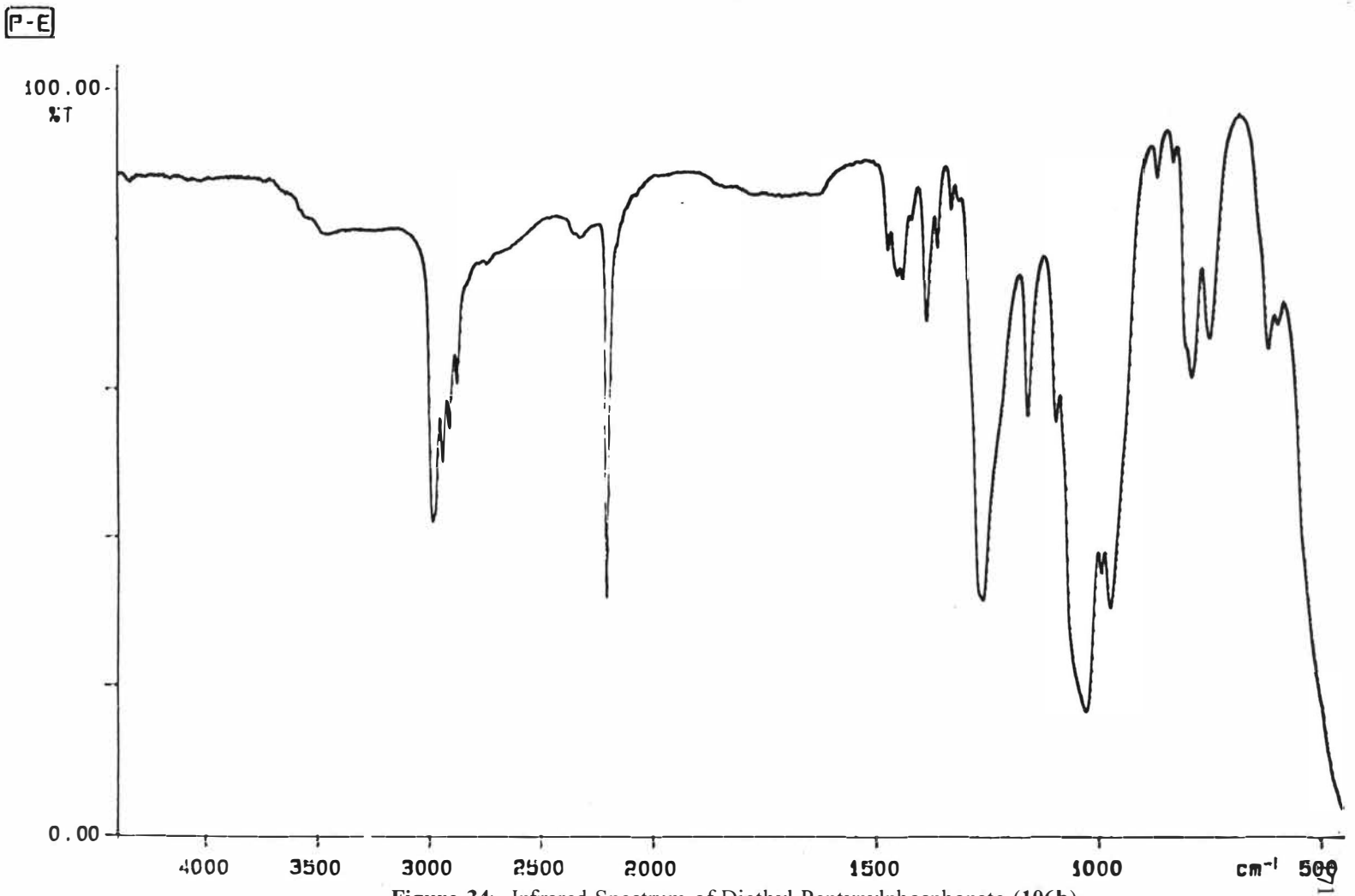


Figure 34: Infrared Spectrum of Diethyl Pentynylphosphonate (**106b**).

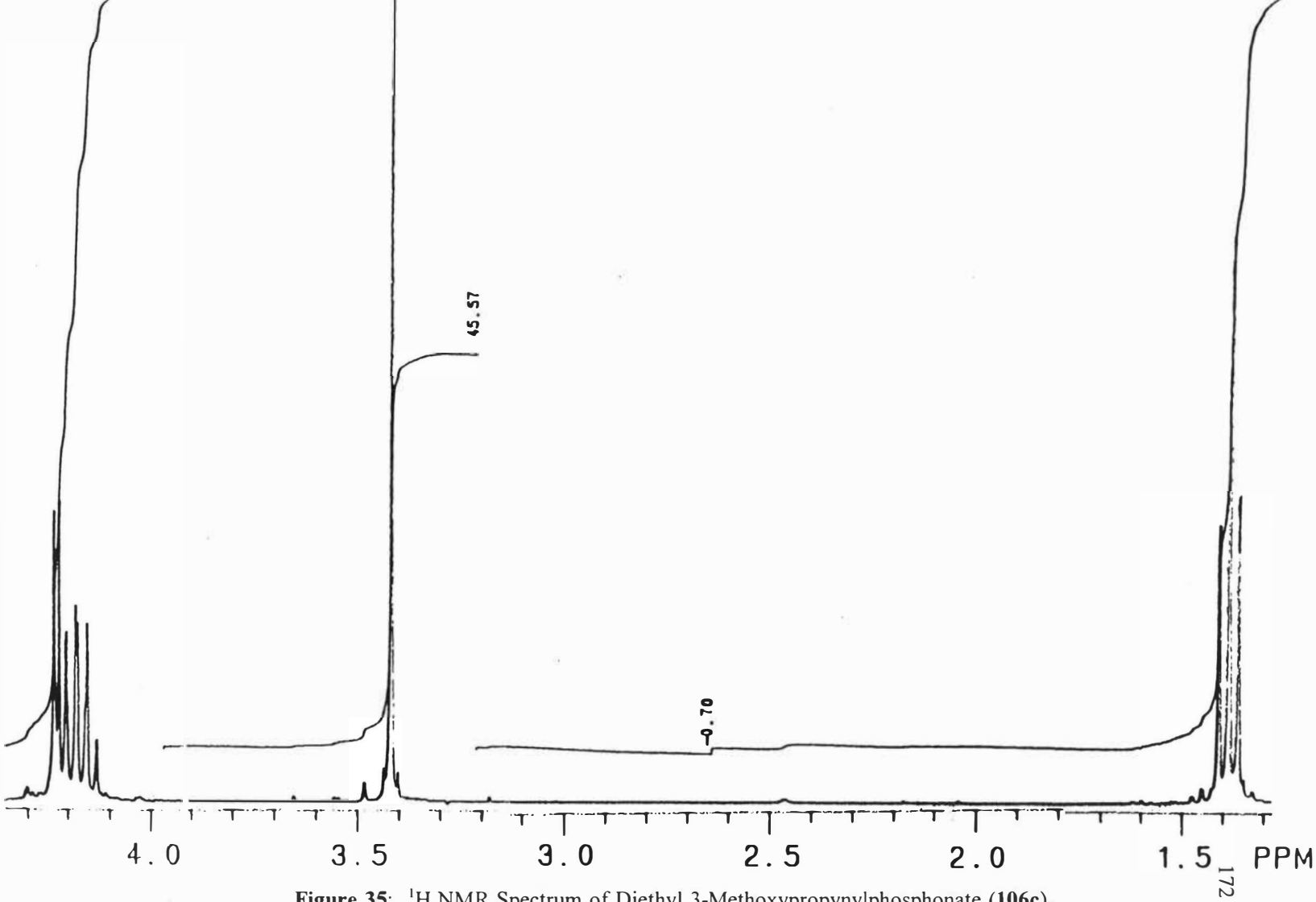


Figure 35: ^{1}H NMR Spectrum of Diethyl 3-Methoxypropynylphosphonate (**106c**).

