Zinc-Mediated Chain Extension of β-Keto Phosphonates

Christopher A. Verbicky and Charles K. Zercher*

Department of Chemistry, University of New Hampshire, Durham, New Hampshire 03824

ckz@christa.unh.edu

Received March 9, 2000

A variety of β-keto phosphonates can be converted to γ-keto phosphonates through reaction with ethyl(iodomethyl)zinc. The presence of α-alkyl substituents, Lewis basic functionality, and modestly acidic NH-protons are accommodated in substrates of this reaction. Chain extension of β-keto phosphonates that contained olefinic functionality proceeded more quickly than cyclopropanation; however, it was not possible to effect the chain extension to the exclusion of cyclopropane formation. A primary reason for this imperfect chemoselectivity appears to be the slow chain extension of β-keto phosphonates. Nevertheless, the simplicity, the scope, and efficiency of this method serve to make it an attractive alternative to the established methods for γ-keto phosphonate formation.

Introduction

The phosphonate moiety plays many roles in organic chemistry.[1] Most often employed with respect to its anion-stabilizing ability, the phosphonate unit is applied frequently to the functionalization and manipulation of the carbon skeleton. Moreover, the diverse ways in which the phosphonate group can be removed, like elimination of an oxaphosphatane or reduction with dissolving metals, have made the phosphonate group an essential functionality to organic chemists.

In addition to its synthetic utility, the phosphonate unit has been recognized as an attractive isosteric replacement for the biologically relevant phosphate moiety and as a transition state analogue for mimicking hydrolysis reactions. A wide range of biologically active phosphonate-containing compounds have been identified, including compounds which are active as anti-viral, insecticides, anti-acidosis agents, and antibiotics.[2]

One particular subset of phosphonates that have been demonstrated to have diverse biological activity is the γ-keto phosphonates. Molecules of this type possess diverse biological activity ranging from herbicides and fungicides (**1**)[3] to antihypertensive agents (**2**).[4] Compound **3** has been proposed as a treatment for osteoporosis,[5] while compounds **4**[6] and **5**[7] exhibit activity as inhibitors of matrix-metalloprotease (MMP-2) and kininogenase, respectively. The γ-keto phosphonic acids are represented in compounds such as **6**, which is an inhibitor of 5-alanine levulinic acid dehydratase, an early enzyme on the tetrapyrrole biosynthetic pathway.[8] Another amino acid derived γ-keto phosphonate **7** was identified as a tight binding inhibitor of D-alanine:D-alanine ligase, an essential enzyme in bacterial wall synthesis.[9] Facile reduction of the carbonyl within the γ-keto phosphonate provides easy access to biologically relevant γ-hydroxy phosphonates.[3,10]

Synthetic approaches to γ-keto phosphonates have been varied. The first method (eq 1) designed for the formation of γ-keto phosphonates involved the addition of silyl phosphites to α,β-unsaturated carbonyls.[11] The lack of specific reaction conditions and unreported product ratios led other research groups to study this reaction in greater detail.[2d,12] Competition between 1,2- and 1,4-addition pathways were observed, yet the 1,4 addition pathway could be optimized when reactions were performed at 180 °C in a sealed tube. The utility of this general strategy for the preparation of γ-keto phosphonates and their derivatives was enhanced when it was reported that the addition of catalytic or stoichiometric

(1) (a) Hilderbrand, R. L. *The Role of Phosphonates in Living Systems*; CRC Press: Boca Raton, 1983. (b) Engel, R. *Synthesis of Carbon-Phosphorous Bonds*; CRC Press: Boca Raton, 1988. (c) Wiemer, D. F. *Tetrahedron* **1997**, *53*, 16609.

(2) (a) McClure, C. K.; Mishra, P. K.; Grote, C. W. *J. Org. Chem.* **1997**, *62*, 2437. (b) Mori, I.; Iwasaki, G.; Hayakawa, K. *Yuki Gosei Kagaku Kyokaishi* **1996**, *56*, 514. (c) Chakravarty, P. K.; Combs, P.; Toth, A.; Greenlee, W. J. *Tetrahedron Lett.* **1987**, *28*, 611. (d) Evans, D. A.; Hurst, K. M.; Takacs, J. M. *J. Am. Chem. Soc.* **1978**, *100*, 3467. (e) Collomb, D.; Chantegrel, B.; Deshayes, C. *Tetrahedron* **1996**, *52*, 10455.

(3) Mori, I.; Iwasaki, G.; Scheidegger, A.; Koizumi, S.; Hayakawa, K.; Mano, J. PCT Int. Appl. WO 92-JP485 920417; *Chem. Abstr.* **1993**, *118*, 124547.

(4) Karanewsky, D. S.; Dejneka, T. Eur. Pat. Appl. EP 87-104477 870326, 1987; US Appl. 844635, 1986; *Chem. Abstr.* **1988**, *109*, 129685.

(5) Isomura, Y.; Sakamoto, S.; Abe, T. Japan Patent Appl. JP 87-271433 871026; *Chem. Abstr.* **1989**, *111*, 174388.

(6) Kluender, H. C. E.; Benz, G. H. H. H.; Brittelli, D. R.; Bullock, W. H.; Combs, K. J.; Dixon, B. R.; Schneider, S.; Wood, J. E.; Vanzandt, M. C.; Wolanin, D. J.; Wilhelm, S. M. US Pat. Appl. US 95-539409 951106; *Chem. Abstr.* **1998**, *129*, 161412.

(7) Szelke, M.; Evans, D. M.; Jones, D. M. PCT Int. Appl. WO 94-GB1887 940831; *Chem. Abstr.* **1995**, *123*, 257409.

(8) (a) Patchett, A. A.; Thornberry, N. A.; Bull, H. G.; Taub, D.; Wilson, K. E. *BCPC Monogr.* **1989**, *42* (Prospects Amino Acid Biosynth. Inhib. Crop Prot. Pharm. Chem.), 109−118. (b) Chakravarty, P. K.; Greenlee, W. J.; Parson, W. H.; Patchett, A. A.; Combs, P.; Roth, A.; Busch, R. D.; Mellin, T. N. *J. Med. Chem.* **1989**, *32*, 1886.

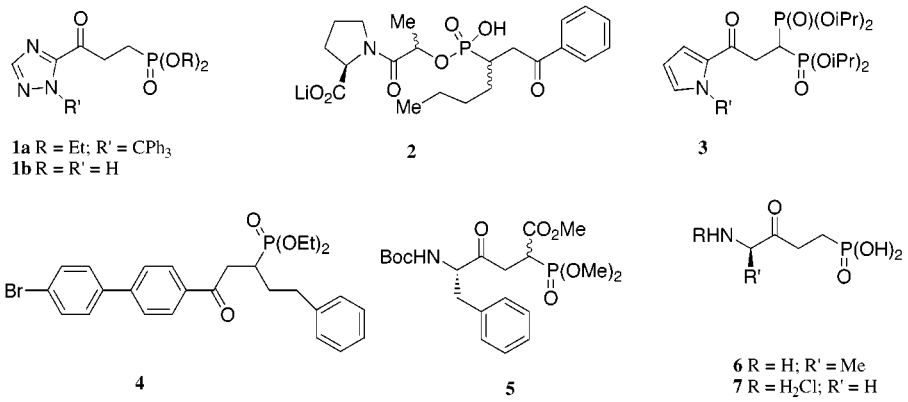
(9) Appleton, D.; Duguid, A. B.; Lee, S.-K.; Ha, Y.-J.; Ha, H.-J.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 89.

