Ring Expansion Reactions of Cyclic β-Keto Phosphonates

Suzanne M. Ruder* and Vithalanand R. Kulkarni

Department of Chemistry, Virginia Commonwealth University, Richmond, Virginia 23284-2006

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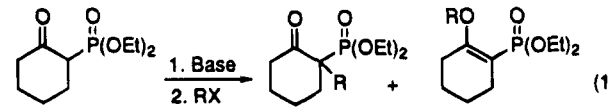
Phosphonate stabilized anions derived from a variety of cyclic β-keto phosphonates were shown to react with dimethyl acetylenedicarboxylate to afford [n + 2] ring expansion products. Highly substituted medium sized rings containing phosphonate functionality were thus obtained in reasonable yields. The reaction was found to proceed via a tandem Michael–aldol–fragmentation mechanism to give the ring enlarged products. An alternate competing pathway involving an "abnormal Michael" reaction was also shown to exist, resulting in a net 1,3-phosphorus migration, without ring expansion. Furthermore, the electronic and steric character of the carbonyl moiety of the cyclic β-keto phosphonates were shown to be very crucial in determining the course of the reaction.

Introduction

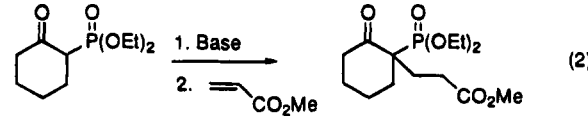
Phosphonate-stabilized carbanions have traditionally found wide application in organic synthesis, especially in connection with the Horner–Wadsworth–Emmons (HWE) condensation with aldehydes and ketones to afford alkenes.[1,2] However, relatively little work has been reported regarding the reactions of phosphonate stabilized carbanions with electrophiles other than aldehydes and ketones. These examples mainly involve reactions of acyclic phosphonates. For example, anions obtained from acyclic α-phosphono esters[3,4] and methylenebis(phosphonates)[5] have been reported to react with electrophiles such as unsaturated esters in Michael type reactions. In addition, Wiemer has recently reported that anions derived from cyclic β-keto phosphonates undergo condensation with epoxides;[6] however, we have found no other examples of the reaction of cyclic β-keto phosphonates with other electrophiles.

Reactions involving phosphonate stabilized carbanions generated from cyclic β-keto phosphonates have been limited in part due to the fact that they have been relatively inaccessible until recently, since they cannot be synthesized by the traditional Arbuzov reaction.[7] However, Wiemer and co-workers have recently developed several useful methods for the preparation of cyclic β-keto phosphonates from cyclic ketones using electrophilic phosphorus reagents.[8–10] We were interested in preparing cyclic β-keto phosphonates bearing functionalized side chains as templates for use in ring expansion reactions. Thus, we began an investigation of the base induced reaction of these cyclic β-keto phosphonates with a variety of electrophiles. For example, we have recently shown that alkylation of 2-(diethoxyphosphinyl)cyclohexanone using ion pair extractive–phase transfer catalyzed conditions, affords a mixture of C- and O-alkylated products depending on the nature of the alkyl halide utilized (eq 1).[11]



(1)

In addition, the Michael reaction of cyclic β-keto phosphonates with activated alkenes and alkynes results in 1,4-addition products as shown in eq 2.[12] However, in the presence of molar amounts of base, only a retro-Michael reaction occurs to afford unreacted starting material.



(2)

In this paper, we describe the Michael reaction of phosphonate stabilized anions with dimethyl acetylenedicarboxylate (DMAD). Although it has been reported that Michael addition of carbocyclic β-keto esters,[13,14] sulfonium ylides,[15] and enamines[16] with activated alkynes such as DMAD result in (n + 2) ring expanded products, we have found no reports of an analogous reaction with cyclic β-keto phosphonates. The synthesis of (n + 2) ring expanded compounds by this method would also demonstrate the capability of the phosphonate group to induce heterolytic fragmentation reactions. We thus decided to investigate the reaction of the carbanions derived from cyclic β-keto phosphonates with DMAD under aprotic Michael reaction conditions as shown in eq 3.

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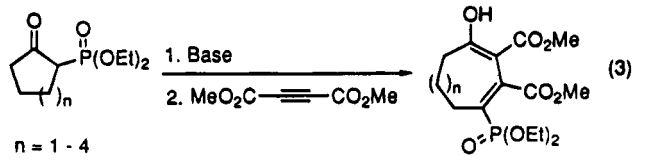


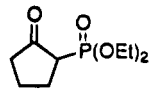
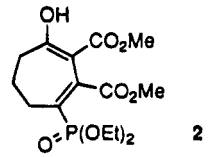
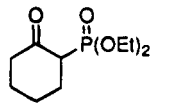
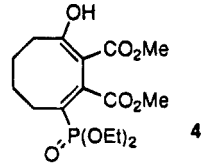
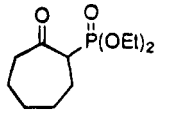
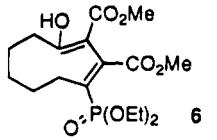
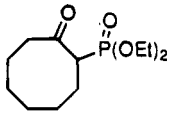
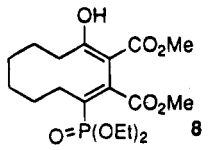
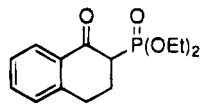
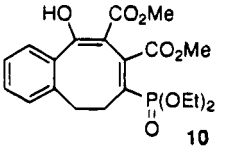
(3)

The aforementioned methodology would provide access to highly substituted medium sized rings containing phosphonate functionality. The synthesis of functionalized medium sized rings has traditionally been difficult to accomplish due to the unique structural characteristics which makes use of standard ring forming reactions impossible for their construction.[17] Ring expansion methodology[18,19] is commonly utilized to prepare medium sized rings from smaller ring precursors. Expanding the scope of the ring expansion methodology by including phosphonates would be beneficial, since the phosphonate group could subsequently be reacted in an intramolecular HWE reaction to afford bridgehead alkenes common to a number of biologically active natural products.