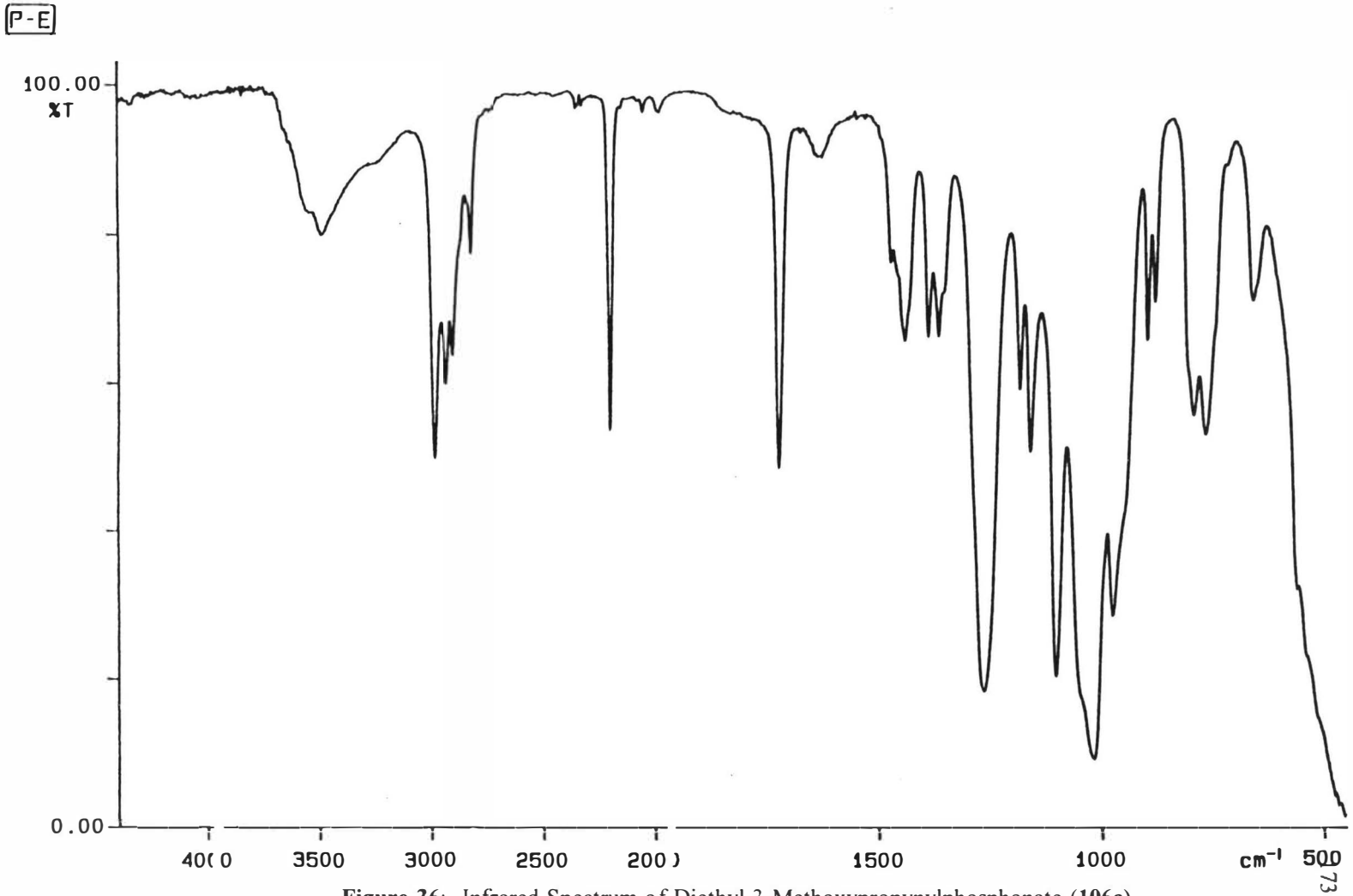


Figure 36: Infrared Spectrum of Diethyl 3-Methoxypropynylphosphonate (**106c**).

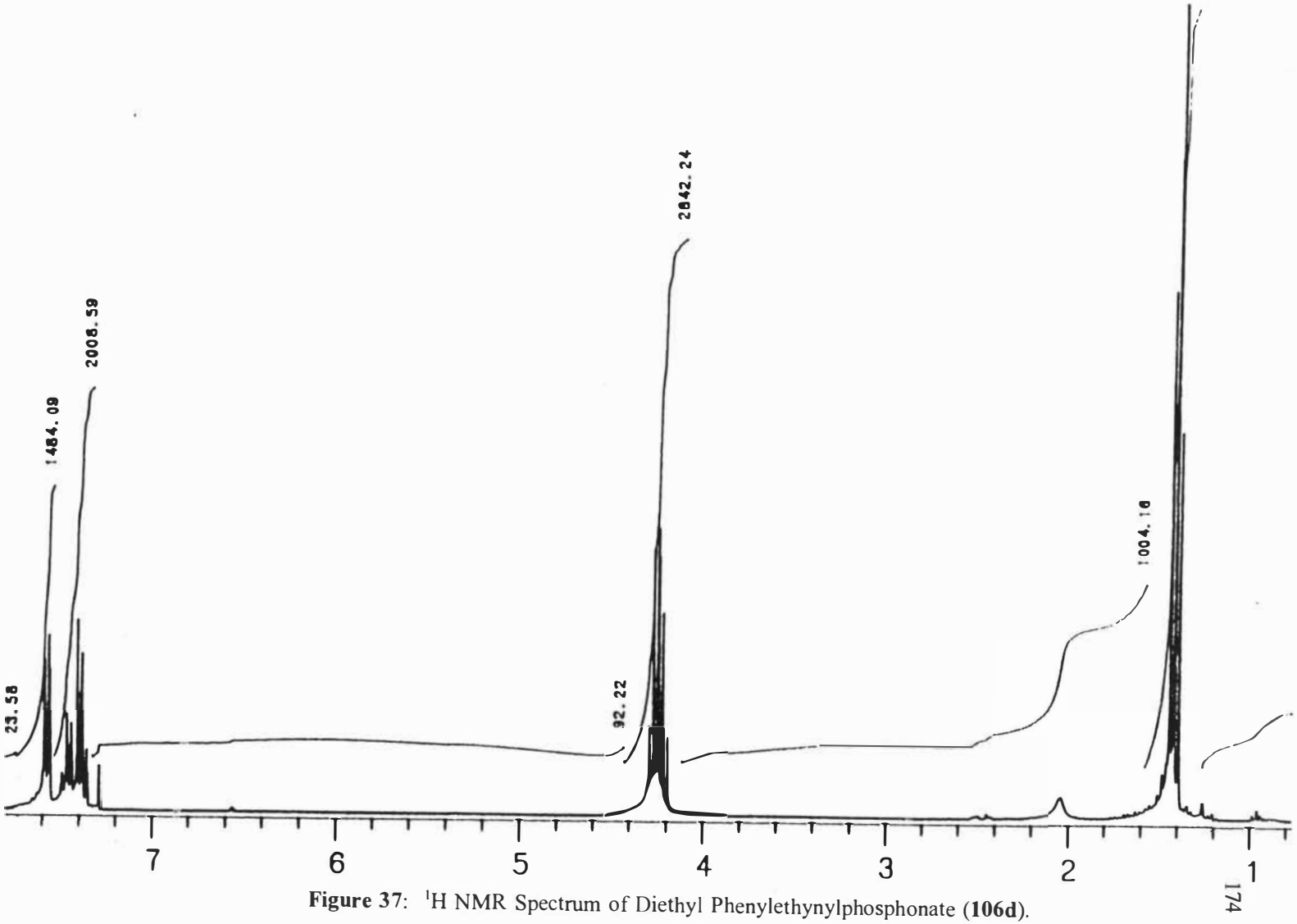


Figure 37: ^{1}H NMR Spectrum of Diethyl Phenylethynylphosphonate (**106d**).

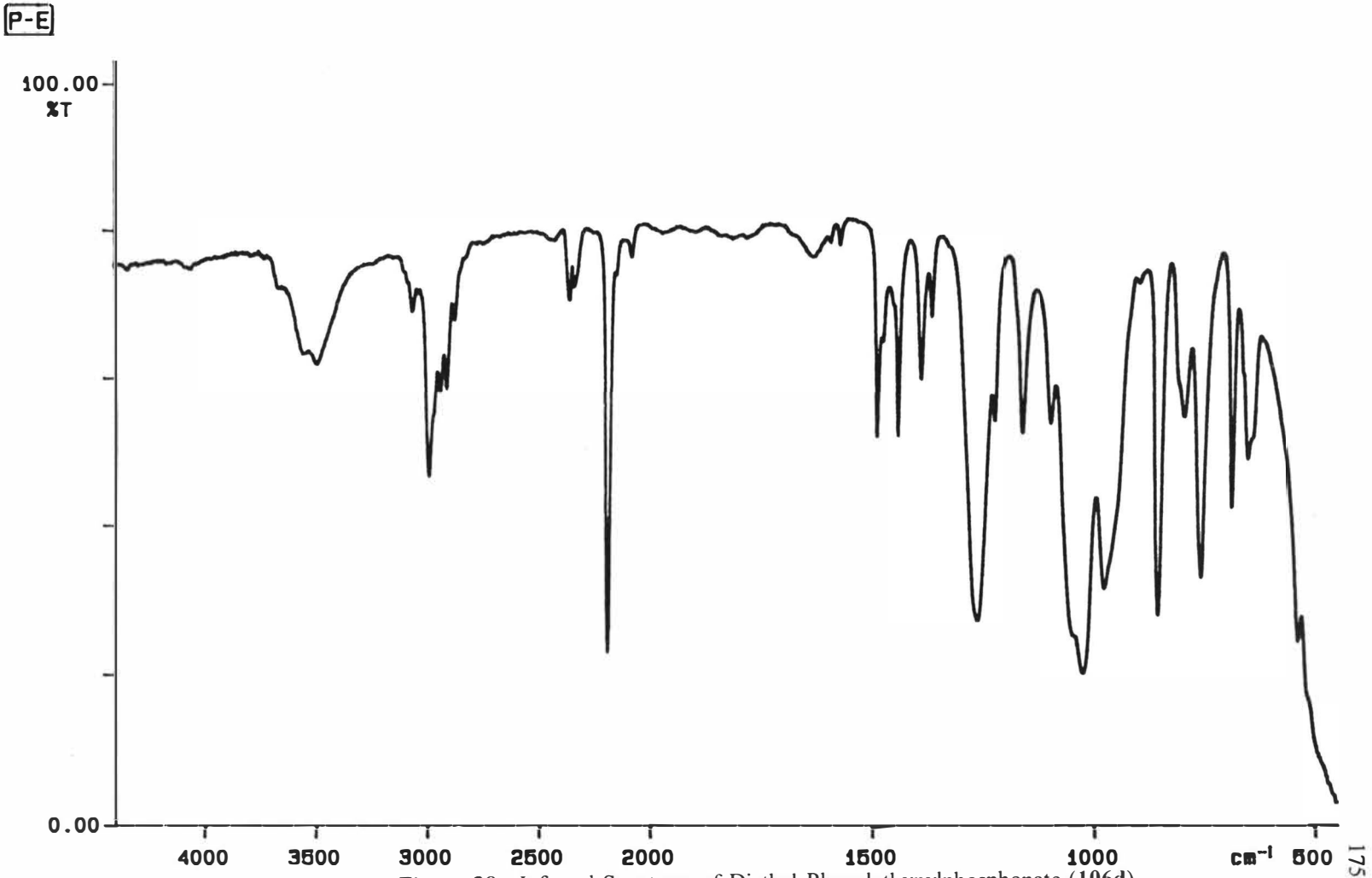


Figure 38: Infrared Spectrum of Diethyl Phenylethynylphosphonate (**106d**).