(10) (a) Mori, I.; Kimura, Y.; Nakano, T.; Matsunaga, S.; Iwasaki, G.; Ogawa, A.; Hayakawa, K. *Tetrahedron Lett.* **1997**, *38*, 3543. (b) Crooks, S. L.; Robinson, M. B.; Koerner, J. F.; Johnson, R. L. *J. Med. Chem.* **1986**, *29*, 1988. (c) Mori, I.; Iwasaki, G.; Kimura, Y.; Matunaga, S.; Ogawa, A.; Nakano, T.; Buser, H.-P.; Hatano, M.; Tada, S.; Hayakawa, K. *J. Am. Chem. Soc.* **1995**, *117*, 4411.

(11) Birum, G. H.; Richardson, G. A. US Patent 3 113 139, 1963; *Chem. Abstr.* **1964**, *60*, 5551d.

(12) Liotta, D.; Sunay, U.; Ginsberg, S. *J. Org. Chem.* **1982**, *47*, 2229.

10.1021/jo000343f CCC: $19.00
Published on Web 08/10/2000



1a R = Et; R' = CPh_3
1b R = R' = H

2

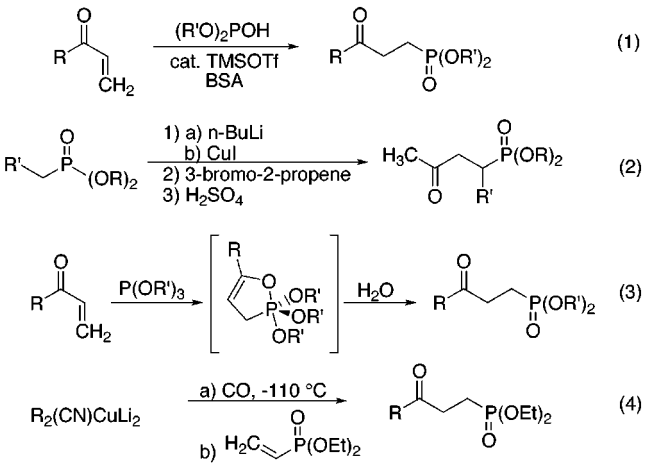
3

4

5

6 R = H; R' = Me
7 R = H_2Cl; R' = H

Lewis acids facilitated similar conjugate additions of phosphonic acid derivatives.

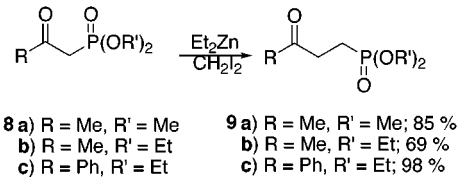


In 1979 Savingac and co-workers reported a strategy (eq 2) in which a phosphonate-stabilized nucleophile was treated with 2,3-dihalopropenes.[13] Hydrolysis of the resulting vinyl halide with sulfuric acid released the γ-keto functionality. Although the procedure provides simple γ-keto phosphonic acids in good yields, its application is limited by the harsh conditions in the hydrolysis step.

A route to γ-keto phosphonates reported by Gorenstein[14] and further developed by McClure and co-workers[15] invoked the conjugate addition (eq 3) of a trialkyl phosphite to an α,β-unsaturated ketone and hydrolysis of the intermediate oxaphosphorane. The utility of this method was enhanced by the nucleophilic character of the intermediate oxaphosphorane, which facilitated stereoselective aldol reactions resulting in formation of β-substituted-γ-keto phosphonates.

Yet another strategy for the formation of γ-keto phosphonates was reported by Kabalka (eq 4) in which an acyl anion generated from a higher order cuprate was added to a vinyl phosphonate.[16] Conjugate addition results in formation of a phosphonate anion that can be alkylated with allylic halides to provide α-substituted-γ-keto phosphonates. However, the reaction requires use of the easily polymerizable vinyl phosphonates and was not reported with β-substituted vinyl phosphonates.

Scheme 1



8 a) R = Me, R' = Me
b) R = Me, R' = Et
c) R = Ph, R' = Et

9 a) R = Me, R' = Me; 85 %
b) R = Me, R' = Et; 69 %
c) R = Ph, R' = Et; 98 %

We recently reported a zinc carbenoid-mediated approach to γ-keto esters,[17] which is believed to proceed through the intermediacy of a cyclopropyl zinc alkoxide. We report herein the application of this chain extension reaction to β-keto phosphonates. The ease with which β-keto phosphonates can be generated, coupled with the simplicity of the one-step chain extension reaction, serves to make this zinc-mediated method very attractive for the preparation of γ-keto phosphonates. The scope and limitations of this approach are included in this report.

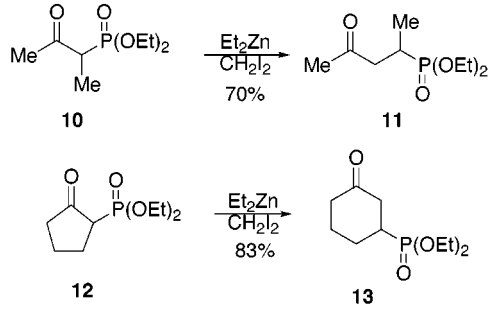
Results and Discussion

In a fashion similar to that observed with the β-keto esters, treatment of simple β-keto phosphonates **8** with the Furukawa-modified Simmons−Smith reagent[18] provided rapid and efficient preparation of the γ-keto phosphonate **9** (Scheme 1).

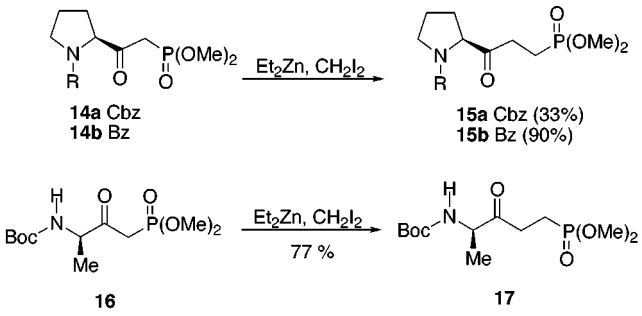
Only a limited number of phosphonate esters were surveyed, yet the type of phosphonate ester had little influence on the efficiency of the reaction. The most significant difference between β-keto esters and the β-keto phosphonates was the rate with which the reaction proceeded. While the chain extension of β-keto esters is typically complete within minutes, the chain extension of β-keto phosphonates required reaction times on the order of 2 h for complete consumption of starting material. Although the reaction proceeds with as few as 3 equiv of the presumed ethyl(iodomethyl)zinc[19] species and at temperatures as low as 0 °C, the conversion of simple, unfunctionalized β-keto phosphonates was optimized with 6 equiv of both diethyl zinc and methylene iodide at room temperature. The reaction is remarkably clean, and a single product was observed through chromatographic and spectroscopic (NMR) analysis of the crude

(13) Savignac, P.; Breque, A.; Mathey, F.; Varlet, J.-M.; Collignon, N. *Synth. Commun.* **1979**, *9*, 287.
(14) Gorenstein, D.; Westheimer, F. H. *J. Am. Chem. Soc.* **1970**, *92*, 634.
(15) (a) Ramirez, F. *Synthesis* **1974**, 90. (b) McClure C. K.; Jung, K.-Y. *J. Org. Chem.* **1991**, *56*, 2326. (c) McClure, C. K.; Grote, C. W. *Tetrahedron Lett.* **1991**, *32*, 5313.
(16) Li, N.-S.; Yu, S.; Kabalka, G. W. *Organometallics* **1999**, *18*, 1811.
(17) Brogan, J. B.; Zercher, C. K. *J. Org. Chem.* **1997**, *62*, 6444.
(18) Furakawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53.
(19) Charette, A. B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1996**, *118*, 4539.