Results and Discussion

We thus proceeded to investigate in great detail the reactions of a variety of cyclic β-keto phosphonates with the activated alkyne, DMAD. In this paper we report preparation of highly functionalized medium sized rings via (n + 2) ring expansion of cyclic β-keto phosphonates. As shown in Table 1, cyclic β-keto phosphonates **1**, **3**, **5**, **7**, and **9** underwent reaction with DMAD in the presence of sodium hexamethyldisilazane (NaHMDS) to afford (n + 2) ring enlarged products **2**, **4**, **6**, **8**, and **10** in moderate yields. The IR spectra of ring enlarged products exhibited common trends, including a strong ester absorption at 1720 cm^{-1}, and absorptions at 1650 and 1590 cm^{-1} indicating the presence of a conjugated double bond. Additionally, the enolic proton of the ring enlarged products was observed as a strong D_2O exchangeable signal at approximately 13 ppm in the ^1H NMR spectra. On the basis of the observation of the strong enolic signal in the ^1H NMR, as well as lack of a ketonic carbonyl peak in the ^{13}C NMR, it was concluded that the ring expanded products exist predominately as the enol tautomer shown. For example, compound **4** was found to exist exclusively in the enol form based on the NMR spectra. The ^1H NMR of **4** showed an enolic proton at 13.1 ppm which integrated to one proton, and only one set of methoxy protons. In addition, the enolic C-1 carbon appeared, in the ^{13}C NMR, at 180 ppm, while no ketonic carbonyl was observed. Three signals due to the unsaturated carbons C-2, C-3, and C-4 occurred at 100, 140, and 135 ppm, respectively. Although ring expanded compounds **2**, **4**, and **10** exist exclusively as the enol tautomer, larger membered ring systems **6** and **8** had some keto content. As determined by ^1H NMR, 87% of compound **6** was found to exist in the enol form. Thus, ^1H NMR of **6** showed the presence of four methoxy signals, as well as both the enolic signal at 12.7 ppm and the ketonic C-2 hydrogen as a doublet at 6.24 ppm. Additionally, the ^{13}C NMR exhibited an enolic C-1 signal at 182 ppm and a ketonic carbonyl C-1 signal at 201 ppm. The larger amount of enol character for the seven- and eight-membered ring systems **2**, **4**, and **10** is not surprising since it has been shown that the enol character of cyclic β-keto esters[20,21] as well as β-diketones[22] varies based on the ring size. For example, decreasing enol character was observed with increasing ring size of β-diketones,[22] a trend analogous to that observed in our systems.

Table 1. Ring Expansion of Cyclic β-Keto Phosphonates

Phosphonate	Ring Expansion Product	% Enol[a]	Yield (%)[b]
 **1**	 **2**	100	54
 **3**	 **4**	100	52
 **5**	 **6**	87	60
 **7**	 **8**	86	57
 **9**	 **10**	100	37

[a] Ratio determined from ^1H NMR. [b] Isolated yield.

The mechanism for this (n + 2) ring expansion reaction is based on a Michael initiated ring closure (MIRC)[23] reaction. MIRC reactions involve an initial Michael reaction to form an enolate followed by an intramolecular ring closure. Several examples of tandem Michael–aldol MIRC reactions exist in the literature.[24–26] In order to afford ring expanded products, however, the MIRC reaction must be followed by a fragmentation reaction. The mechanism for formation of ring expanded products appears to proceed via a tandem Michael–aldol–fragmentation reaction as shown in Scheme 1. For example, phosphonate stabilized anion **11**, generated from reaction of **3** with NaHMDS, undergoes Michael reaction with DMAD to afford allenolate **12**. This anion subsequently undergoes an intramolecular aldol condensation (ring closure) to give cyclobutene **13**. Retro aldol-like fragmentation of the cyclobutene intermediate then occurs to give ring enlarged adduct **14**. The formation of this

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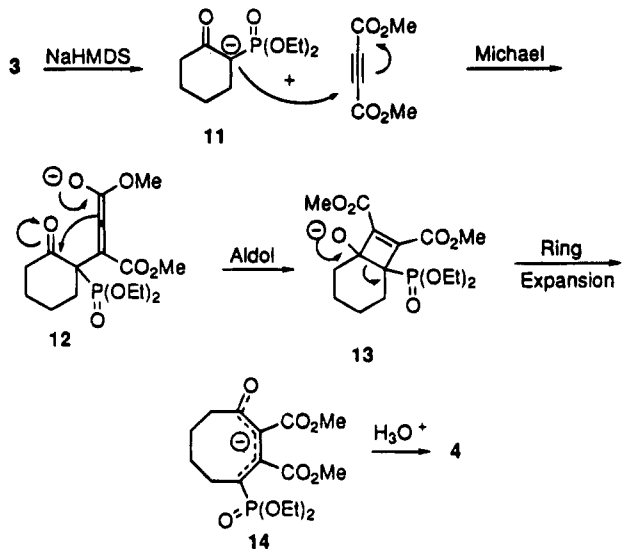
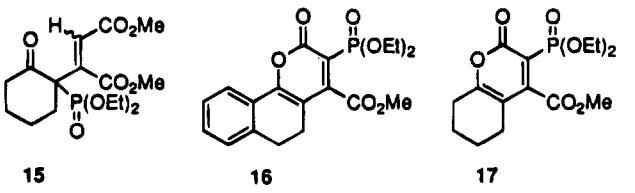
Scheme 1. Proposed Mechanism for Ring Expansion



highly delocalized phosphonate stabilized anion perhaps serves as the driving force for fragmentation. Upon aqueous workup, the anion **14** reacts to form the more stable enol form **4**. This mechanistic interpretation is similar to that proposed for the ring expansion of cyclic β-keto esters upon reaction with DMAD.[13]

After investigating the optimal conditions for the reactions of **3** with DMAD, we found that the best yields of ring expanded products were obtained on using NaHMDS or KHMDS as the base, in toluene at 0–5 °C for 7–8 h. However, THF was found to be a superior solvent compared to toluene in the reaction of 2-(diethoxyphosphinyl)cyclopentanone (**1**), due to the poor solubility of the sodium salt of **1** in toluene. Although use of NaH or KH as the base also afforded ring expanded products, the yields were not consistent, in part due to the difficulty in drying and handling small amounts of the hydride reagent. Upon reaction of **3** with KH and DMAD, significant amounts of Michael adduct **15** were obtained, as evidenced by the vinylic signal at 6.25 ppm in the ^{1}H NMR spectrum. As expected, the reaction of **3** with DMAD under protic conditions (cat. KOH/t-BuOH) gave exclusively the Michael adduct **15**, as a 5:1 mixture of *E* and *Z* isomers, respectively. Michael adduct **15** was also formed in the presence of molar excess of Et_3N in CH_2Cl_2. Although Et_3N has been utilized to initiate tandem Michael–aldol reactions in related systems,[27] this weak base was not capable of inducing an aldol-like attack of allenolate **12** and resulted only in formation of **15**. Finally, use of Cs_2CO_3 in CH_3CN, a system which Deslongchamps and co-workers have employed in the intramolecular Michael addition of β-keto esters with alkynones,[28] resulted in formation of a 1:2 mixture of ring expanded product **4** and Michael adduct **15**, respectively. Although the use of LiHMDS as the base gave only unreacted starting material, the use of NaHMDS or KHMDS in toluene, however, led to sole formation of the ring expanded products. It was thus clear that stronger bases such as metal hydrides or silazides are essential in order to initiate (*n* + 2) ring expansion reactions in cyclic β-keto phosphonates.



Isolation of Michael adduct **15** from reactions which employed wet KH or Cs_2CO_3 confirmed the presence of allenolate **12** as an intermediate in the ring expansion reaction. In addition, **15** (prepared as a 5:1 mixture of geometrical isomers on reacting **3** with DMAD using a catalytic amount of KOH in t-BuOH) was converted to ring expanded product **4** upon treatment with base. For example, partial conversion to ring expanded product **4** occurred when treating **15** with 2 equiv of Cs_2CO_3 in acetonitrile at 75 °C for 48 h. Treatment of **15** with NaHMDS in toluene resulted in a complex mixture of products, containing small amounts of **4**. Efforts to induce an intramolecular ketone–alkene coupling[29,30] by treating the Michael adduct **15** with SmI_2 met with little success.