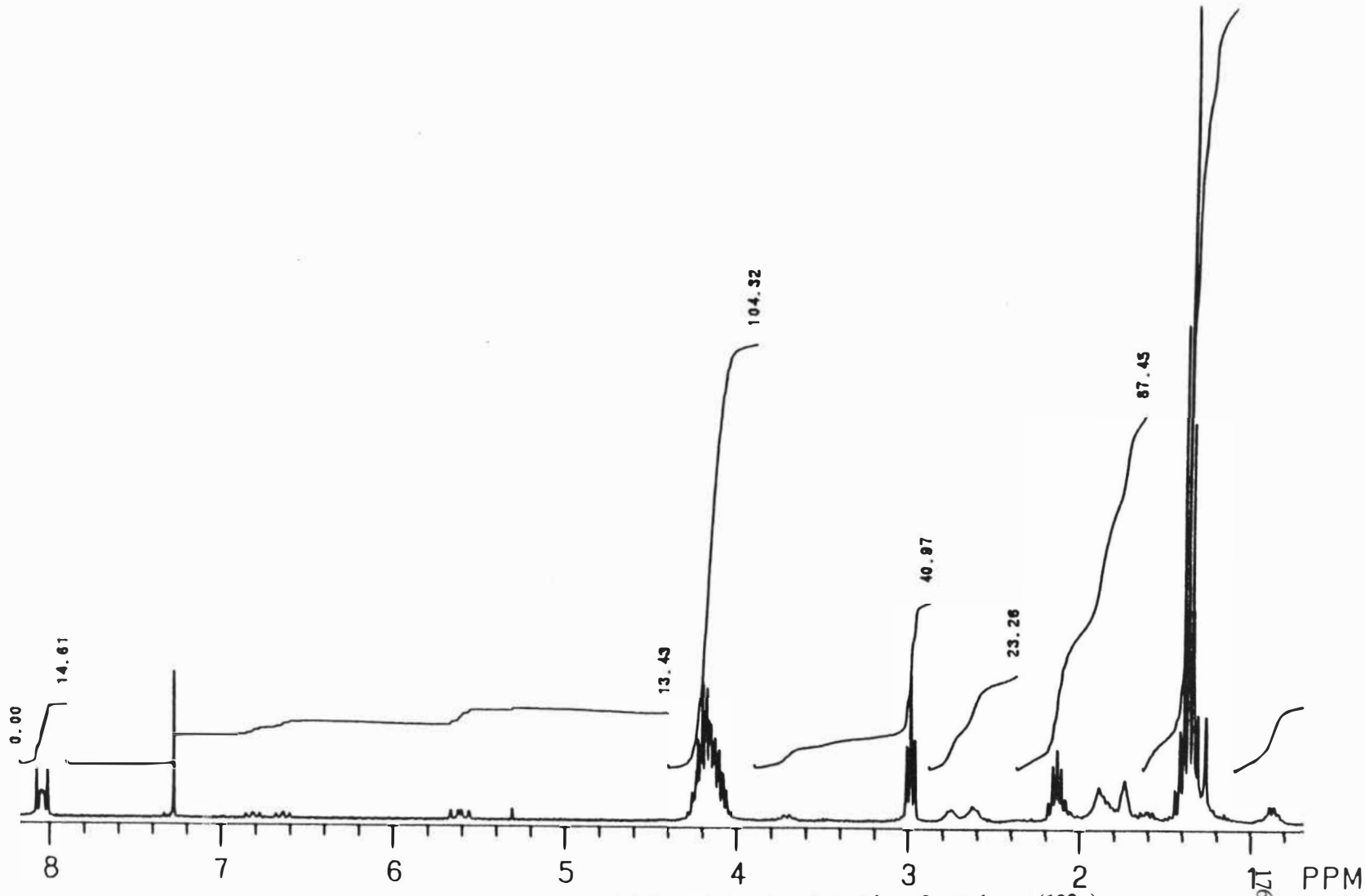


Figure 39: ^{1}H NMR Spectrum of 2-Diethylphosphonyl cyclohept-2-ene-1-one (**122a**).

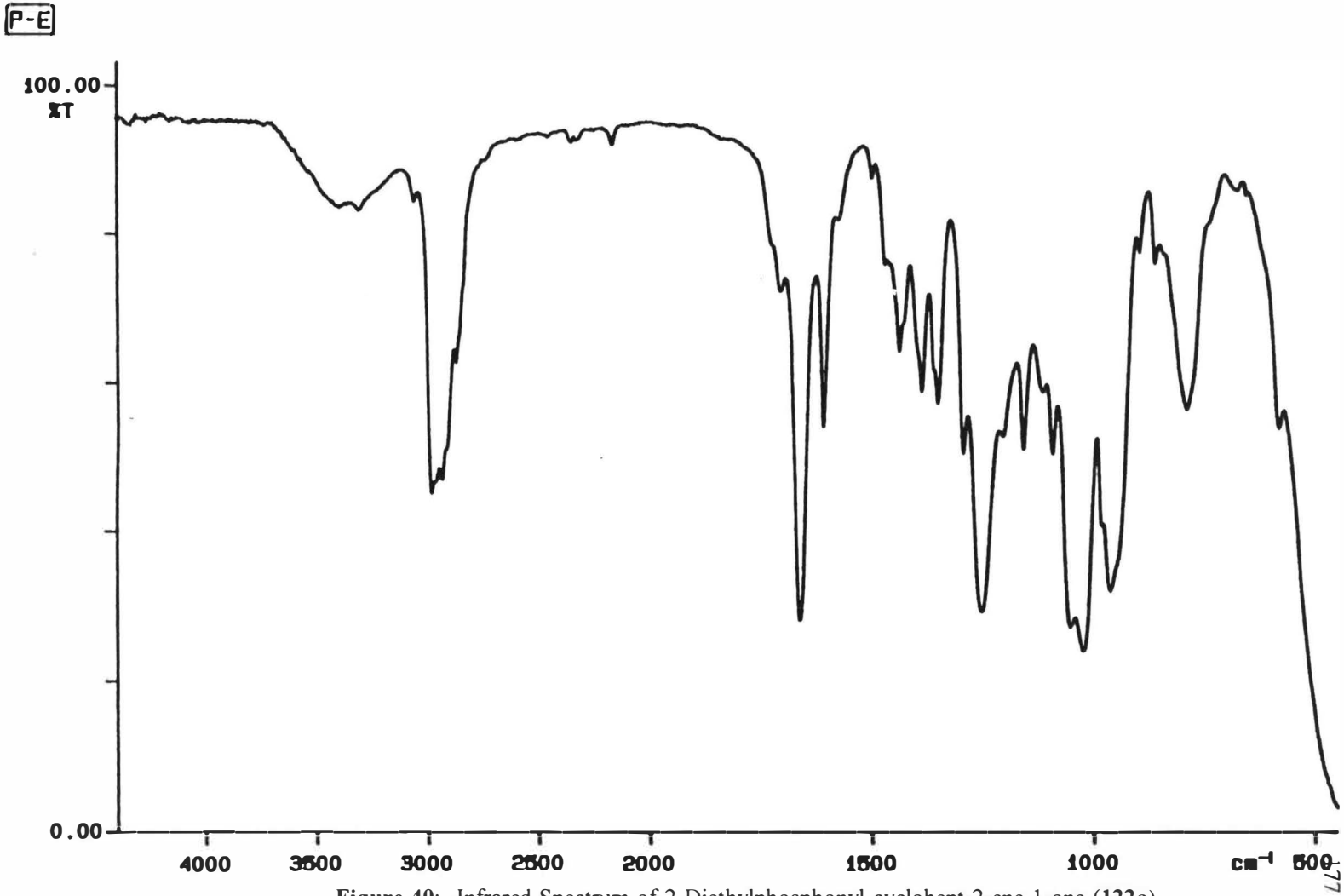


Figure 40: Infrared Spectrum of 2-Diethylphosphonyl cyclohept-2-ene-1-one (**122a**).