Scheme 2



Scheme 3



reaction mixtures. Isolated yields of these polar materials were optimized through thorough extraction of the reaction mixture.

In contrast to the zinc-mediated chain extension of β-keto esters, the presence of α-substitution on the β-keto phosphonate did not diminish the efficiency of the chain extension reaction. Although 6 h were required for the consumption of the starting β-keto phosphonate **10**,[20] an efficient chain extension reaction (70%) ensued (Scheme 2).

Analysis of the product **11** was performed by ^{1}H, ^{13}C, and DEPT experiments and indicated the presence of a methyl group with $^{2}J_{PC} = 5.2$ Hz, $^{3}J_{PH} = 18.3$ Hz, and a methine carbon with $^{1}J_{PC} = 143.7$ Hz. These data confirmed that that the new methylene group was incorporated adjacent to the carbonyl and that the substituted carbon (the original α-carbon) was adjacent to phosphorus. Movement of the alkyl substituent to the position adjacent to the phosphonate is consistent with the results from the chain extension reaction of β-keto esters and supports the presence of the proposed cyclopropyl alkoxide intermediate. Exposure of cyclopentanone derivative **12**[21] to ethyl(iodomethyl)zinc resulted in efficient ring expansion and provided cyclohexanone **13**.

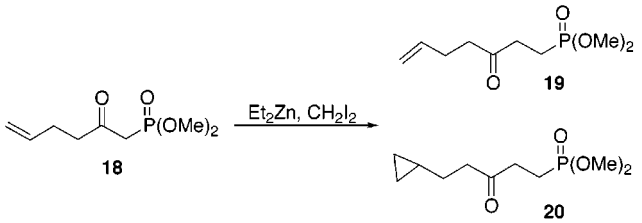
The potential impact of extraneous Lewis basic functionality and the presence of additional acidic protons had not been addressed in the study of β-keto esters. Preparation of amino acid-derived β-keto phosphonates **14a**, **14b**, and **16** was accomplished through modification of the method reported by Koskinen (Scheme 3).[22]

Treatment of the Cbz-proline derivative (**14a**) with ethyl(iodomethyl)zinc led to product (**15a**) formation which was contaminated with an unidentified byproduct. A reduction in the reaction time prevented formation of the reaction byproduct; however, unreacted starting material resulted in a diminished yield of γ-keto phosphonate **15a** (33%; 62% BORSM). In contrast, the benzoyl-protected β-keto phosphonate **14b** underwent a remarkably efficient transformation (90%), thereby indicating that the presence of additional Lewis basic functionality presents no specific hindrance to the chain extension reaction. The successful chain extension of the β-keto phosphonate **16** derived from Boc-alanine revealed that urethane functionality is tolerated in the chain extension reaction and demonstrated that the presence of a modestly acidic NH does not hinder the reaction.

The Furukawa-modified Simmons−Smith reagent is typically used for the cyclopropanation of olefinic systems. As such, cyclopropanation of alkene functionality might be expected to compete with the chain extension process. Therefore, two olefin-containing β-keto phosphonates **18** and **21** were prepared and subjected to the chain extension conditions. In contrast to the β-keto ester substrates, it was not possible to effect chain extension of β-keto phosphonates to the exclusion of cyclopropanation.

Efforts to effect chain extension of a β-keto phosphonate **18** that possessed a neutral alkene are described in Table 1. Three basic strategies were utilized for the chain extension reaction, including two strategies (B and C) in which the zinc enolate was formed prior to addition/formation of the carbenoid. The reaction conditions studied included (A) an excess of zinc carbenoid being formed prior to addition of the phosphonate; (B) the zinc enolate, generated through addition of 1 equiv of diethyl zinc to the β-keto phosphonate, being added to a preformed solution of the carbenoid; and (C) the zinc enolate being generated by reaction with excess diethyl zinc, followed by direct addition of methylene iodide. Each of these reaction conditions was successful at effecting chain extension, although, regardless of time or number of equivalents of the carbenoid, cyclopropanation of the

Table 1. Attempted Chain Extension of 18

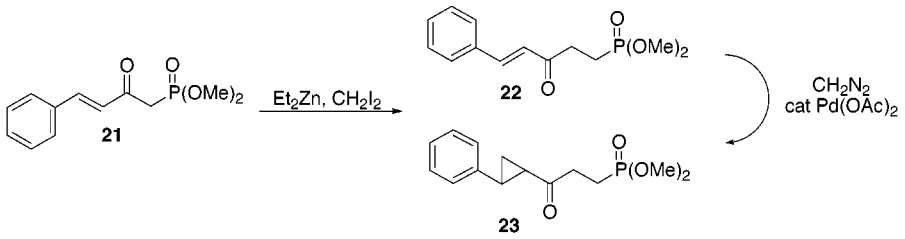


entry	method[a]	equiv[b]	time[c]	temp, °C	yield, %	ratio (**18**:**19**:**20**)
1	A	6	180	25	80[d]	0:1:1[e]
2	A	6	40	25	75[d]	0:2:1[e]
3	A	3	20	25	*f*	4:4:1[g]
4	A	6	25	0	*f*	1
5	B	6	25	25	*f*	0:3:1[g]
6	C	6	30	25	*f*	0:3:1[g]
7	C	6	10	25	*f*	1:7.8:1.3[g]
8	C	h	30	25	*f*	1.4:6.6:1[g]
9	C	6	30	0	*f*	3.1:8:1[g]

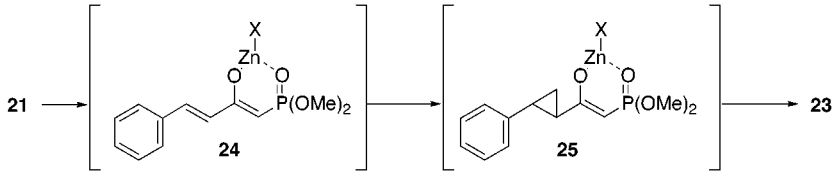
[a] Method A: β-keto phosphonate added to preformed carbenoid. Method B: the β-keto phosphonate was mixed with 1 equiv of diethyl zinc prior to its addition to the carbenoid. Method C: excess diethyl zinc added to the β-keto phosphonate, followed by addition of methylene iodide. [b] Ratio of carbenoid (1:1, Et_2Zn:CH_2I_2) to β-keto phosphonate **18**. [c] Reaction time after addition of the carbenoid [d] Isolated yield of the inseparable mixture of **19** and **20**. [e] Determined by ^{1}H NMR analysis of purified material. [f] No purification was attempted. [g] Determined by analysis of ^{1}H NMR of crude reaction mixture. [h] Ratio of reagents was 6:3:1 (Et_2Zn, CH_2I_2, **18**).

(20) Coutrot, P.; Ghribi, A. *Synthesis* **1986**, (8), 661.
(21) (a) Hammond, G. B.; Calogeropoulou, T.; Wiemer, D. F. *Tetrahedron Lett.* **1986**, *27*, 4265. (b) Calogeropoulou, T.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1987**, *52*, 4185.
(22) Koskinen, A. M. P.; Krishe, M. J. *Synlett* **1990**, 665.

Scheme 4



Scheme 5



chain extension product was observed. Without exception, the chain extension reaction occurs more rapidly than cyclopropanation.