The ring expansion reaction of substituted cyclic β-keto phosphonates was also explored, in order to determine the effect of electronic and steric factors on the course of the reaction. When the β-keto phosphonate **9**, derived from tetralone, was reacted with DMAD using the aforementioned conditions, two main products were isolated after chromatography on alumina. Consequently, the ring enlarged product **10** was isolated in 37% yield and the lactonized product **16** in 29% yield. The ^{1}H NMR spectrum of the crystalline product **16** showed a single methoxy peak, suggesting the loss of methanol from the initial adduct. This was further confirmed since the molecular weight of the crystalline compound **16** was found to be 392 from the FABMS spectrum. Moreover, since the ^{1}H NMR spectrum of the purified compound **16** contained peaks which were absent from the ^{1}H NMR spectrum of the crude product mixture, it was concluded that some chemical reaction had occurred during chromatography.

The proposed mechanism for the formation of the lactonized product **16** is shown in Scheme 2. Reaction of **9** with base followed by DMAD proceeds to generate the allenolate **18** as a result of Michael addition. At this stage, ring closure via attack of the anion on the phosphorus, instead of the carbonyl, leads to cyclic intermediate **19**. Similar attack of allenolate anions on the phosphorus of phosphonium salts has been documented.[31,32] Fragmentation of this intermediate affords **20**, and after aqueous workup mixtures of enones **21** and **22** are formed. The net result of this reaction is thus a 1,3-phosphorus migration which is similar to the "abnormal Michael"[33] reaction. Lactonization to form crystalline product **16** occurred after chromatography on silica gel or alumina, or after attempts to distill the product mixture. Formation of **16** was also accomplished by refluxing the crude product mixture in THF in the

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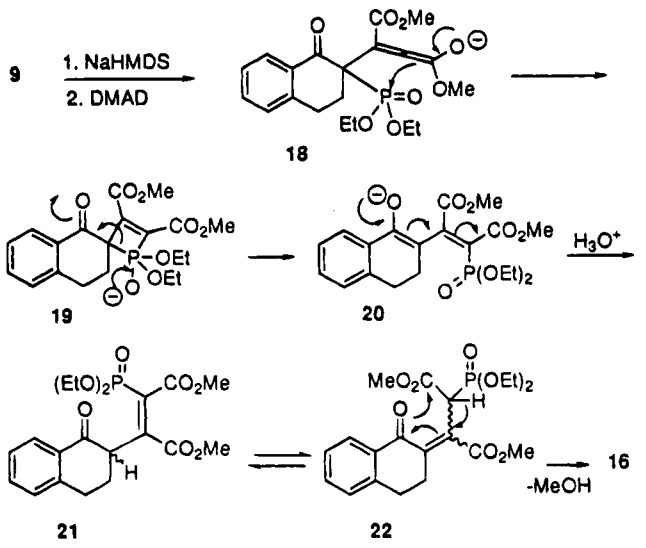
Scheme 2. Proposed Mechanism for "Abnormal Michael" Pathway



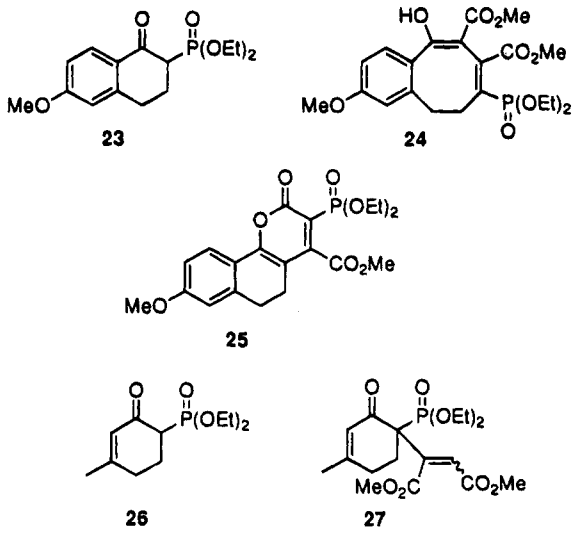
presence of sulfuric acid. The presence of **21** and **22** in the crude mixture was indicated by signals at 190 and 187.5 ppm in the ^{13}C NMR and peaks at 17.2 and 18 ppm in the ^{31}P NMR. These signals disappeared after refluxing the crude mixture in acid. The resulting product contained a signal at 10 ppm in the ^{31}P NMR, corresponding to the lactonized product **16**. The open chain precursor of the lactonized product **16** thus exists as a mixture of tautomers **21** and **22**.

Upon further examination of the reaction of tetralone phosphonate **9**, we found that the ratio of ring expanded product **10** to "abnormal Michael" product **16** was dependent on the counterion utilized. When KHMDS was used as the base in the reaction of **9** with DMAD, a slight excess of the "abnormal Michael" product **16** was formed (1.5:1 ratio of **16**:**10** by ^1H NMR). However, when NaHMDS was used, the major product was found to be the ring expanded product **10** (1:1.5 ratio of **16**:**10** by ^1H NMR). Use of LiHMDS afforded only unreacted keto phosphonate **9**.

Small amounts of "abnormal Michael" byproducts were also observed in the tandem Michael–aldol reaction of other cyclic β-keto phosphonates. For example, lactonized "abnormal Michael" byproduct **17** was isolated in 13% yield from the reaction of **3** with DMAD, while the corresponding byproduct could not be isolated in pure form in the reaction of **1**. A consistent trend was seen in the GC chromatogram of the product mixtures resulting from reaction of cyclic β-keto phosphonates and DMAD. In addition to the major peak for the $(n + 2)$ ring expanded products and a small peak due to some unreacted starting material, the GC trace for these reactions always consisted of a peak at a higher retention time, corresponding to the "abnormal Michael" product.

The lactonized product **16** is similar to that obtained by Frew and co-workers, who reported that the sodium salt of 2-(ethoxycarbonyl)-1,2-dihydro-1-methylindol-3-one on reaction with DMAD afforded only lactonized products.[34] Additionally, lactones **16** and **17** both show two high field alkene carbon resonances at around 110 ppm, which is characteristic of α,β,γ,δ-unsaturated ester systems present in α-pyrones and coumarins. While investigating the ene reaction of alkenes and DMAD, McCulloch and co-workers[35] have distinguished between five- and six-membered ring lactones on the basis of IR evidence. The IR absorption of the lactones **16** and **17** around 1733 cm^{-1} is identical to that of similar unsaturated δ-lactones.[36]

Electronic effects on the ring expansion reaction were also investigated by studying the reactions of phosphonates **23** and **26**. The reaction of the phosphonate **23**, derived from methoxytetralone, with DMAD afforded a complex mixture of products, consisting in part of Michael adduct, ring enlarged product **24**, "abnormal Michael" product **25**, and approximately 25% of unreacted starting material. It appears that electron delocalization into the carbonyl group deactivates this site for the nucleophilic attack necessary to afford ring enlarged product. Thus, the initial Michael adduct undergoes attack on the phosphonate to afford the "abnormal Michael" product, or undergoes a retro-Michael reaction to afford starting material. Upon reaction of unsaturated phosphonate **26** with KHMDS and DMAD, no addition products were formed and only unreacted phosphonate was isolated. However, when protic conditions (KOH/t-BuOH) were utilized, **26** reacted with DMAD to generate good yields of Michael adduct **27**, as a 4:1 mixture of *E* and *Z* isomers, respectively. Therefore, the initial Michael addition step must occur in both protic and aprotic solvents. In the absence of a proton source, the allenolate anion undergoes a retro-Michael reaction to give starting material rather than an intramolecular aldol reaction with the less activated carbonyl to give ring expansion products.