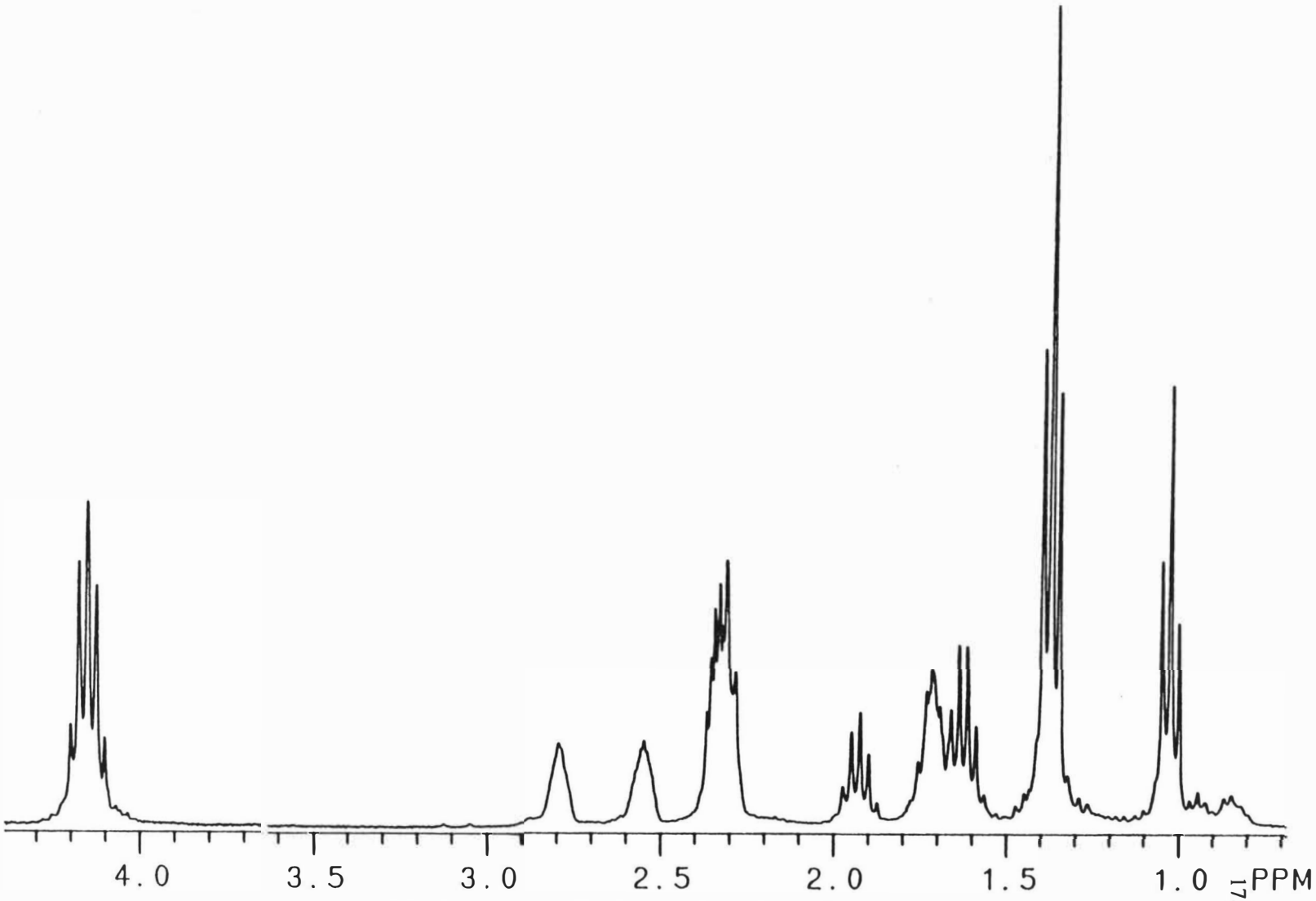


Figure 41: ^{1}H NMR Spectrum of 2-Diethylphosphonyl-3-propyl cyclohept-2-ene-1-one (**122b**).

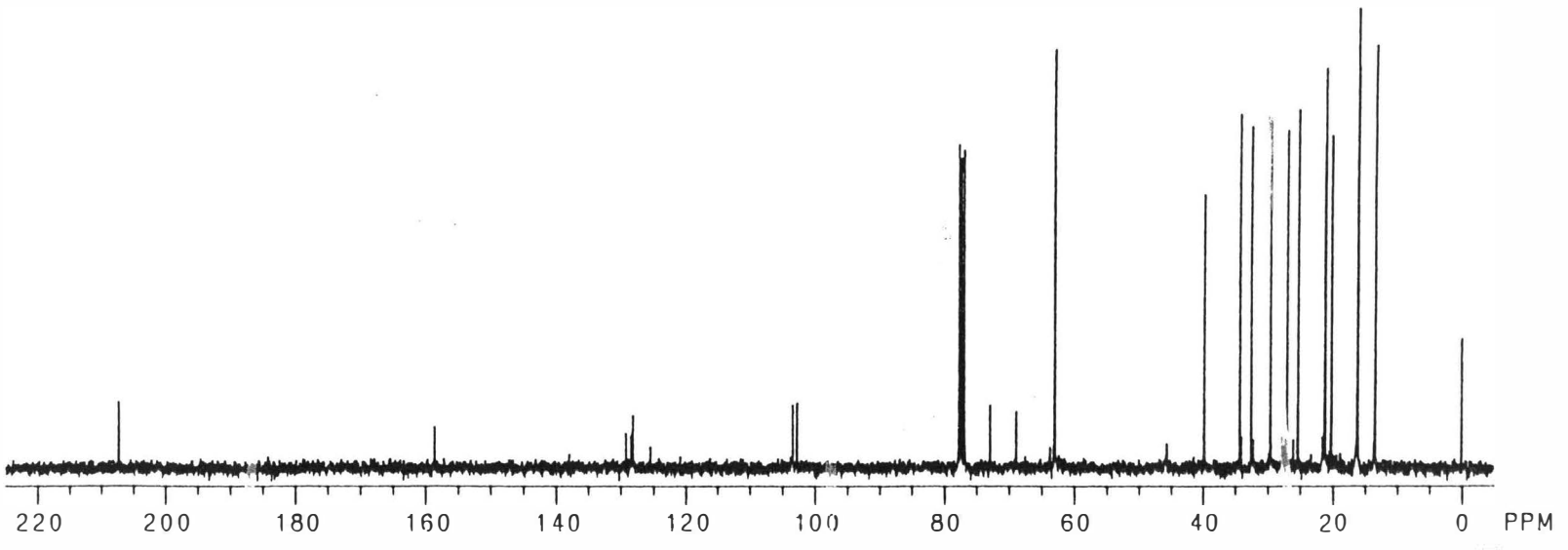


Figure 42: ^{13}C NMR Spectrum of 2-Diethylphosphonyl-3-propyl cyclohept-2-ene-1-one (**122b**).

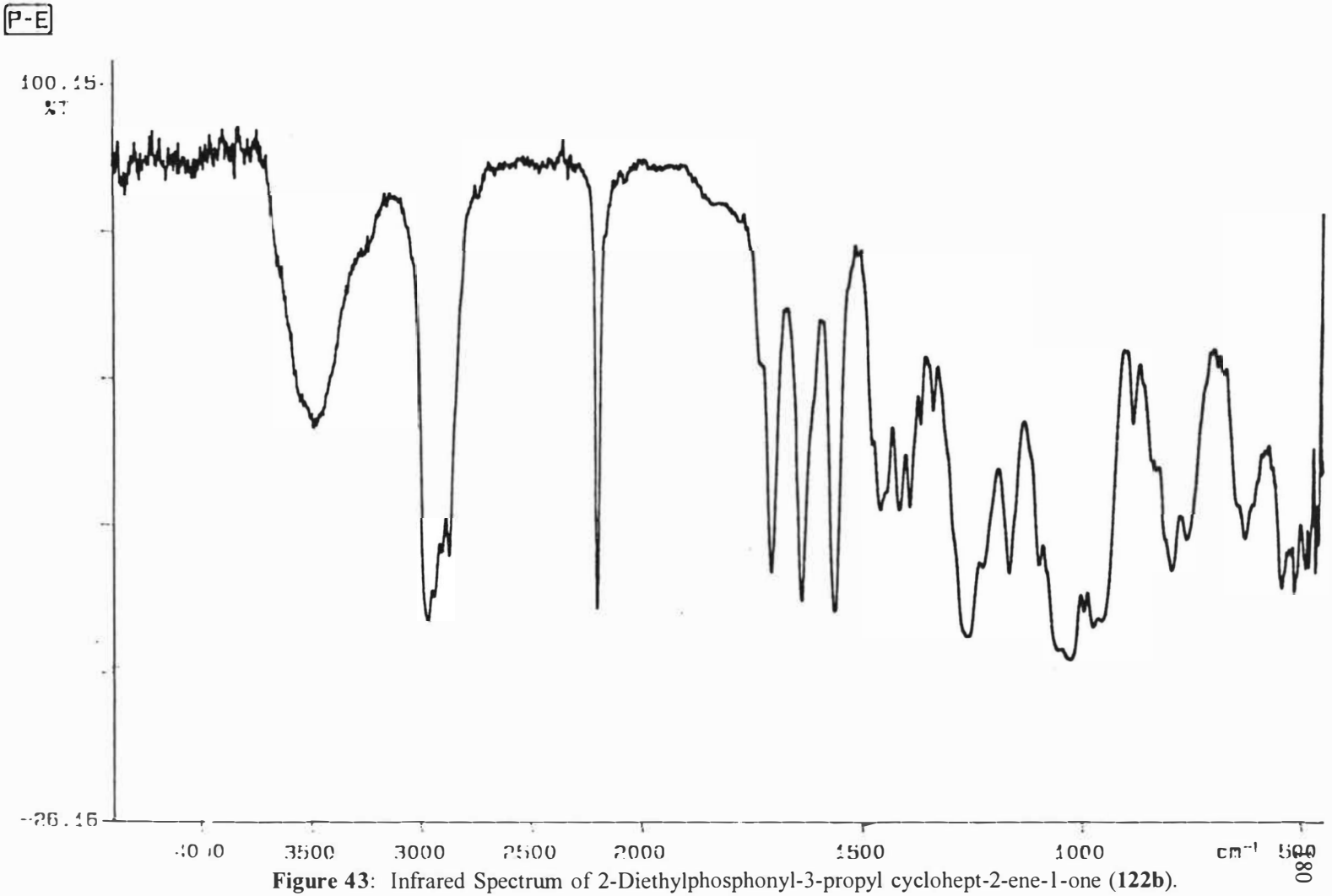


Figure 43: Infrared Spectrum of 2-Diethylphosphonyl-3-propyl cyclohept-2-ene-1-one (**122b**).