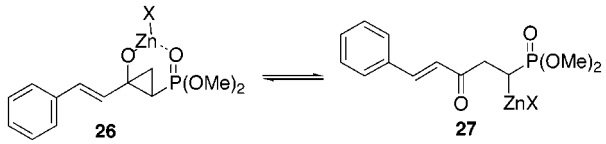
The chain extension of β-keto phosphonate **21**, which contained an electron-deficient alkene, was studied. The generation of **22** was optimized through the use of 3.25 equiv of ethyl(iodomethyl)zinc at 25 °C for 30 min; however, once again the formation of **22** was contaminated with a second product believed to be the cyclopropane **23** (Scheme 4).

In response to difficulties in the separation of the two products, transformation of the crude reaction mixture into the cyclopropanated material **23** was desired. Re-exposure of the inseparable product mixture to the ethyl(iodomethyl)zinc (chain extension reaction conditions) provided no additional cyclopropane; however, exposure of the mixture to diazomethane and catalytic $Pd(OAc)_2$ facilitated the smooth conversion to cyclopropane **23** and confirmed the identity of the cyclopropane as the second product of the chain extension reaction.[23]

Formation of cyclopropane **23** from the electron-deficient alkene **21** with an electrophilic zinc-carbenoid appears unusual. It is worth noting that efforts to cyclopropanate **22** with an electrophilic zinc carbenoid failed to provide **23**. However, deprotonation of compound **21** when exposed to the chain extension reaction conditions makes the "electron-deficient olefin" of **21** part of a cross-conjugated electron-rich π-system. The allylic hetereoatom of **24** seems to be an appropriate handle for formation of cyclopropane **25**, which when followed by chain extension of the enolate could account for the formation of **23** (Scheme 5). Although chain extension prior to cyclopropane formation appears to be an unlikely explanation for the formation of **23**, cyclopropanation of the "electron-deficient olefin" might be possible if the hypothetical cyclopropyl alkoxide intermediate **26** provided a heteroatom handle for subsequent cyclopropanation. Since it was unclear how much of the cyclopropyl zinc alkoxide **26** existed in solution or whether the cyclopropane underwent ring-opening to a Reformatsky-type intermediate **27**, NMR studies of the reaction were initiated (Scheme 6).

Addition of excess diethylzinc to an NMR tube which contained a deuterated-methylene chloride solution of

Scheme 6



β-keto phosphonate **8a** resulted in the rapid generation of ethane and a compound **28**, which gave spectra consistent with the removal of an α-proton and formation of an enolate. In situ generation of the carbenoid by addition of diiodomethane to this solution resulted in the rapid consumption of the enolate and formation of a second intermediate.[24] The NMR spectra were quite complex and included resonances for propylzinc iodide, a decomposition product derived from ethyl(iodomethyl)-zinc. No direct evidence has been observed that the second, persistent intermediate is the hypothetical cyclopropyl alkoxide. In fact, the downfield shift of the methyl group in the ^1H NMR, the presence of a ketone resonance in the ^{13}C NMR spectrum, and comparison with literature data suggest that the persistent intermediate is the open-chain organometallic species **27** akin to a phosphonate−Reformatsky reagent. An aqueous quench of the reaction mixture provided chain extension product **9a**. These NMR data suggest that formation of **23** is unlikely to result from cyclopropanation of the cyclopropyl alkoxide intermediate **26**.

Summary

In summary, a variety of β-keto phosphonates can be converted to γ-keto phosphonates through reaction with ethyl(iodomethyl)zinc. The presence of α-alkyl substituents, Lewis basic functionality, and modestly acidic NH protons are accommodated in substrates of this reaction. In contrast to the trend observed with β-keto esters, it was not possible to perform chain extension of β-keto phosphonates to the exclusion of olefin cyclopropanation. A primary reason for this poor chemoselectivity appears

(23) Denmark, S. E.; Stavenger, R. A.; Faucher, A.-M.; Edwards, J. P., *J. Org. Chem.* **1997**, *62*, 3375.

(24) Alkylation of the enolate with methylene iodide followed by substitution of iodine for the zinc cannot be ruled out in a mechanistic description of this NMR experiment. However, the absence of olefin formation (resulting from elimination of the β-iodide) in the NMR studies and the inability to alkylate the zinc enolate of a β-keto ester with methylene iodide (unpublished results, R. Hilgenkamp and C. Zercher, University of New Hampshire) argue against alkylation of the β-keto phosphonate with methylene iodide.

to be the slow chain extension of β-keto phosphonates. Nevertheless, the simplicity, the scope, and the efficiency of this method serve to make it an attractive alternative to the established methods for γ-keto phosphonate formation.

Experimental Section

A. General Experimental Section. All reactions were run in oven-dried glassware under a nitrogen atmosphere and stirred with Teflon-coated magnetic stir-bars. The terms concentrated in vacuo or under reduced pressure refer to the use of a rotary-evaporator. Reagents were purchased from commercial suppliers and used without further purification. Diethyl zinc was used both as a solution (1.0 M in hexanes) and neat. Methylene iodide (CH_2I_2) was purchased both from Sigma-Aldrich and Lancaster chemical companies; when purchased from Lancaster, non-oxidized copper wire was added as a stabilizer. Compounds **10**[20] and **12**[21] were prepared according to literature procedures. Column chromatography was performed on EM Science flash silica gel (35−75 μm). Mobile phases were used as noted. Thin layer chromatography (TLC) was carried out on EM Science F254 glass plates and visualized by UV and anisaldehyde or phosphomolybdic acid stains. The term R_f refers to the use of the specified solvent system in TLC analysis. Combustion analysis (CHN) and low resolution mass spectroscopy were performed by the University of New Hampshire Instrumentation Center on a Perkin-Elmer 2400 analyzer. High-resolution mass spectroscopy was performed at the University of California Riverside Mass Spectrometry Facility.

Dimethyl (3-Oxobutyl)phosphonate (9a). Into a flask containing 5 mL of methylene chloride was added 1.8 mL (1.8 mmol) of a 1.0 M solution of diethylzinc in hexane under an inert atmosphere. This solution was cooled to 0 °C, and a solution of 0.48 g (0.15 mL, 1.8 mmol) of methylene iodide dissolved in 1 mL of methylene chloride was added slowly. The reaction was allowed to warm to room temperature over 5 min, during which time a white precipitate formed. A solution containing 50 mg (0.13 mmol) of dimethyl (2-oxopropyl)-phosphonate **8a** dissolved in 1 mL of methylene chloride was added, and the reaction was allowed to stir at room temperature. The starting material appeared by TLC to be consumed within 1 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride, and the aqueous layer was extracted three times with 5 mL portions of diethyl ether. The combined extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica (ethyl acetate; $R_f = 0.1$) to yield 46 mg (85%) of γ-keto phosphonate **9a** as a clear colorless oil:[25] ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.75 (d, 6H, J_{PH} = 10.8 Hz), 2.75 (ddd, 2H, J_{HH} = 15.3, 7.6 Hz, J_{PH} = 11.8 Hz), 2.19 (s, 3H), 2.04 (ddd, 2H, J = 15.3, 7.6 Hz, J_{PH} = 18 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 205.8 (d, J_{PC} = 14.5 Hz), 52.7 (d, J_{PC} = 6.5 Hz), 36.3 (d, J_{PC} = 3.9 Hz), 29.9, 18.5 (d, J_{PC} = 143.8 Hz); IR (film) 3650−3400, 2950, 2850, 1710. Anal. Calcd for $C_6H_{13}O_4P$: C, 40.00; H, 7.27. Found: C, 40.27; H, 7.47.