In order to study the steric effects on the ring expansion of various keto phosphonates, the reactions of (±)-camphor and (±)-norbornanone phosphonates were, thus, investigated. The phosphonate derived from (±)-camphor, **28**, did not undergo any addition with DMAD, and hence, only starting material was recovered. The sterically crowded nature of the carbanion derived from **28** has also been noted by Wiemer and co-workers, who recently reported that **28** did not undergo nucleophilic addition to epoxides in the presence of base.[6] To investigate whether steric hindrance was inhibiting the initial

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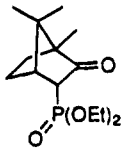
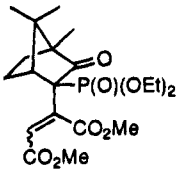
(36) Pettit, G. R.; Knight, J. C.; Herald, C. L. *J. Org. Chem.* **1970**, *35*, 1393–1398.

Michael reaction from occurring, or whether steric effects were preventing the subsequent aldol attack and hence forcing a retro-Michael reaction, the reaction was explored under protic conditions. When **28** was reacted with DMAD under protic conditions, no Michael adduct **29** was isolated and only starting material was recovered. Thus, it appears that **28** is too hindered to allow approach of DMAD to give the initial Michael adduct.

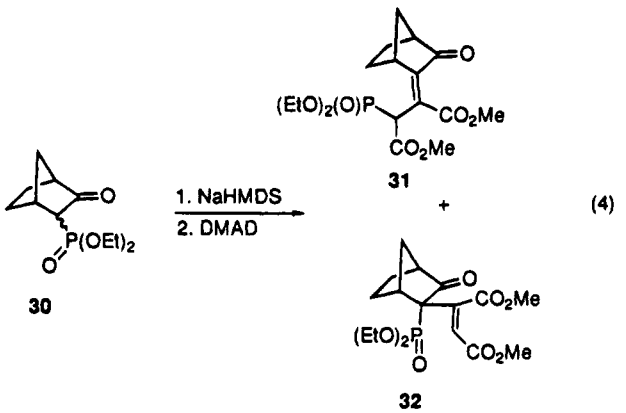


28



29

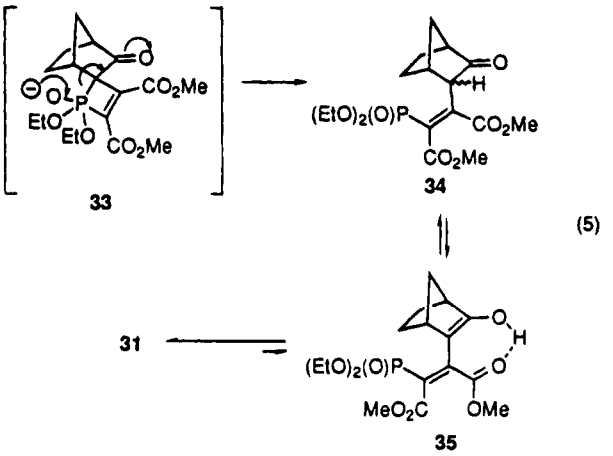
On the other hand, when the phosphonate derived from (±)-norbornanone, **30**, was reacted with NaHMDS and DMAD, a Michael reaction occurred to afford 54% of the "abnormal Michael" product **31** (64% based on unreacted starting material) and 8% of Michael adduct **32** (eq 4). Both **31** and **32** were obtained as single diastereomers and the latter compound also existed exclusively as the *E* geometrical isomer.



30 **31** + **32** (4)

Although the "abnormal Michael" byproduct was found to exist as tautomer **31** after silica gel column chromatography, ^{1}H and ^{13}C NMR of the crude product mixture revealed presence of mainly tautomers **34** and **35** along with a minor amount of tautomer **31**. For example, the ^{13}C NMR of crude product mixtures contained signals at 205 ppm corresponding to tautomer **34** and signals at 188 and 98.4 ppm corresponding to the C-1 and C-2 enolic carbons of tautomer **35**. Furthermore, the ^{1}H NMR of the product mixture also showed presence of an enolic proton at 14 ppm. Slow tautomerization of the crude product, containing mainly **34** and **35**, occurred over several days to afford predominately the diastereomer **31**. This was evident based on the ^{1}H NMR which now contained additional singlets at 3.8 and 3.84 ppm, corresponding to the methoxy protons of **31** and its epimer, as well as the original singlets at 3.74 and 3.77 ppm, corresponding to the methoxy protons of tautomers **34** and **35**. The ^{1}H NMR of the product isolated after silica gel column chromatography of this mixture, however, revealed presence of only the diastereomer **31**. Hence, the enol–keto equilibrium between **34**, **35**, and **31** must lie in favor of ketone **31**.

The formation of **31** appears to proceed via the pathway noted in eq 5. Initial Michael reaction followed by attack on the phosphorus leads to cyclic intermediate **33**, thus, establishing the geometry around the double bond. Fragmentation of **33** followed by protonation initially forms a mixture of ketone **34** and enol **35**. It can be envisioned that protonation occurs from the least hindered top face of **35** to afford diastereomer **31**, resulting in a net 1,5-prototropic shift. A somewhat similar, facially selective protonation of the enol of a carboxylic acid has been recently reported.[37] Since no ring expanded product was isolated in the reaction of **30** with DMAD, the allenolate intermediate must exclusively attack the phosphorus, giving solely the "abnormal Michael" product **31**. Thus both geometric and steric factors appear to be very important in this reaction, since attack of the allenolate anion on the carbonyl group is totally precluded.



33 **34** (5) **31** **35**

The "abnormal Michael" product **31** could be converted back to a mixture of **34** and **35**, similar to that obtained from the crude reaction mixtures. For example, when the sodium enolate of **31** in toluene was stirred overnight and quenched with excess acetic acid and 2 N HCl, tautomerization of **31** to a mixture consisting of mainly **34** and **35** and small amounts of **31** resulted. The ^{13}C NMR showed six signals in the ester carbonyl region corresponding to each of the two carbomethoxy groups of **31**, **34**, and **35**. In addition to ester carbonyl signals at 165.5, 167.3, 172.8, and 167.3 ppm, the presence of two strong doublets at 169.5 and 168.9 ppm (J_{CP} = 12 Hz) confirmed the trans relationship[38] between the phosphonate and carbomethoxy groups of the alkene linkage as shown in **34** and **35**. On the other hand, when the sodium enolate of **31** in THF was subjected to the same quenching experiment, the original diastereomer **31** was recovered without any epimerization or tautomerization. Additionally, mere stirring of **31** in toluene in the absence of acid and base did not result in tautomerization of **31** to **34** and **35**.