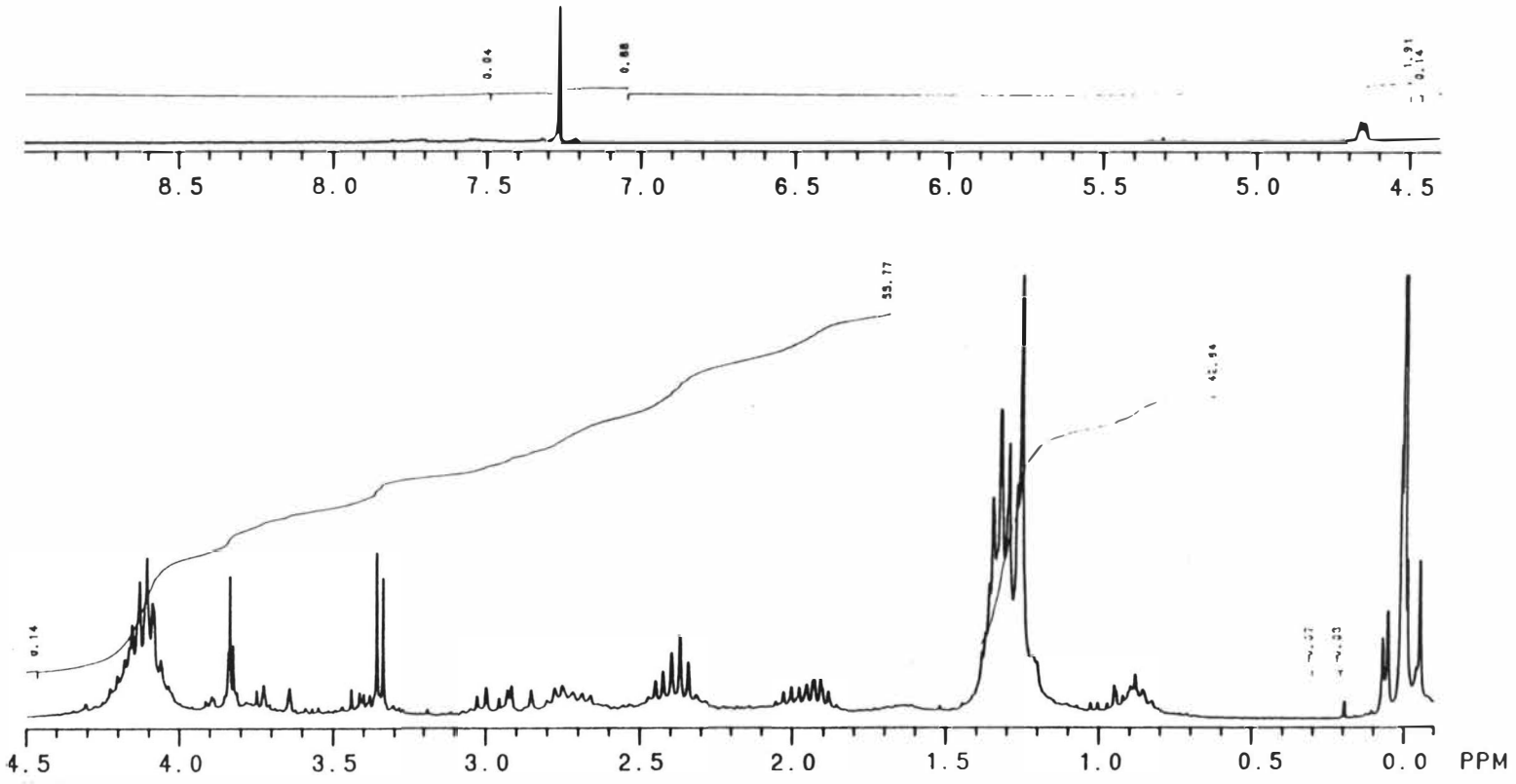


Figure 44: ^{1}H NMR Spectrum of 2-Diethylphosphonyl-3-methoxymethyl cyclohept-2-ene-1-one (**122c**).

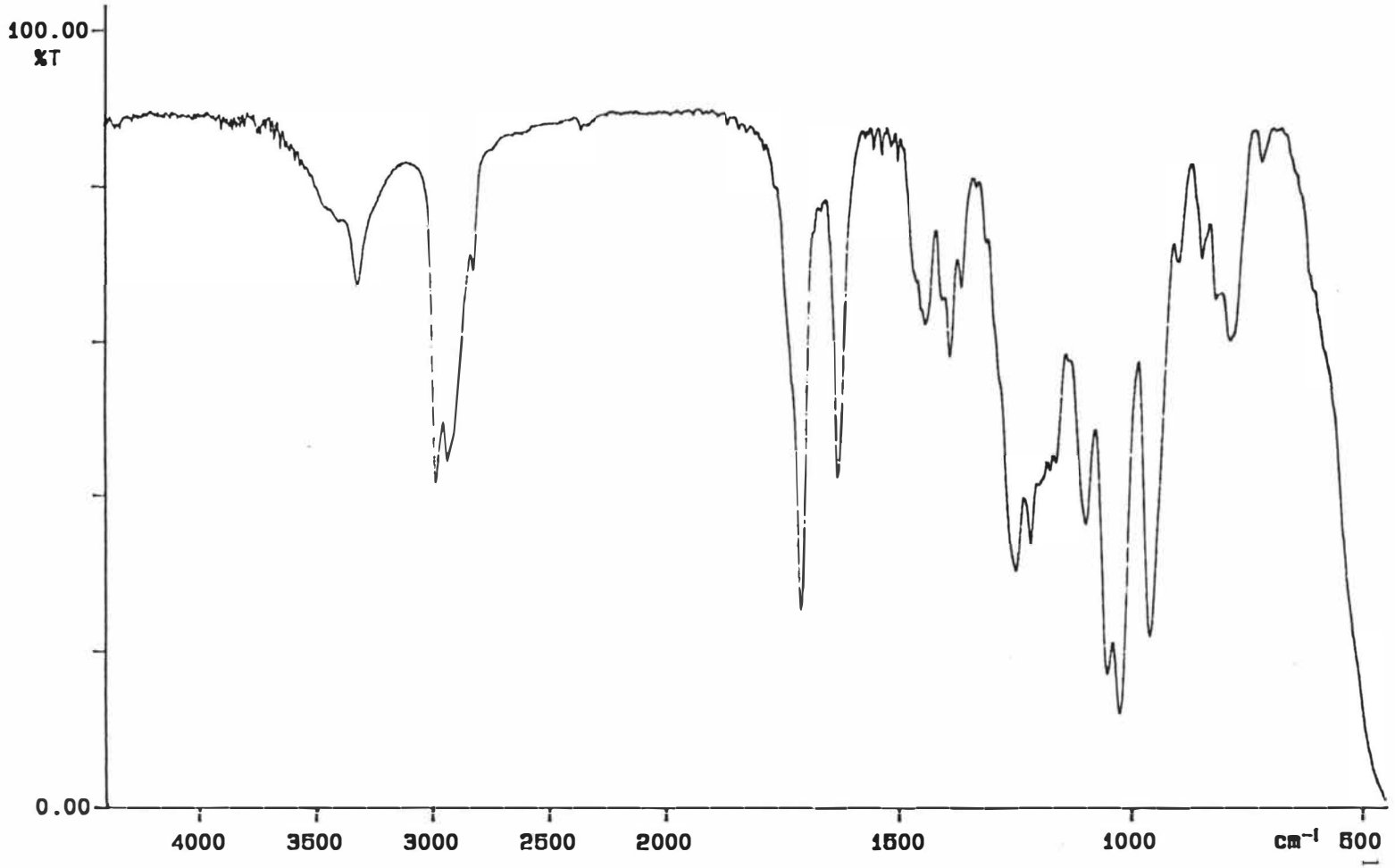


Figure 45: Infrared Spectrum of 2-Diethylphosphonyl-3-methoxymethyl cyclohept-2-ene-1-one (**122c**).