Diethyl (3-Oxobutyl)phosphonate (9b). Into a flask containing 40 mL of methylene chloride was diluted 3.1 mL (3.1 mmol) of a 1.0 M solution of diethylzinc in hexane under an inert atmosphere. The solution was cooled to 0 °C, and a solution of 830 mg (0.25 mL, 3.1 mmol) of methylene iodide dissolved in 1 mL of methylene chloride was slowly added. The reaction was allowed to warm to room temperature, during which time a white precipitate formed. A solution cotaining 101 mg (0.10 mL, 0.52 mmol) of diethyl (2-oxopropyl)phosphonate **9a** dissolved in 1 mL of methylene chloride was added, and the reaction was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous ammonium chloride, and the aqueous layer was extracted three times with 10 mL of diethyl ether. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica (ethyl acetate; $R_f = 0.2$) to give 74 mg (69%) of γ-keto phosphonate **9b** as a clear yellow liquid that provided spectra which were in agreement with those reported in the literature:[26] ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.09 (m, 4H), 2.75 (ddd, 2H, J = 15.4, 7.7 Hz, J_{PH} = 11.5 Hz), 2.19 (s, 3H), 2.02 (ddd, 2H, J = 15.4, 7.7 Hz, J_{PH} = 18 Hz), 1.32 (t, 6H, J = 7.0 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 205.7 (d, J_{PC} = 15.1 Hz), 61.7 (d, J_{PC} = 6.6 Hz), 36.3 (d, J_{PC} = 3.6 Hz), 29.7, 19.4 (d, J_{PC} = 143.7 Hz), 16.4 (d, J_{PC} = 6.1 Hz).

Diethyl (3-Oxo-3-phenylpropyl)phosphonate (9c). Into a flask containing 40 mL of methylene chloride was added 2.3 mL (2.3 mmol) of a 1.0 M solution of diethylzinc in hexane under an inert atmosphere. A solution containing 616 mg (0.19 mL, 2.3 mmol) of methylene iodide dissolved in 1 mL of methylene chloride was added slowly at room temperature, at which time a white precipitate formed. The reaction was stirred for 5 min, and a solution containing 100 mg (0.39 mmol) of diethyl (2-oxo-2-phenylethyl)phosphonate **8c** dissolved in 1 mL of methylene chloride was added. Upon addition of the β-ketophosphonate, some precipitate disappeared. The reaction was stirred for 2 h at room temperature and was quenched with saturated ammonium chloride. The aqueous phase was extracted three times with 10 mL of diethyl ether. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was chromatographed on silica (ethyl acetate; $R_f = 0.23$) to give 103 mg (98%) of γ-keto phosphonate **9c** as a clear yellow liquid that provided spectra which were in agreement with those reported in the literature:[27] ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.58 (m, 1H), 7.48 (m, 2H), 4.12 (m, 4H), 3.30 (ddd, 2H, J = 15.6, 7.9 Hz, J_{PH} = 10.7 Hz), 2.19 (ddd, 2H, J = 15.6, 7.9 Hz, J_{PH} = 17.7 Hz), 1.33 (t, 6H, J = 7 Hz); ^{13}C (90 MHz, $CDCl_3$) δ 197.4 (d, J_{PC} = 15.8 Hz), 136.3133.4, 128.7, 128.1, 61.8 (d, J_{PC} = 6.6 Hz), 31.7 (d, J_{PC} = 3.0 Hz), 19.7 (d, J_{PC} = 143.8 Hz), 16.5 (d, J_{PC} = 5.9 Hz); IR (film) 3044, 2987, 2924, 1687.

Diethyl (1-Methyl-3-oxobutyl)phosphonate (11). Into 10 mL of methylene chloride was diluted 1.6 mL (1.6 mmol) of a 1.0 M solution of diethylzinc in hexane under an inert atmosphere. The solution was cooled to 0 °C. A 1 mL methylene chloride solution containing 429 mg (0.13 mL, 1.6 mmol) of methylene iodide was added slowly to the stirring diethylzinc solution. The reaction mixture was allowed to warm to room temperature, and 50 mg (0.24 mmol) of diethyl (1-methyl-2-oxopropyl)phosphonate **10** was added as a solution in 1 mL of methylene chloride. The reaction mixture was allowed to stir for 6 h. (A decrease in reaction time results in the recovery of unreacted starting material.) The reaction was quenched with saturated aqueous ammonium chloride, and the aqueous phase was extracted with three 10 mL portions of diethyl ether. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Chromatography on silica gel (ethyl acetate; $R_f = 0.2$) provided 37 mg (70%) of γ-keto phosphonate **11** as a clear yellow oil that provided spectra which were consistent with those reported in the literature:[13] ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.10 (m, 4H), 2.88 (m, 1H), 2.48 (m, 2H), 2.17 (s, 3H), 1.32 (td, 6H, J = 7.1, J_{PH} = 1.6 Hz), 1.16 (dd, 3H, J = 7.0 Hz, J_{PH} = 18.3 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 205.9 (d, J_{PC} = 15.1 Hz), 61.9 (d, J_{PC} = 7.0 Hz), 61.8 (d, J_{PC} = 7.2 Hz), 44.1 (d, J_{PC} = 2.1 Hz), 30.5, 26.2 (d, J_{PC} = 143.7 Hz), 16.6 (d, J_{PC} = 5.7 Hz), 13.9 (d, J_{PC} = 5.2 Hz); IR (film) 3515, 2994, 1708.

Diethyl (3-Oxocyclohexyl)phosphonate (13). Into 20 mL of methylene chloride was diluted 3.1 mL (3.1 mmol) of a 1.0 M solution of diethylzinc in hexane. The solution was cooled to 0 °C under an inert atmosphere. A solution containing 429 mg (0.25 mL, 3.12 mmol) of methylene iodide dissolved in 1 mL of methylene chloride was added slowly to the diethylzinc solution. The reaction mixture was allowed to warm to room temperature, and a white precipitate formed. A solution of 100 mg (0.52 mmol) of diethyl (2-oxocyclopentyl)phosphonate[21b] **12**

(25) Appleton, D.; Duguid, A. B.; Lee, S.-K.; Ha, Y.-J.; Ha, H.-J.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 89.

(26) McClure, C. K.; Jung, K.-Y. *J. Org. Chem.* **1991**, *56*, 867.

(27) Yu, J.-W.; Huang, S. K. *Org. Prep. Proced. Int.* **1997**, *29*, 214.

dissolved in 1.5 mL of methylene chloride was added to the zinc-carbenoid solution. The reaction was allowed to stir for 4 h at room temperature and quenched with saturated aqueous ammonium chloride. The aqueous phase was extracted twice with 10 mL of methylene chloride. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica (ethyl acetate; $R_f = 0.2$) to provide 94 mg (83%) of γ-keto phosphonate **13** as a clear yellow oil that provided spectra which were consistent with those reported in the literature:[28] ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.12 (m, 4H), 2.45 (m, 4H), 2.16 (m, 3H), 1.78 (m, 2H), 1.34 (t, 6H, $J = 7.1$ Hz); ^{13}C (90 MHz, $CDCl_3$) δ 208.8 (d, $J_{PC} = 16.5$ Hz), 61.9 (d, $J_{PC} = 4.0$ Hz), 61.8 (d, $J_{PC} = 4.0$ Hz), 41.0 (d, $J_{PC} = 2.0$ Hz), 40.5 (d, $J_{PC} = 5.3$ Hz), 35.8 ($J_{PC} = 145.7$ Hz), 25.9 (d, $J_{PC} = 19.1$ Hz), 24.3 (d, $J_{PC} = 4.6$ Hz), 16.4 (d, $J_{PC} = 5.3$ Hz).