The purified product **31**, existing as a single diastereomer, was characterized by IR, ^{1}H, ^{13}C, and ^{31}P NMR. The IR spectrum showed two ester carbonyl absorptions at 1754 and 1729 cm^{-1}, a conjugated carbonyl at 1680 cm^{-1}, and a weak absorption for the double bond at 1622 cm^{-1}. In the ^{1}H NMR, the methine proton flanked by the ester and phosphonate groups appeared as a multiplet at 3.8 ppm. In the ^{13}C NMR, a carbonyl signal appeared at 201 ppm and the methine carbon occurred

(37) Jones, D. K.; Liotta, D. C.; Choi, W.-B.; Volante, R. P.; Reider, P. J.; Shinkai, I.; Churchill, H. R. O.; Lynch, J. E. *J. Org. Chem.* **1994**, *59*, 3749–3751.

(38) Ohler, E.; Zbiral, E. *Monatsh. Chem.* **1984**, *115*, 493–508.

at 46.7 ppm as a strong doublet (J_{CP} = 131 Hz). Additionally, a single peak at 22.3 ppm was observed in the ^{31}P NMR. Evidence for the geometry of the alkene linkage in **31** was obtained from the uncharacteristically high, long range J_{CP} value of 18 Hz, in the ^{13}C NMR, for one of the methylene carbons. This confirmed the proximity of the phosphonate group to the norbornanone ring. X-ray crystal structure data could not be obtained to ascertain the relative configuration of **31**, as neither **31** nor its thioketal, phosphonic acid, or semicarbazide derivatives exist as solids. Lactonization of **31** did not occur after several attempts to induce it via chromatography on silica gel, or on refluxing in THF in the presence of sulfuric acid.

Michael addition of **30** with DMAD proceeded easily using catalytic KOH in t-BuOH to afford **32** in 64% NMR yield, along with minor amounts of other isomers. The ^1H NMR spectrum of the product mixture showed the presence of three vinyl signals at 6.78, 6.45, and 6.3 ppm in a ratio of 1:1:4, and the ^{31}P NMR spectrum contained three major signals at 21, 20.7, and 18.9 ppm with the same ratio. The ^{13}C NMR of the Michael adduct **32** showed a doublet at 62.9 ppm for the carbon containing the phosphonate group, while the ^{31}P NMR signal occurred at 18.9 ppm, and the vinyl proton absorption occurred at 6.3 ppm in the ^1H NMR. The above NMR data was identical to that of the Michael byproduct isolated in the reaction of **30** with DMAD under aprotic conditions. The diastereoselectivity observed in the Michael reaction obviously results from preferential exo attack of DMAD. This stereochemical assignment of **32** was confirmed by applying the Karplus correlation between the dihedral angle ϕ(PCCC) and the $^3J_{PC}$[39] values obtained from the ^{13}C NMR data. The dihedral angle ϕ(PCCC) between the bridged methylene and the phosphorus is 180°, when the phosphonate is in the endo position, thus a large coupling value would be expected. In the ^{13}C NMR the methylene signal appears at 36.6 ppm as a doublet with $^3J_{PC}$ = 16 Hz, thus confirming the structure of **32** as shown.

In summary, it has been demonstrated that phosphonate-stabilized anions react readily as Michael donors with the activated alkyne, DMAD. This reaction afforded moderate yields of medium sized rings containing a phosphonate functional group via a tandem Michael–aldol–fragmentation reaction. In addition, for the first time the ability of the phosphonate group to induce retro aldol-like fragmentation reactions has been demonstrated. Investigation into the scope of this reaction with DMAD also revealed an alternate reaction pathway (the "abnormal Michael" reaction) existed, in which the nucleophile generated from the initial Michael addition, attacked the phosphorus, leading to a net 1,3-migration of the phosphonate. The verification that phosphonates can be utilized in ring expansion methodology, could further lead to use of phosphonate based substrates in related fragmentation reactions such as the deMayo reaction. Further efforts are underway in our labs to study HWE reactions of the ring expanded products.

Experimental Section

Toluene was distilled from CaH_2 and DMAD was distilled from $CaCl_2$, both immediately prior to use. All reactions were carried out under a positive pressure of nitrogen or argon. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75.61 MHz in $CDCl_3$ using TMS as an internal standard. ^{31}P NMR spectra were recorded at 121.7 MHz using phosphoric acid as the external standard. IR spectra were obtained from neat films. Column chromatography was performed on E. M. Science silica gel 60 (230–400 mesh) or Fisher neutral alumina (60–235 mesh). Analyses by gas chromatography were performed on a Shimadzu GC-14A using a methyl 5% silicone glass capillary column (0.32 mm × 15 m). NaHMDS and KHMDS were purchased from Aldrich Chemical Co. as 0.6 M and 0.5 M solutions, respectively, in toluene. Cyclic β-keto phosphonates **1**, **3**, **9**, **23**, **26**, **28**, **30** and **5**, and **7** were prepared according to the procedures listed in references 8 and 9, respectively, and were dried over $MgSO_4$ immediately prior to use. Elemental analyses were conducted at Atlantic Microlabs, Norcross, GA. HRMS analyses were conducted at UCR Mass Spec facility, Riverside, CA.

1-Hydroxy-2,3-bis(methoxycarbonyl)-4-(diethoxyphosphinyl)cyclohepta-1,3-diene (2). 2-(Diethoxyphosphinyl)-cyclopentanone (**1**) (126 mg, 0.57 mmol) was dissolved in THF (5 mL), and NaHMDS (1.15 mL, 0.69 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 45 min, cooled to 0 °C, and then DMAD (85 μL, 0.69 mmol) in THF (7 mL) was added to the solution. The ice bath was removed and the reaction allowed to stir at room temperature for 4 h and then quenched with AcOH (90 μL) in Et_2O (0.2 mL). The solvent was removed in vacuo and the product extracted into CH_2Cl_2. The CH_2Cl_2 solution was further washed with water and brine and then dried over Na_2SO_4 and concentrated. The product obtained was purified by column chromatography on neutral alumina (10.3 g, Grade IV). Elution with CH_2Cl_2 removed crude "abnormal Michael" product, and gradient elution with EtOAc and 1–5% AcOH/EtOAc yielded **2** (112 mg, 54%) as a light yellow oil: IR (film) 2954, 1732, 1650, 1578, 1443, 1338, 1304, 1244, 1214, 1049, 1024, 967 cm^{-1}; ^1H NMR δ 13.25 (s, 1H), 4.15 (m, 4H), 3.8 (s, 3H), 3.75 (s, 3H), 2.35 (m, 6H), 1.35 (t, J = 7 Hz, 6H); ^{13}C NMR δ 183.2, 170.8, 167.8 (d, J_{CP} = 9 Hz), 143.3 (d, J_{CP} = 12 Hz), 133.3 (d, J_{CP} = 181 Hz), 99.8 (d, J_{CP} = 21 Hz), 62.3, 62.2, 52.3, 51.9, 35.1, 32.2, 29.0 (d, J_{CP} = 9 Hz), 16.4, 16.3; ^{31}P NMR 17.0. Anal. Calcd for $C_{15}H_{23}O_8P$: C, 49.73; H, 6.39. Found: C, 49.76; H, 6.35.