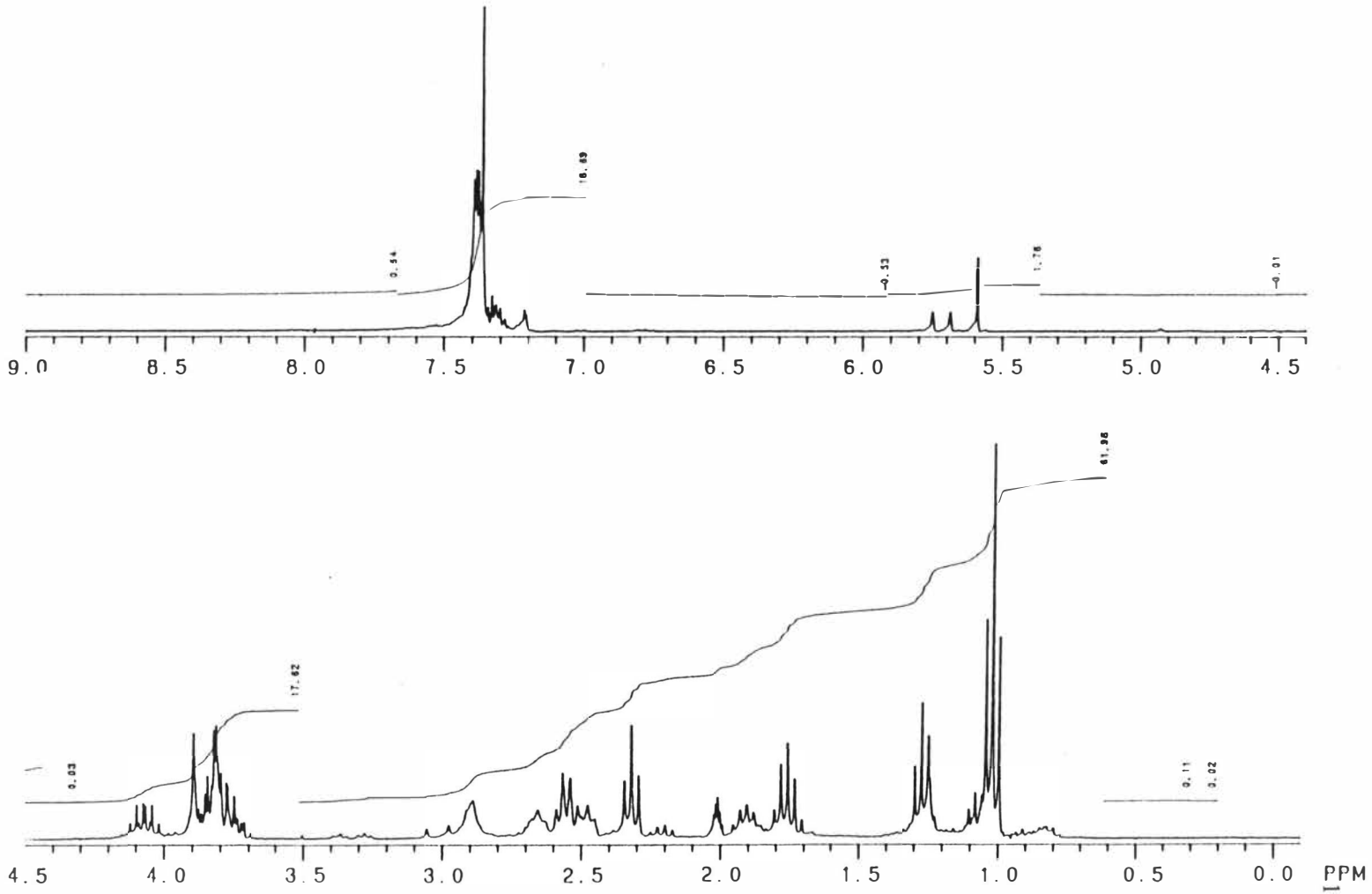


Figure 46: ^{1}H NMR Spectrum of 2-Diethylphosphonyl-3-phenyl cyclohept-2-ene-1-one (**122d**).

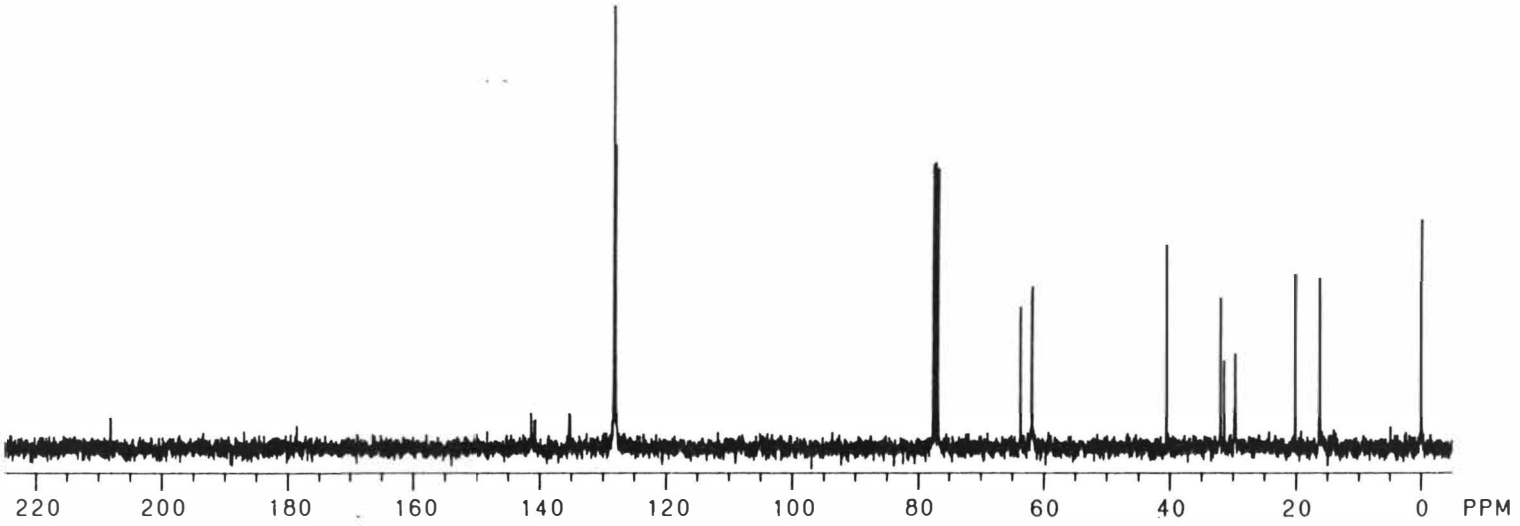


Figure 47: ^{13}C NMR Spectrum of 2-Diethylphosphonyl-3-phenyl cyclohept-2-ene-1-one (**122d**).

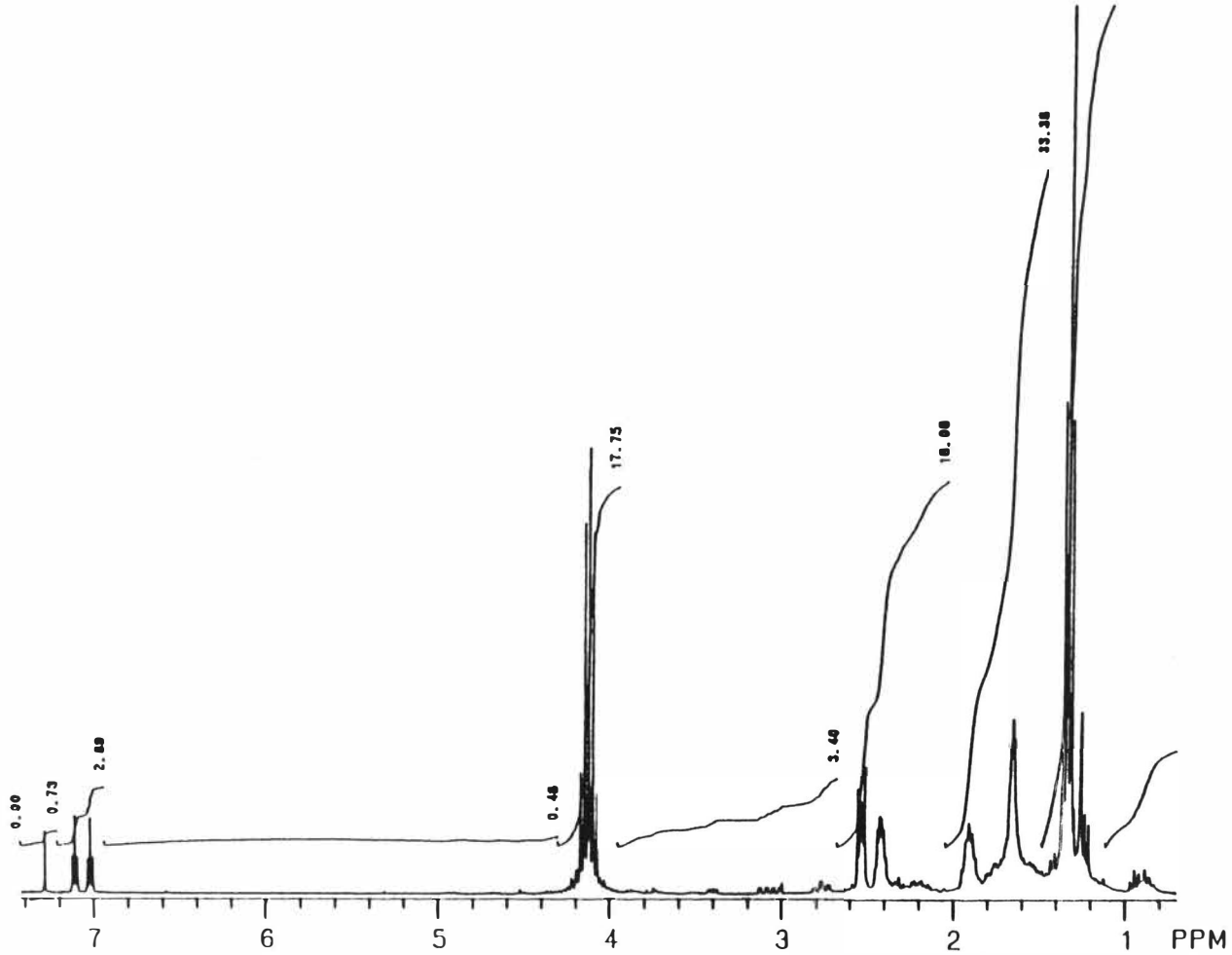


Figure 48: ^{1}H NMR Spectrum of 2-Diethylphosphonylcyclooct-2-ene-1-one (**122e**).