(*S*)-1-Carboxybenzyl-2-(2-(dimethylphosphono)-1-oxo)-ethylpyrrolidine (14a). Into 20 mL of THF was dissolved 1.89 g (1.65 mL, 15.2 mmol) of dimethyl methylphosphonate, and the solution was cooled to −78 °C under an inert atmosphere. To this solution was added 7.0 mL (16 mmol) of a 2.25 M solution of *n*-butyllithium in pentane via syringe pump [0.15 mL/min]. Following the addition of *n*-butyllithium, the reaction mixture was allowed to stir at −78 °C for an additional 90 min and then a solution containing 2.0 g (7.6 mmol) of (*S*)-1-carboxybenzyl-2-carboxymethylpyrrolidine[29] dissolved in 8 mL of THF was added via syringe pump [0.3 mL/min]. The reaction mixture was allowed to stir for 12 h, during which time the temperature slowly increased to −50 °C. The reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted twice with 10 mL portions of diethyl ether, followed by two 10 mL portions of ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate; $R_f = 0.13$) to give 2.33 g (86%) of β-keto phosphonate **14a** as a clear slightly yellow oil that appeared by NMR to be a mixture of rotamers (~1:1 at 25 °C): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.2−5.0 (m, 2H), 4.55−4.40 (m, 1H), 3.82−3.73 (m, 6H), 3.73−3.62 (m, 1H), 3.60−3.46 (m, 1H), 3.33−3.14 (m, 1H), 3.13−2.84 (m, 1H), 2.26−1.98 (m, 2H), 1.97−1.79 (m, 2H); ^{13}C (90 MHz, $CDCl_3$) δ 201.0 (d, $J_{PC} = 6.6$ Hz), 155.1, 154.2, 136.5, 136.3, 128.2, 128.1, 128.0, 127.8, 67.2, 67.1, 65.9, 65.6, 53.0, 47.3, 46.8, 38.3 (d, $J_{PC} = 132.0$ Hz), 37.3 (d, $J_{PC} = 132.7$ Hz), 29.5, 28.4, 24.4, 23.5; IR (film) 3473, 2966, 2875, 1701. Anal. Calcd for $C_{16}H_{22}NO_6P$: C, 54.08; H, 6.24; N, 3.94. Found: C, 53.95; H, 6.26; N, 3.95.

1-Benzoyl-2-(1-oxo-2-(dimethylphosphono)ethyl)pyrrolidine (14b). Into 30 mL of THF was dissolved 1.86 mL (17.2 mmol) of dimethyl methylphosphonate, and the solution was cooled under an inert atmosphere to −78 °C. To this stirring solution was added 8.4 mL (18.9 mmol) of a 2.25 M solution of *n*-butyllithium in pentane by syringe pump [0.15 mL/min]. Following the *n*-butyllithium addition, the reaction was allowed to stir for 90 min at −78 °C and 2.0 g (8.6 mmol) of 1-benzoyl-2-carboxymethylpyrrolidine[30] was added as a solution in 15 mL of THF by syringe pump [0.15 mL/min]. The reaction was allowed to stir at −78 °C for 2 h and then allowed to warm to room temperature. The reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with three 20 mL portions of methylene chloride, and the combined organic extracts were dried over $MgSO_4$. The concentrated residue was chromatographed on silica (1:1, ethyl acetate:acetone; $R_f = 0.4$) to give 1.53 g (52%) of β-keto phosphonate **14b** as a viscous, clear, colorless oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.6−7.56 (m, 2H), 7.45−7.32 (m, 3H), 4.82 (dd, 1H, $J = 7.9$, 6.4 Hz), 3.83 (d, 3H, $J_{PH} = 6.1$ Hz), 3.80 (d, 3H, $J_{PH} = 6.1$ Hz), 3.75−3.60 (m, 1H), 3.59−3.2 (m, 3H), 2.32−2.20 (m, 1H), 2.19−2.0 (m, 2H), 1.95−1.83 (m, 1H); ^{13}C (90 MHz, $CDCl_3$) δ 200.9, 169.8, 135.6, 130.4, 128.3, 127.3, 65.7, 53.0, 50.4, 39.3 (d, $J_{PC} = 130.3$ Hz), 28.3, 25.6; IR (film) 3473, 2959, 1728, 1616; HRMS (CI, DCl/CH_4) $[M + H]^+$ calcd for $C_{15}H_{21}NO_5P$ 326.1157, found 326.1164.

1-Carboxybenzyl-2-(3-(dimethylphosphono)-1-oxo)propylpyrrolidine (15a). Into 10 mL of methylene chloride was diluted 1.2 mL (1.2 mmol) of a 1.0 M solution of diethylzinc in hexane. To this stirring solution of diethylzinc was slowly added a solution of 330 mg (0.1 mL, 1.2 mmol) of methylene iodide dissolved in 1.0 mL of methylene chloride. The reaction mixture was allowed to stir at ambient temperature for 15 min, and a solution containing 70 mg (0.2 mmol) of β-keto phosphonate **14a** in 1.0 mL of methylene chloride was added. After stirring for an additional 45 min, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with two 10 mL portions of methylene chloride, and the combined organic extracts were dried over $MgSO_4$. The concentrated residue was chromatographed on silica (1:1, ethyl acetate:acetone; $R_f = 0.34$ for **15a**) to give 24 mg (33%) of γ-keto phosphonate **15a** as a clear yellow liquid and 32 mg (46%) of the starting β-keto phosphonate. [An increase in reaction time was found to result in the consumption of starting material, but at the expense of subsequent chemistry that appeared to consume the product.] Two rotameric forms were observable by NMR: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.41−7.2 (m, 10H), 5.18−5.00 (m, 4H), 4.42 (dd, 1H, $J = 8.5$, 4.0 Hz), 4.34 (dd, 1H, $J = 8.5$, 4.2 Hz), 3.8−3.5 (m, 16H), 2.86−2.65 (m, 4H), 2.22−1.85 (m, 12H); ^{13}C (90 MHz, $CDCl_3$) δ 207.1, 207.0, 155.1, 154.2, 136.6, 136.3, 128.5, 128.1, 128.0, 127.8, 67.1, 64.9, 64.7, 52.4, 47.3, 46.8, 32.4, 31.8, 29.9, 28.9, 24.4, 23.6, 18.0 (d, $J_{PC} = 144.4$ Hz), 18.8 (d, $J_{PC} = 144.6$ Hz); IR (film) 3459, 2945, 1695; HRMS (EI) M^+ calcd for $C_{17}H_{24}NO_6P$ 369.1341, found 369.1342.

1-Benzoyl-2-(1-oxo-3-(dimethylphosphono)propyl)pyrrolidine (15b). Into 20 mL of methylene chloride were added 1.8 mL (1.8 mmol) of a 1.0 M solution of diethylzinc in hexane and a solution of 500 mg (0.15 mL, 1.84 mmol) of methylene iodide in 1 mL of methylene chloride. The reaction was allowed to stir for 10 min, during which time a white precipitate formed. A solution of 100 mg (0.31 mmol) of β-keto phosphonate **14b** dissolved in 1.0 mL of methylene chloride was added. The reaction was allowed to stir at room temperature for 3 h and was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted three times with 10 mL portions of methylene chloride. The combined extracts were dried over $MgSO_4$, and the concentrated residue was chromatographed on silica (1:1, ethyl acetate:acetone) to give 94 mg (90%) of γ-keto phosphonate **15b** as a clear yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.57−7.54 (m, 2H), 7.46−7.3 (m, 3H), 4.73 (dd, 1H, $J = 8.3$, 5.8 Hz), 3.9−3.4 (m, 10H), 3.02−2.85 (m, 2H), 2.28−1.8 (m, 4H); ^{13}C (90 MHz, $CDCl_3$) δ 206.3 (d, $J_{PC} = 13.9$), 169.7, 135.8, 130.4, 128.3, 127.3, 64.8, 52.5 (d, $J_{PC} = 5.3$ Hz), 52.4 (d, $J_{PC} = 5.3$ Hz), 50.3, 32.9, 28.4, 25.5, 18.0 (d, $J_{PC} = 144.6$ Hz); IR (film) 3459, 2952, 1722, 1623; HRMS (CI, DCl/CH_4) $[M + H]^+$ calcd for $C_{16}H_{23}NO_5P$ 340.1314, found 340.1302.