1-Hydroxy-2,3-bis(methoxycarbonyl)-4-(diethoxyphosphinyl)cycloocta-1,3-diene (4). General Procedure for the Condensation of Cyclic β-Keto Phosphonates with DMAD. 2-(Diethoxyphosphinyl)cyclohexanone (**3**) (520 mg, 2.22 mmol) was combined with toluene (7 mL) and cooled to 0 °C. NaHMDS (4.44 mL, 2.66 mmol) was added slowly at 0 °C. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 h and then cooled again to 0 °C, followed by dropwise addition of DMAD (314 μL, 2.55 mmol). After stirring for 8–10 h at 0 °C the reaction was quenched by adding glacial acetic acid (0.65 mL) followed by ice cold 2 N HCl (1.1 mL). Benzene (10 mL) was added to the mixture, and the phases were separated. The aqueous phase was further extracted with benzene (3 × 7 mL). The combined organic phases were washed with water and brine and then dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was subjected to column chromatography on silica gel (3:1 CH_2Cl_2/EtOAc) to afford **17** (99 mg, 13%). Further elution afforded **4** (430 mg, 52%) as a light yellow oil: IR (film) 2950, 1727, 1649, 1603, 1449, 1337, 1298, 1245, 1217, 1051, 1022, 964 cm^{-1}; ^1H NMR δ 13.1 (d, J = 2.1 Hz, 1H, D_2O exchangeable), 4.16 (m, 4H), 3.78 (s, 3H), 3.74 (s, 3H), 2.67 (m, 1H), 2.48 (m, 1H), 2.23 - 1.56 (m, 6H), 1.36 (t, J = 7 Hz, 3H), 1.34 (t, J = 7 Hz, 3H); ^{13}C NMR δ 179.8 (d, J_{CP} = 2 Hz), 171.6, 168.2 (d, J_{CP} = 10 Hz), 140.3 (d, J_{CP} = 13 Hz), 134.3 (d, J_{CP} = 173 Hz), 99.3 (d, J_{CP} = 20 Hz), 62.5 (d, J_{CP} = 6 Hz), 62.0 (d, J_{CP} = 6 Hz), 52.3, 51.9, 32.8, 31.1 (d, J_{CP} = 10 Hz) 24.7, 22.8, 16.4 (d, J_{CP} = 6 Hz), 16.3 (d, J_{CP} = 6 Hz); ^{31}P NMR 16.9. Anal. Calcd for $C_{16}H_{25}O_8P$: C, 51.06; H, 6.65. Found: C, 50.96; H, 6.78.

Abnormal Michael Product 17. This product was found to decompose slowly: IR (film) 2951, 1735, 1630, 1519, 1436, 1378, 1262, 1238, 1167, 1056, 1020, 974, 833 cm^{-1}; ^1H NMR δ 4.17 (m, 4H), 3.96 (s, 3H), 2.6 (br t, J = 6.2 Hz, 2H), 2.33 (br

(39) Quin, L. D. In *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis*; Verkade, J. G., Quin, L. D., Eds.; VCH: Deerfield Beach, 1987; pp 391–424.

t, J = 5.7 Hz, 2H), 1.79 (m, 4H), 1.34 (t, J = 7 Hz, 6H); ^{13}C NMR δ 165.9, 165.3 (d, J_{CP} = 7 Hz), 159.3 (d, J_{CP} = 12 Hz), 158.6 (d, J_{CP} = 8 Hz), 109.7 (d, J_{CP} = 192 Hz), 110.1 (d, J_{CP} = 12 Hz), 63.4, 63.3, 53, 28.3, 22.85, 21.8, 21.2, 16.4, 16.3; HRMS calcd for $C_{15}H_{21}O_7P$ (M^+) 344.1069, found 344.1016.

1-Hydroxy-2,3-bis(methoxycarbonyl)-4-(diethoxyphosphinyl)cyclonona-1,3-diene (6). According to the general procedure, a solution of 2-(diethoxyphosphinyl)cycloheptanone **(5)** (307 mg, 1.24 mmol) in toluene was treated with NaHMDS (2.5 mL, 1.49 mmol) and DMAD (175 μL, 1.42 mmol) and stirred for 4 h. The product mixture was directly purified by column chromatography on silica gel. Elution with 5:1 CH_2Cl_2/EtOAc yielded **6** (291 mg, 60%) as a light yellow oil: IR (film) 2951, 1721, 1651, 1599, 1443, 1322, 1232, 1218, 1050, 1023, 964 cm^{-1}; ^{1}H NMR (keto/enol tautomers) δ 12.72 (s, 0.87H), 6.24 (d, J = 2.2 Hz, 0.13H), 4.25 (m, 0.26H), 4.06 (m, 3.74H), 3.81 (s, 0.4H), 3.79 (s, 2.6H), 3.76 (s, 0.4H), 3.73 (s, 2.6H), 3.35–3.05 (m, 2H), 2.9–2.41 (m, 2H), 2.01–1.77 (m, 2H), 1.65–1.46 (m, 4H), 1.4 (t, J = 7 Hz, 0.4H), 1.33 (t, J = 7 Hz, 3H), 1.25 (t, J = 7 Hz, 2.6H); ^{13}C NMR (of enol form) δ 182.1 (d, J_{CP} = 2.5 Hz), 171.6 (d, J_{CP} = 1.6 Hz), 168 (d, J_{CP} = 29 Hz), 144.2 (d, J_{CP} = 180 Hz), 138.0 (d, J_{CP} = 9 Hz), 101.6 (d, J_{CP} = 10 Hz), 62.4 (d, J_{CP} = 7 Hz), 62.2 (d, J_{CP} = 7 Hz), 52.5, 51.8, 35.5, 31.2 (d, J_{CP} = 8 Hz), 29.7 (d, J_{CP} = 3 Hz), 27.8, 25.9, 16.4 (d, J_{CP} = 6 Hz), 16.3 (d, J_{CP} = 6 Hz); ^{31}P NMR 17.5 (enol tautomer), 16.4 (keto tautomer). Anal. Calcd for $C_{17}H_{27}O_8P$: C, 52.31; H, 6.97. Found: C, 52.38; H, 6.98.