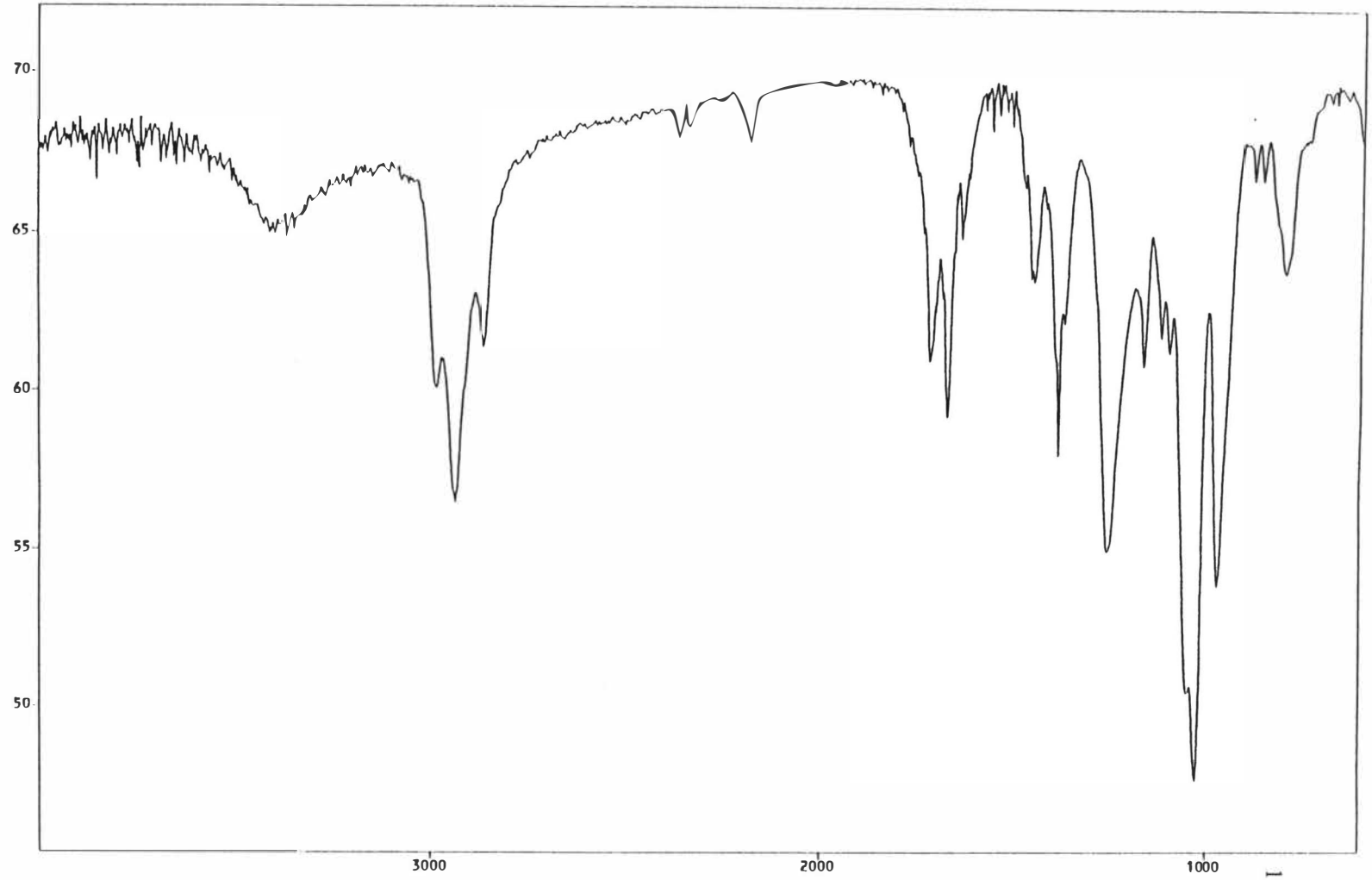


Figure 49: Infrared Spectrum of 2-Diethylphosphonylcyclooct-2-ene-1-one (**122e**)

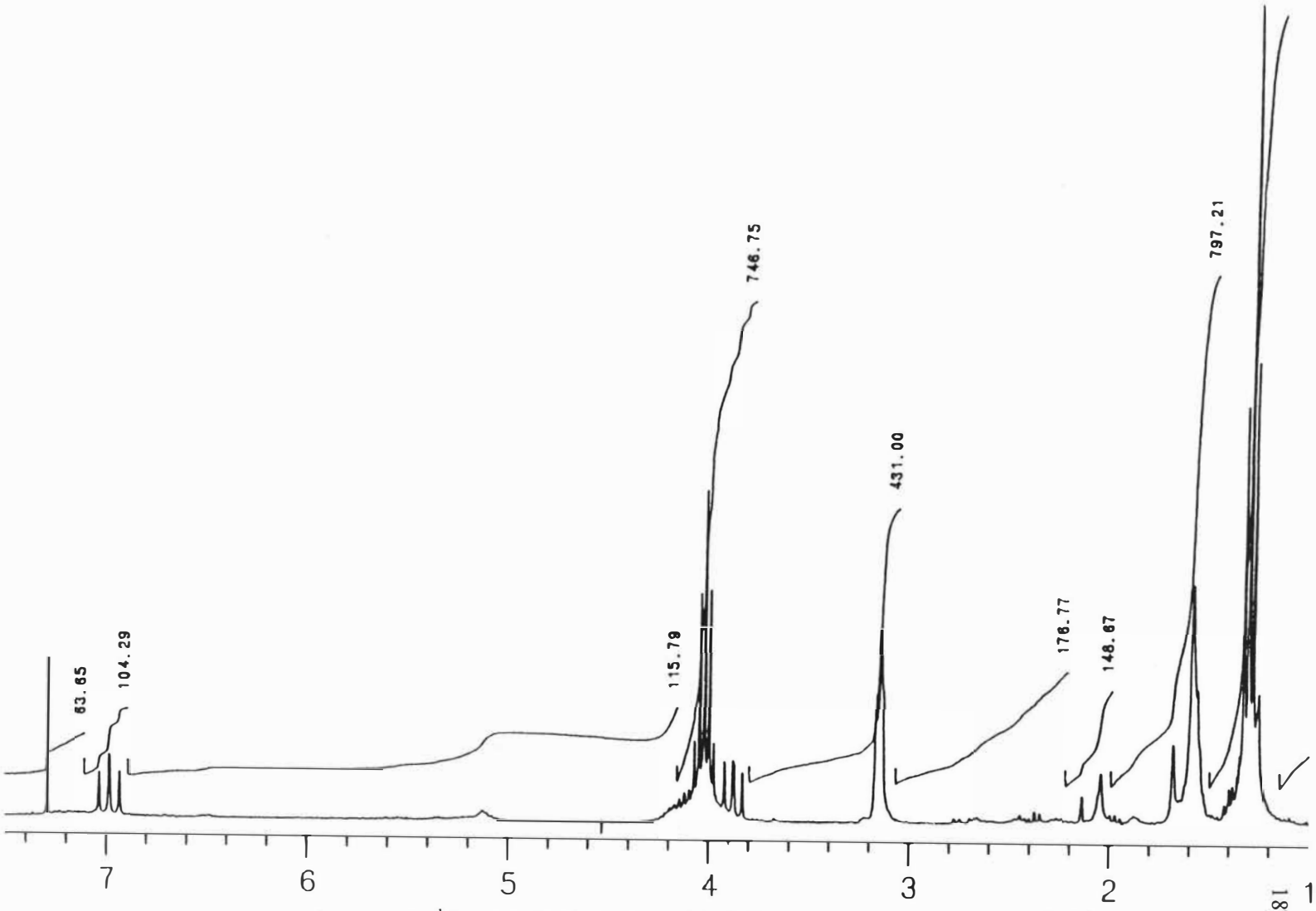


Figure 50: ^{1}H NMR Spectrum of (2-Pyrrolidinyl)vinyl Diethylphosphonate (**124**).

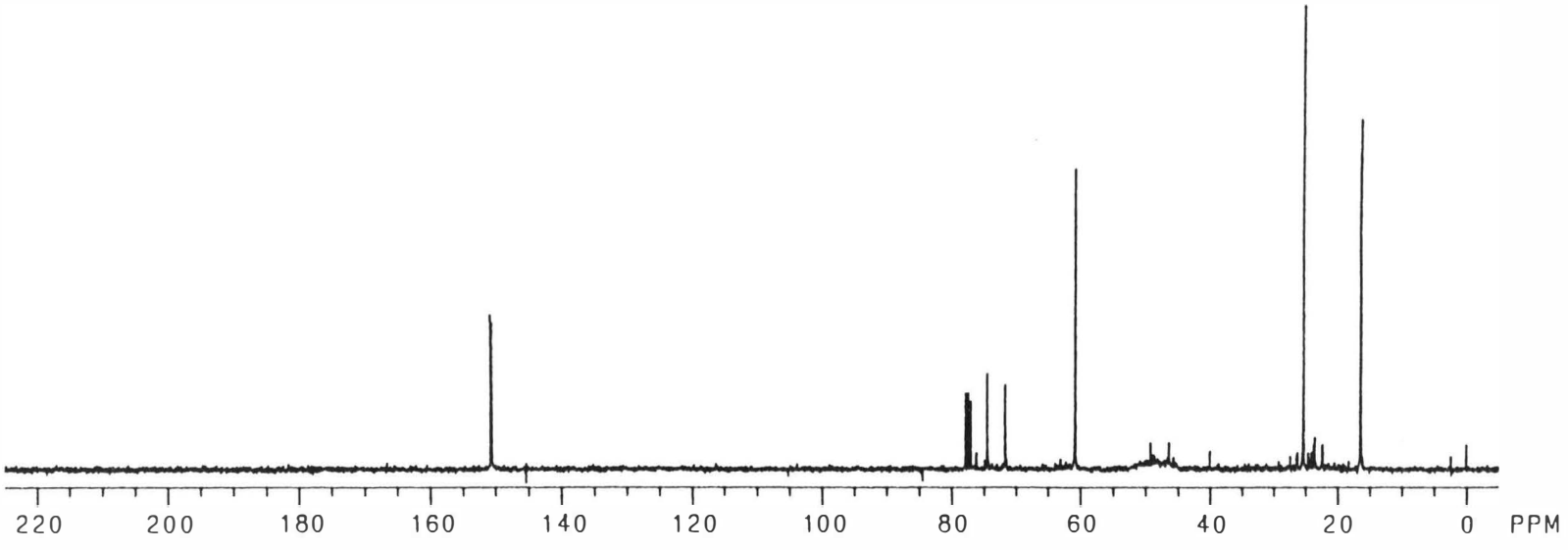


Figure 51: ^{13}C NMR Spectrum of (2-Pyrrolidinyl)vinyl Diethylphosphonate (**124**).