(*R*)-Dimethyl (2-Oxo-4-*N*-(carboxy-*tert*-butyl)aminobutyl)phosphonate (16). Into 20 mL of THF was dissolved 1.19 g (1.0 mL, 9.6 mmol) of dimethyl methylphosphonate, and the solution was cooled to −78 °C. To this stirring THF solution was added 4.7 mL (10.6 mmol) of a 2.25 M of *n*-butyllithium in hexane via syringe pump [0.15 mL/min]. The reaction was stirred at −78 °C for 90 min, after which a solution containing 1.03 g (1.0 mL, 4.8 mmol) of Boc-alanine methyl ester dissolved into 10 mL of THF was added via syringe pump [0.15 mL/min]. The reaction was stirred for an additional 8 h at −78 °C. The reaction mixture was allowed to warm to ambient temperature and quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted thrice with 10 mL portions of methylene chloride. The combined organic extracts were dried over $MgSO_4$, and the concentrated residue was chromatographed on silica (1:4, acetone:ethyl acetate; $R_f = 0.54$) to give 715 mg (50%) of β-keto phosphonate **16** as a clear yellow tinted oil that provided spectra which were

(28) Crooks, S. L.; Robinson, M. B.; Koerner, J. F.; Johnson, R. L. *J. Med. Chem.* **1986**, *29*, 1988.

(29) (a) Metzger, H.; Seelert, K. *Angew. Chem.* **1963**, *75*, 919. (b) König, H.; Metzger, H.; Seelert, K. *Chem. Ber.* **1965**, *98*, 3712.

(30) Amine, Y.; Nishi, S.; Izawa, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 620.

consistent with those reported in the literature:[2c] ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.45−5.35 (NH), 4.4−4.3 (m, 1H), 3.80 (d, 3H, J_{PH} = 11.3 Hz), 3.79 (d, 3H, J_{PH} = 11.2 Hz), 3.31 (dd, 1H, J = 22.5 Hz, J_{PH} = 14.2 Hz), 3.12 (dd, 1H, J = 22.2 Hz, J_{PH} = 14.2 Hz), 1.45 (s, 9H), 1.36 (d, 3H, J = 7.1 Hz); ^{13}C (90 MHz, $CDCl_3$) δ 201.9, 155.3, 80.0, 56.0, 53.2 (d, J_{PC} = 3.3 Hz), 53.1 (d, J_{PC} = 2.6 Hz), 37.7 (d, J_{PC} = 130.0 Hz), 28.3, 17.0; IR (film) 3303, 2973, 1708, 1525.

(*R*)-Dimethyl (3-Oxo-4-*N*-(carboxy-*tert*-butyl)aminopentyl)phosphonate (17). Into 20 mL of methylene chloride was diluted 2.0 mL (2 mmol) of a 1.0 M solution of diethylzinc in hexane under an inert atmosphere ,and a solution of 532 mg (0.16 mL, 2.04 mmol) of methylene iodide dissolved in 1.0 mL of methylene chloride was added slowly. The solution was stirred for 15 min, and a solution of 100 mg (0.34 mmol) of β-keto phosphonate **16** dissolved in 2.0 mL of methylene chloride was added. The reaction was allowed to stir for 45 min at which time TLC analysis indicated consumption of the starting material. The reaction was quenched with saturated aqueous ammonium chloride, and the aqueous layer was extracted with three 10 mL portions of methylene chloride, followed by five 10 mL portions of ethyl acetate. The combined organic extracts were dried over $MgSO_4$, and the concentrated residue was chromatographed on silica (1:1, acetone:ethyl acetate; R_f = 0.3) to give 81 mg (77%) of γ-keto phosphonate **17** as a clear yellow oil, which provided spectra that agree with those found in the literature:[8b] ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.17 (bs, 1H), 4.31 (m, 1H), 3.73 (d, 6H, J_{PH} = 10.9 Hz), 2.89−2.68 (m, 2H), 2.17−2.02 (m, 2H), 1.44 (s, 9H), 1.33 (d, 3H, J = 7.2 Hz); ^{13}C (90 MHz, $CDCl_3$) δ 207.4 (d, J_{PC} = 13.3 Hz), 155.2, 80.0, 55.1, 52.5 (d, J_{PC} = 5.3 Hz), 31.9, 28.3, 18.3 (d, J_{PC} = 144.6 Hz), 17.6; IR (film) 3437, 2973, 1708.

Dimethyl (2-Oxo-5-hexenyl)phosphonate (18). A slurry of sodium hydride (116 mg (2.9 mmol) of a 60% dispersion in mineral oil) in 20 mL of THF was cooled to 0 °C under an inert atmosphere. To this solution was added 241 mg (0.2 mL, 1.45 mmol) of dimethyl (2-oxopropyl)phosphonate **8a**. The reaction was allowed to warm to room temperature, and a white precipitate developed. The mixture was cooled to −78 °C, and 0.64 mL (1.45 mmol) of a 2.25 M solution of *n*-butyllithium in pentane was added slowly. During the addition the white precipitate appeared to dissolve slightly and a light yellow color developed. The stirring solution was allowed to warm slowly to room temperature at which time 175 mg (0.13 mL, 1.45 mmol) of 3-bromopropene was added dropwise. The reaction was allowed to stir for 1 h and quenched with saturated aqueous ammonium chloride, which was accompanied by violent gas evolution. The aqueous layer was extracted three times with 10 mL portions of diethyl ether, and the combined organic extracts were dried over $MgSO_4$. The concentrated residue was chromatographed on silica (ethyl acetate; R_f = 0.23) to give 127 mg (42%) of β-keto phosphonate **18** as a clear viscous oil with a slight yellow tint: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.79 (ddt, 1H, J = 16.8, 10.3, 6.5 Hz), 5.08 (dd, 1H, J = 17.1, 1.5 Hz), 4.98 (dd, 1H, J = 10.1 Hz, 1.5 Hz) 3.79 (d, 6H, J_{PH} = 11.2), 3.10 (d, 2H, J_{PH} = 22.7), 2.73 (t, 2H, J = 7.2), 2.33 (td, 2H, J = 7.2, 6.5 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 202.3 (d, J_{PC} = 6.6 Hz), 137.4, 115.5, 53.0 (d, J_{PC} = 6.5 Hz), 43.1, 41.3 (d, J_{PC} = 127.5 Hz), 27.3; IR (film) 2952, 2910, 1715; HRMS (EI) M^+ calcd for $C_8H_{15}O_4P$ 206.0708, found 206.0699.