1-Hydroxy-2,3-bis(methoxycarbonyl)-4-(diethoxyphosphinyl)cyclodeca-1,3-diene (8). According to the general procedure, a solution of 2-(diethoxyphosphinyl)cyclooctanone **(7)** (171 mg, 0.65 mmol) in toluene was treated with NaHMDS (1.3 mL, 0.78 mmol) and DMAD (95 μL, 0.773 mmol) and stirred for 4 h. The product obtained was purified by column chromatography on silica gel. Elution with 4:1 CH_2Cl_2/EtOAc yielded **8** (151 mg, 57%) as a light yellow oil: IR (film) 2950, 1720, 1649, 1596, 1441, 1305, 1238, 1213, 1049, 1023, 964 cm^{-1}; ^{1}H NMR (keto/enol tautomers) δ 12.76 (s, 0.86H), 5.80 (d, J = 2.2 Hz, 0.14H), 4.20 (m, 0.28H), 4.05 (m, 3.72H), 3.83 (s, 0.43H), 3.78 (s, 2.57H), 3.74 (s, 0.43H), 3.71 (s, 2.57H), 3.38–3.2 (m, 1H), 2.9–2.6 (m, 1H), 2.52–2.38 (m, 1H), 2.28–2.15 (m, 1H), 1.85–1.39 (m, 8H), 1.32 (t, J = 7Hz, 3H), 1.25 (t, J = 7Hz, 3H); ^{13}C NMR (of enol form) δ 180.2, 171.7, 167.8 (d, J_{CP} = 30 Hz), 146.8(d, J_{CP} = 176 Hz), 137.4 (d, J_{CP} = 10 Hz), 101.1 (d, J_{CP} = 9 Hz), 62.4 (d, J_{CP} = 6 Hz), 62.1 (d, J_{CP} = 7 Hz), 52.5, 51.7, 31.1 (d, J_{CP} = 7 Hz), 30.6, 28.0, 27.1 (d, J_{CP} = 3 Hz), 22.2, 21.9, 16.4, 16.3; ^{31}P NMR 17.6 (enol tautomer), 16.3 (keto tautomer). Anal. Calcd for $C_{18}H_{29}O_8P$: C, 53.46; H, 7.23. Found: C, 53.41; H, 7.28.

1-Hydroxy-2,3-bis(methoxycarbonyl)-4-(diethoxyphosphinyl)-7,8-benzocycloocta-1,3-diene (10). According to the general procedure, a solution of phosphonate **9** (326 mg, 1.156 mmol) in toluene (2 mL) was treated with NaHMDS (2.3 mL, 1.4 mmol) and DMAD (163 μL, 1.33 mmol) and stirred for 10 h. The product obtained was purified by column chromatography on neutral alumina (23.5 g, Grade IV). Elution with CH_2Cl_2 yielded crude "abnormal Michael" product **16** as greenish yellow crystals. Further elution with EtOAc then 5% HOAc/EtOAc yielded **10** (179 mg, 37%) as a light yellow oil: IR (film) 2990, 2952, 1727, 1651, 1610, 1588, 1441, 1345, 1299, 1261, 1210, 1049, 1022, 964 cm^{-1}; ^{1}H NMR δ 13.25 (s, 1H), 7.4 (m, 1H), 7.25 (m, 2H), 7.13 (m, 1H), 3.88–3.54 (m, 4H), 3.8 (s, 3H), 3.68 (s, 3H), 3.28–3.06 (m, 2H), 2.98–2.72 (m, 2H), 1.23 (t, J = 7 Hz, 3H), 1.13 (t, J = 7 Hz, 3H); ^{13}C NMR δ 175.4 (d, J_{CP} = 2 Hz), 171.1, 167.2 (d, J_{CP} = 8 Hz), 142.4 (d, J_{CP} = 11 Hz), 137.4, 136.7 (d, J_{CP} = 174 Hz), 135, 130.4, 129.9, 128.7, 126.1, 101.8 (d, J_{CP} = 20 Hz), 62.2 (d, J_{CP} = 5 Hz), 62.1 (d, J_{CP} = 7 Hz), 52.3, 52.2, 32.8 (d, J_{CP} = 2 Hz), 30.5 (d, J_{CP} = 10 Hz), 16.3 (d, J_{CP} = 6 Hz), 16.0 (d, J_{CP} = 6 Hz); ^{31}P NMR 15.9. Anal. Calcd for $C_{20}H_{25}O_8P$: C, 56.60; H, 5.94. Found: C, 56.42; H, 5.95.

Abnormal Michael Product 16. Crude **16** was further purified on silica gel (3:1 CH_2Cl_2/EtOAc) to afford pure **16** (132 mg, 29%): IR (film) 2984, 2905, 1732, 1621, 1504, 1455, 1259, 1032, 970, cm^{-1}; ^{1}H NMR δ 7.96 (d, J = 7 Hz, 1H), 7.46–7.23 (m, 3H), 4.23 (m, 4H), 4.0 (s, 3H), 2.96 (t, J = 7 Hz, 2H), 2.62 (t, J = 7 Hz, 2H), 1.36 (t, J = 7 Hz, 6H); ^{13}C NMR δ 165.3 (d, J_{CP} = 7 Hz), 160 (d, J_{CP} = 1.5 Hz), 158.8 (d, J_{CP} = 13 Hz), 158.1 (d, J_{CP} = 8 Hz), 138.3, 132.2, 128.1, 127.5, 126.9, 124.5, 109.1 (d, J_{CP} = 13 Hz), 109 (d, J_{CP} = 193 Hz), 63.5, 63.4, 53.3, 27.0, 21.9, 16.4, 16.3; ^{31}P NMR 10.0; FABMS m/z (rel intensity) 392 (M^+, 30). Anal. Calcd for $C_{19}H_{21}O_7P$: C, 58.17; H, 5.39. Found: C, 57.92; H, 5.33.

2-(Diethoxyphosphinyl)-2-[1′,2′-bis(ethoxycarbonyl)-ethylenyl]cyclohexanone (15). DMAD (86 μL, 0.702 mmol) was added in a dropwise fashion to a solution of phosphonate **3** (149 mg, 0.638 mmol) in t-BuOH (0.6 mL) at room temperature. KOH (30 μL of 30% solution in methanol) was added midway through addition of DMAD, when the contents turned yellow. Addition of DMAD was completed and the reaction mixture was stirred for 1.5 h at 35 °C. HCl (30 μL of a 10% solution) and water (1 mL) were added to quench the reaction and the contents were extracted into methylene chloride (2 × 3 mL). The organic layer was dried over Na_2SO_4 and solvent evaporated under vacuum to give **15** as a 5:1 mixture of E- and Z-isomers. Purification by chromatography on silica gel (2:1 CH_2Cl_2:EtOAc) afforded **15** (191 mg, 80%) as a mixture of isomers: IR 2952, 1732, 1631, 1431, 1249, 1049, 1021, 961 cm^{-1}; ^{1}H NMR (of major E-isomer) δ 6.25 (d, J = 5.2 Hz, 1H), 4.2 (m, 4H), 3.8 (s, 3H), 3.75 (s, 3H), 2.58 (m, 2H), 2.45 (m, 2H), 2.0–1.75 (m, 4H), 1.32 (t, J = 7 Hz, 6H). The vinyl proton of the minor Z isomer occurs further downfield at 6.66 ppm (d, J = 2.1 Hz) due to the cis relationship with the adjacent ester group. Additionally, the J_{HP} value for the minor Z-isomer (J = 2.1 Hz) would be expected to be smaller than that of the major E-isomer (J = 5.2 Hz) since the distance between the vinyl proton and the phosphorus is much greater. ^{13}C NMR (of major E-isomer) δ 205.6 (d, J_{CP} = 6 Hz), 166.9 (d, J_{CP} = 5 Hz), 165.1 (d, J_{CP} = 3 Hz), 144 (d, J_{CP} = 9 Hz), 125.9 (d, J_{CP} = 8 Hz), 63.6 (d, J_{CP} = 7 Hz), 63.35 (d, J_{CP} = 7 Hz), 60.8 (d, J_{CP} = 136 Hz), 52.5, 52.1, 40.4 (d, J_{CP} = 2 Hz), 33.3 (d, J_{CP} = 4 Hz), 25.5, 20.6 (d, J_{CP} = 8 Hz), 16.4, 16.3; ^{31}P NMR 20.6. Anal. Calcd for $C_{16}H_{25}O_8P$: C, 51.06; H, 6.69. Found: C, 50.86; H, 6.76.