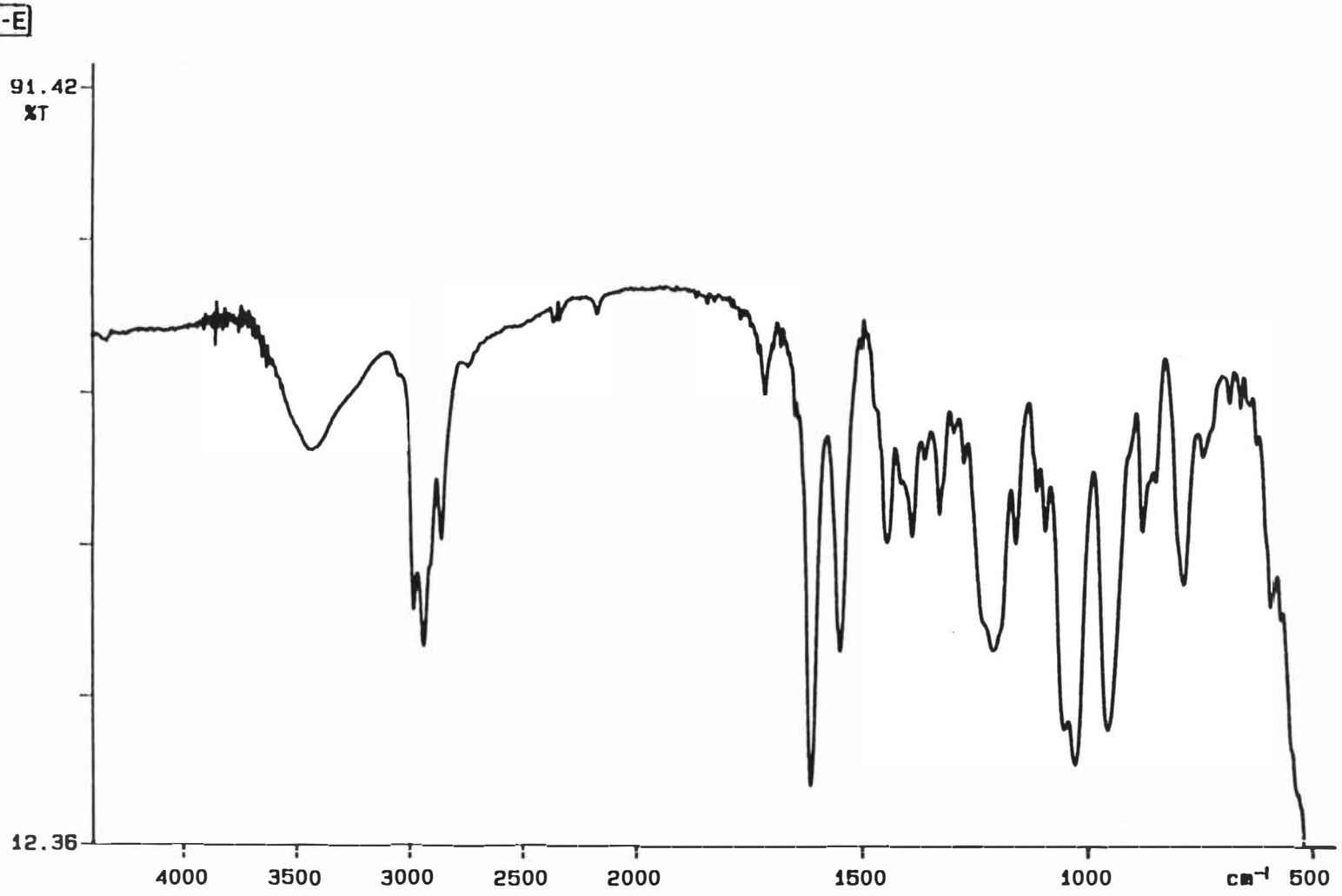


Figure 52: Infrared Spectrum of (2-Pyrrolidinyl)vinyl Diethylphosphonate (**124**).

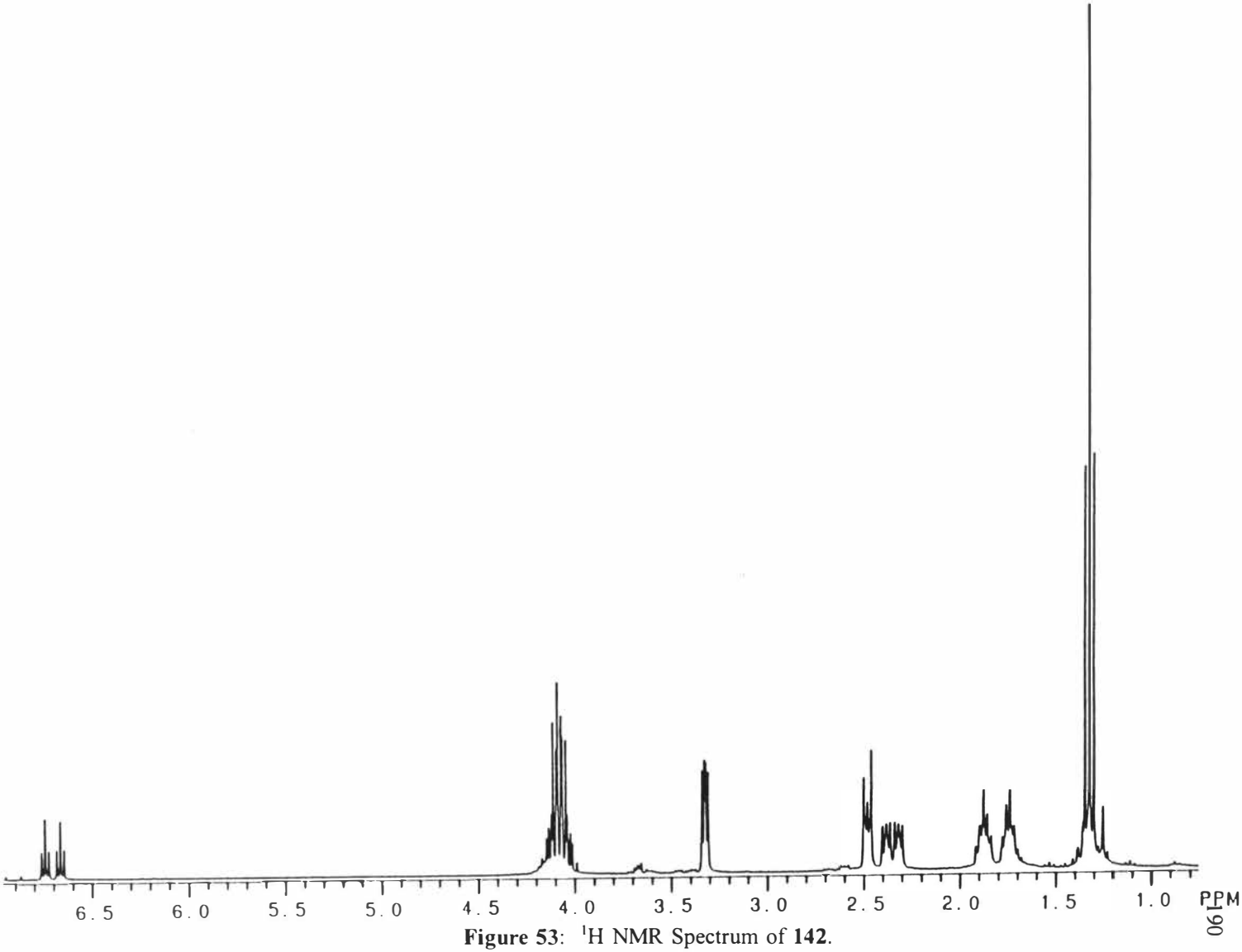


Figure 53: ^{1}H NMR Spectrum of **142**.

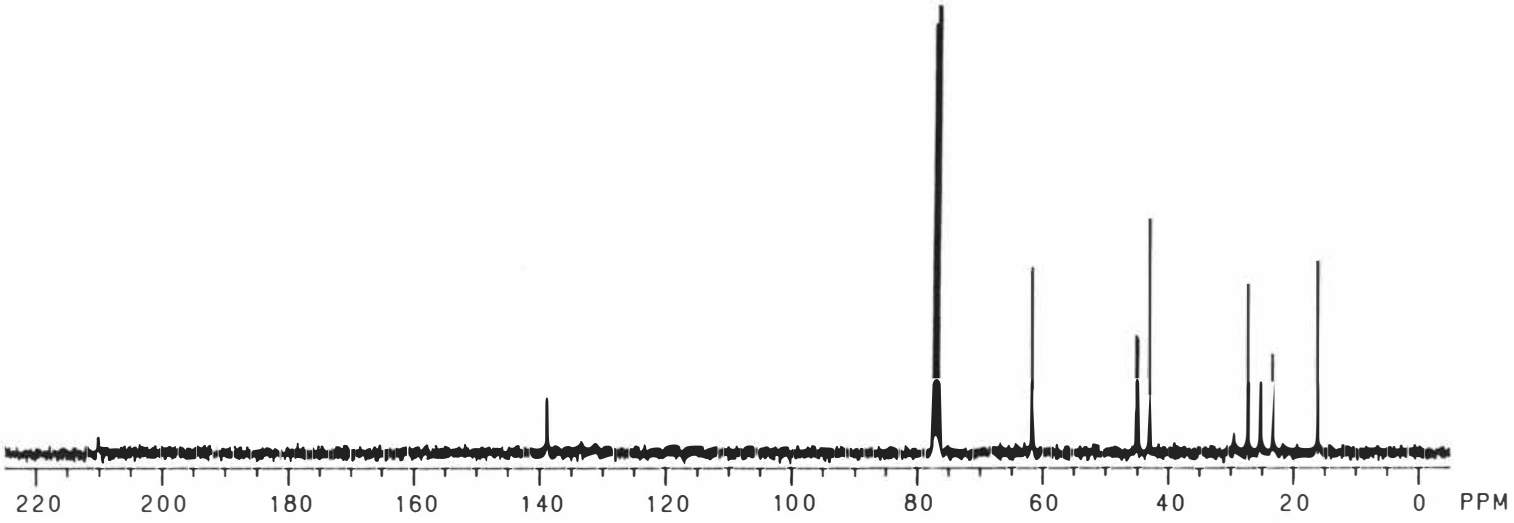


Figure 54: ^{13}C NMR Spectrum of **142**.

Vita