Attempted Chain Extension of Dimethyl (2-Oxo-5-hexenyl)phosphonate (18). Method A (for equivalents and time refer to Table 1). To a solution of *x* equivalents of diethylzinc dissolved in 10 mL of methylene chloride under an inert atmosphere was added *x* equivalents of methylene iodide as a solution in 1 mL of methylene chloride. The reaction was allowed to stir for approximately 15 min (except in entries 7 and 8, which the time was as specified) at the designated temperature, during which time a white precipitate formed. To this solution was added 1 equiv of β-keto phosphonate **18** as a solution in 1.5 mL of methylene chloride. The reaction was allowed to stir for *y* minutes at the designated temperature and quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with three 10 mL portions of ethyl acetate, and the combined organic extracts were dried over $MgSO_4$. The concentrated residue was chromatographed on silica gel (entries 1, 2, and 3 only) (ethyl acetate) to give a clear yellow oil which was found to contain a mixture of chain extended product **19** along with the cyclopropanated product **20**.

Method B. Into 5 mL of methylene chloride was added 0.6 mL (0.6 mmol) of a 1.0 M solution of diethylzinc in hexane. To this solution was added 48 μL (0.6 mmol) of methylene iodide as a solution in 0.5 mL of methylene chloride. The reaction was allowed to stir for approximately 5 min. In a separate flask were combined 0.2 mL (0.2 mmol) of a 1.0 M solution of diethylzinc in hexane and a 1.0 mL methylene chloride solution of 20 mg (0.1 mmol) of β-keto phosphonate **18**. After gas evolution subsided (∼5 min), the phosphonate solution was transferred by syringe to the stirring solution of diethylzinc and methylene iodide. The reaction was allowed to stir for approximately 25 min and was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with three 10 mL portions of ethyl acetate, and the combined organic extracts were dried over $MgSO_4$. The concentrated residue was analyzed by ^{1}H NMR.

Method C (for equivalents and time refer to Table 1)**.** To a solution of 6 molar equiv of diethylzinc diluted to ∼0.1 M into methylene chloride was added 1 molar equiv of β-keto phosphonate **18** as a solution in 1.5 mL of methylene chloride. Upon the addition of β-keto phosphonate **18**, gas evolution was observed. The reaction was allowed to stir for approximately 5 min, and *x* molar equiv of methylene iodide was added as a solution in 1 mL of methylene chloride. The reaction was allowed to stir for the specified time. No precipitate was observed in contrast to the other methods. The reaction was quenched with saturated ammonium chloride, and the aqueous layer was extracted three times with 10 mL portions of ethyl acetate. The organic extracts were combined and dried over $MgSO_4$. The concentrated residue was analyzed by ^{1}H NMR.

Dimethyl (*E*-2-Oxo-4-phenyl-3-butenyl)phosphonate (21). A solution consisting of 1.54 g (1.35 mL, 12.4 mmol) of dimethyl methylphosphonate was dissolved in 25 mL of THF and was cooled to −78 °C. A 2.25 M solution of *n*-butyllithium in hexane (6.0 mL, 13.6 mmol) was added to the phosphonate solution via syringe pump [0.15 mL/min]. The reaction mixture was allowed to stir at −78 °C for 90 min, after which time a 5 mL solution of 1.0 g (6.2 mmol) of methyl *E*-cinnamate was added by syringe pump [0.15 mL/min]. The reaction mixture was allowed to warm to room temperature over a period of 20 h, during which time a brown curdy precipitate formed. The reaction was quenched with 10 mL of 1 M aqueous HCl. The aqueous layer was separated and extracted twice with 20 mL of methylene chloride. The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure, and chromatographed (ethyl acetate; R_f = 0.31) to give 1.33 g (84%) of β-keto phosphonate **21** as a clear, slightly yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.66 (d, 1H, J = 16.1 Hz), 7.59 (m, 2H), 7.38 (m, 3H), 6.88 (d, 1H, J = 16.1 Hz), 3.81 (d, 6H, J_{PH} = 11.3 Hz), 3.34 (d, 2H, J_{PH} = 22.7 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 192.1 (d, J_{PC} = 6.6 Hz), 145.1, 134.1, 131.0, 129.0, 128.7, 125.6, 53 0.2 (d, J_{PC} = 6.3 Hz), 39.9 (d, J_{PC} = 128.3); IR (film) 2952, 2910, 1715; HRMS (EI) M^+ calcd for $C_{12}H_{14}O_4P$ 254.0708, found 254.0695.

Attempted Chain Extension of Dimethyl (*E*−2-Oxo-4-phenyl-3-butenyl)phosphonate (21). A 1.0 M solution (0.88 mL, 0.88 mmol) of diethylzinc in hexane was diluted in 10 mL of methylene chloride under an inert atmosphere. To this stirring solution was added 1 mL of methylene chloride which contained methylene iodide (0.071 mL, 0.88 mmol). The reaction was allowed to stir for approximately 15 min at room temperature, after which time β-keto phosphonate **21** (70 mg, 0.27 mmol) was added as a solution in 1 mL of methylene chloride. The reaction was allowed to stir for 30 min and was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted five times with 5 mL of methylene chloride, and the combined organic extracts were dried over $MgSO_4$. The concentrated residue was chromatographed on silica (ethyl acetate; R_f = 0.16) to give 50 mg of a clear colorless

oil as a mixture (8:1 as determined by ^{1}H NMR) of γ-keto phosphonates **22**[31] and **23**.

Cyclopropanation of the Chain Extension Product Mixture Containing (*trans*-2-Oxo-4-phenyl-3-butenyl)-phosphonate (22 and 23). A mini-diazald kit was charged with 3 mL of 2-(2-ethoxyethoxy)ethanol, 1 mL of a 50% aqueous solution of potassium hydroxide, and 5 mL of diethyl ether. Into the receiving flask were placed the product mixture (70 mg) from one of the chain extension reactions of β-keto phosphonate **21** and approximately 5 mg of palladium(II) acetate dissolved in 5 mL of diethyl ether. The receiving flask was cooled to 0 °C with stirring and the diazald kit mounted securely behind a blast shield. The coldfinger was charged with acetone/CO_2 and the still pot was heated to 70 °C in an oil bath. A solution of 172 mg (0.8 mmol) of diazald [*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide] in 5 mL of diethyl ether was added through an addition funnel at a rate equal to the rate of distillation. Additional diethyl ether was added through the addition funnel to the still pot until the distillate was colorless. The solution in the receiving flask was filtered through silica, and the silica was rinsed with excess (~100 mL) acetone. The concentrated residue was found to contain one compound, which was identified as cyclopropanated phosphonate **23**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.38−7.16 (m, 3H), 7.1−6.97 (m, 2H), 3.74 (d, 3H, J_{PH} = 10.7 Hz), 3.73 (d, 3H, J_{PH} = 10.9 Hz), 2.93−2.85 (m, 2H), 2.53−2.47 (m, 1H), 2.19−2.14 (m, 1H), 2.09−1.99 (m, 2H), 1.68−1.63 (m, 1H), 1.41−1.35 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 205.8 (d, J_{PC} = 14.4 Hz), 139.9, 128.5, 126.6, 126.0, 52.4 (d, J_{PC} = 5.5 Hz), 36.3, 32.0, 29.2, 19.1, 18.3 (d, J_{PC} = 140.4 Hz); HRMS (EI) M^+ calcd for $C_{14}H_{19}O_4P$ 282.1021, found 282.1029.

(31) Edwards, M. L.; Ritter, H. W.; Stemerick, D. M.; Stewart, K. T. *J. Med. Chem.* **1983**, *26*, 431.

Acknowledgment. We acknowledge the support of the University of New Hampshire through a UNH Graduate School Dissertation Year Fellowship for C.A.V.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **9a**, **9b**, **9c**, **11**, **13**, **14a**, **14b**, **15a**, **15b**, **16**, **17**, **18**, **21**, and **23**; an ^{1}H NMR spectrum for the attempted chain extensions of **18** and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000343F