6-(Diethoxyphosphinyl)-6-[1′,2′-bis(ethoxycarbonyl)-ethylenyl]-3-methyl-2-cyclohexen-1-one (27). Following the procedure used for preparation of **15**, DMAD (85 μL, 0.69 mmol) was added to phosphonate **26** (155 mg, 0.63 mmol) in t-BuOH (0.6 mL), followed by KOH (30 μL of 30% solution in methanol). Purification by chromatography on silica gel (3:1 CH_2Cl_2:EtOAc) afforded **27** (196 mg, 80%) as a 4:1 mixture of E- and Z-isomers: IR 2978, 1732, 1665, 1637, 1436, 1251, 1208, 1049, 1023, 967 cm^{-1}; ^{1}H NMR (of major E-isomer) δ 6.15 (d, J = 5 Hz, 1H), 5.93 (br s, 1H), 4.2 (m, 4H), 3.81 (s, 3H), 3.71 (s, 3H), 2.54 (m, 3H), 2.36 (m, 1H), 1.97 (s, 3H), 1.31 (t, J = 7 Hz, 6H). Vinyl proton of minor Z-isomer occurs at 6.64 ppm. ^{13}C NMR (of major E-isomer) δ 192.8 (d, J_{CP} = 6 Hz), 166.85 (d, J_{CP} = 4 Hz), 164.8 (d, J_{CP} = 3 Hz), 163.5, 145.6 (d, J_{CP} = 9 Hz), 126 (d, J_{CP} = 2 Hz), 124.2 (d, J_{CP} = 9 Hz), 63.75 (d, J_{CP} = 7 Hz), 63.35 (d, J_{CP} = 7 Hz), 56.35 (d, J_{CP} = 137 Hz), 52.5, 52.0, 30.4 (d, J_{CP} = 4 Hz), 28.2 (d, J_{CP} = 9 Hz), 24.2, 16.4 (d, J_{CP} = 3 Hz), 16.3 (d, J_{CP} = 2 Hz); ^{31}P NMR 21.0. Anal. Calcd for $C_{17}H_{25}O_8P$: C, 52.58; H, 6.49. Found: C, 52.43; H, 6.52.

Reaction of 3-(Diethoxyphosphinyl)-2-norbornanone (30) with DMAD. According to the general procedure, a solution of 3-(diethoxyphosphinyl)-2-norbornanone **(30)** (1.075g, 4.37 mmol) in 11 mL of toluene was treated with NaHMDS (8.74 mL, 5.24 mmol) and DMAD (617 μL, 5.03 mmol) for 6 h to afford 1.7 g of product. Part of the crude product mixture (1.28 g) was distilled bulb to bulb (1 mm, 120 °C oven temperature) to remove unreacted phosphonate **30** (130 mg) and further purified by column chromatography on silica gel. Elution with 3:1 CH_2Cl_2/EtOAc yielded **32** (106 mg, 8%). Further elution with the same solvent mixture yielded **31** (687 mg, 54 or 64% yield based on recovered starting material).

Abnormal Michael product 31: IR 2954, 1754, 1728, 1678, 1435, 1255, 1043, 1023, 967 cm^{-1}; ^{1}H NMR δ 4.2–4.0 (m, 4H), 3.87 - 3.73 (m, 1H), 3.8 (s, 6H), 3.1 (t, J = 7.5 Hz, 1H), 3.0 (m, 1H), 2.60 (d, J = 14 Hz, 1H), 2.2–1.7 (m, 5H), 1.29 (t, J = 7 Hz, 3H), 1.27 (t, J = 7 Hz, 3H); ^{13}C NMR δ 201.4 (d, J_{CP} = 2 Hz), 167.1 (d, J_{CP} = 3 Hz), 165.5 (d, J_{CP} = 4 Hz), 140.6 (d, J_{CP} = 11 Hz), 134.3 (d, J_{CP} = 10 Hz), 63.2 (d, J_{CP} = 7 Hz), 62.7 (d, J_{CP} = 7 Hz), 53.2, 52.8, 52.4, 46.7 (d, J_{CP} = 131

Hz), 37.5 (d, J_{CP} = 4 Hz), 33.3, 31.4 (d, J_{CP} = 18 Hz), 27.4, 16.3 (d, J_{CP} = 6 Hz), 16.2 (d, J_{CP} = 6 Hz); ^{31}P NMR 22.2. HRMS calcd for $C_{17}H_{26}O_8P$ (MH^+) 389.1365, found 389.1369.

3-(Diethoxyphosphinyl)-3-[1′,2′-bis(ethoxycarbonyl)-ethylenyl]-2-norbornanone (32). Following the procedure used for preparation of **15**, phosphonate **30** (167 mg, 0.68 mmol) was combined with KOH (30 μL of 30% KOH in MeOH), tBuOH (0.6 mL), and DMAD (90 μL, 0.73 mmol) in t-BuOH (0.3 mL). Purification by chromatography on silica gel (3:1 CH_2Cl_2:EtOAc) afforded a mixture of Michael adduct isomers (197 mg, 75%). The major isomer **32** was obtained as a single diastereomer (64% yield as determined by ^{31}P NMR): IR 2986, 1732, 1629, 1435, 1251, 1053, 1022, 969 cm^{-1}; ^{1}H NMR δ 6.3 (d, J = 5.5 Hz, 1H), 4.2 (m, 4H), 3.85 (s, 3H), 3.72 (s, 3H), 2.9 (br d, J = 2 Hz, 1H), 2.72 (br d, J = 4 Hz, 1H), 2.35 (m, 1H), 2.14 (br d, J = 11 Hz, 1H), 1.92 - 1.7 (m, 3H), 1.59 (br t, J = 9 Hz, 1H), 1.32 (t, J = 7 Hz, 6H); ^{13}C NMR δ 209.9, 166.7 (d, J_{CP} = 3 Hz), 164.8 (d, J_{CP} = 4 Hz), 145.4 (d, J_{CP} = 8 Hz), 123.2 (d, J_{CP} = 9 Hz), 63.45 (d, J_{CP} = 8 Hz), 63.3 (d, J_{CP} = 7 Hz), 62.9 (d, J_{CP} = 141 Hz), 52.6, 52.0, 50.5 (d, J_{CP} = 3 Hz), 46.5, 36.6 (d, J_{CP} = 16 Hz), 24.8 (d, J_{CP} = 4 Hz), 24.7, 16.4 (d, J_{CP} = 4 Hz), 16.3 (d, J_{CP} = 3 Hz); ^{31}P NMR 18.9. Anal. Calcd for $C_{17}H_{25}O_8P$: C, 52.58; H, 6.49. Found: C, 52.84; H, 6.47.

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Supplementary Material Available: Copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra for compounds **2**, **4**, **6**, **8**, **10**, **15**, **16**, **17**, **27**, **31**, and **32** (33 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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