Addition of Organometallic Nucleophiles to β-Keto Phosphonates

LoriAnn M. Lentsch and David F. Wiemer*

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242-1294

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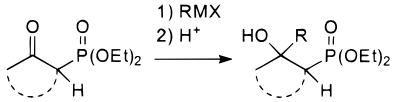
The reaction of some Grignard reagents with β-keto phosphonates results in nucleophilic addition to the carbonyl group to afford β-hydroxy phosphonates with extension of the carbon skeleton. Additions of allylmagnesium reagents have proven particularly efficient, especially in the presence of BF_3·OEt_2. Reactions of allylic zinc reagents with β-keto phosphonates also gave the desired β-hydroxy phosphonates, often in even better yields. With crotyl and prenyl organometallic reagents, the reactions proceed with allylic transposition. Because these allylation reactions expand the functionality of the original substrate, various transformations can be conducted on the initial products to provide convenient access to a variety of new phosphonates.

Recent applications of phosphonates as enzyme inhibitors and metabolic probes,[1] in addition to continuing attention to their more traditional roles as intermediates in organic synthesis,[2] have spurred interest in the preparation of more complex examples.[3] Many β-keto phosphonates can be prepared by well-known methods for formation of the carbon−phosphorus bond, such as the Arbuzov reaction[4] or by acylation of an alkyl phosphonate anion.[5] Whereas both of these classical reactions rely upon use of phosphorus nucleophiles, a number of more contemporary methods for β-keto phosphonate synthesis are based on free radical reactions[6] or electrophilic phosphorus reagents. These later approaches include rearrangements of vinyl phosphates to β-keto phosphonates[7] and reaction of P(III) halides with enolates followed by oxidation.[8] The success of these later reactions in providing access to varied phosphonates has encouraged us to consider other reactions in which an electrophilic phosphorus reagent is paired with a nucleophilic partner. One particularly attractive strategy would involve addition of organometallic nucleophiles to the carbonyl group of β-keto phosphonates (Scheme 1).

Scheme 1



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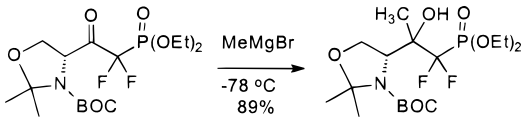
Because such additions would extend the carbon skeleton and may introduce additional functionality, they could significantly expand the range of accessible phosphonates.

A few cases of nucleophilic additions to β-keto phosphonates have been reported. For example, Berkowitz and co-workers have shown that methylmagnesium bromide can be added to the carbonyl group of an α,α-difluoro-β-keto phosphonate (**3**), to give an (α,α-difluoroalkyl)phosphonate analogue of a secondary phosphate (**4**), without attack at phosphorus.[9] Earlier examples from



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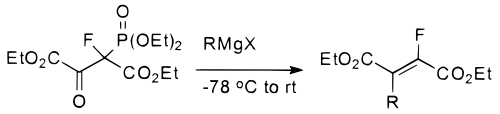

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Burton's group, for example, conversion of phosphonate **5** to olefin **6** by Grignard addition followed by phosphate elimination, also made it appear unlikely that reaction at phosphorus would be competitive with addition to the carbonyl group.[10] However, in these examples a fully substituted α carbon ensured that proton transfer would not be encountered. For more general utility, it would be important to establish whether addition to the carbonyl group of a β-keto phosphonate could be successful even in the presence of a relatively acidic α hydrogen. A

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(6) (a) Peterson, A. C.; Levsen, S. M.; Cremer, S. E. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1996**, *115*, 241−254. (b) Barton, D. H. R.; Gero, S. D.; Quiclet-Sire, B.; Samadi, M. *Tetrahedron* **1992**, *48*, 1627−1636. (c) Wnuk, S.; Robins, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2519−2520.

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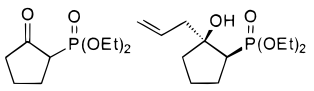
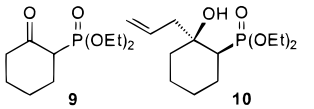
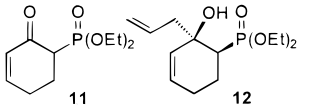
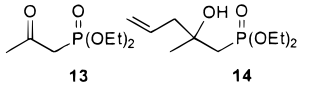
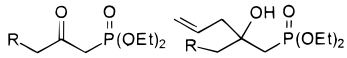
Table 1. Reaction of Allylmagnesium Chloride with β-Keto Phosphonates

Phosphonate	Product	Lewis Acid[a]	% Yie
 **7**	**8**	--	18[b]
		--	61
		$BF_3{\cdot}OEt_2$	78
 **9**	**10**	--	36
		$BF_3{\cdot}OEt_2$	51
 **11**	**12**	--	29
		$BF_3{\cdot}OEt_2$	62
 **13**	**14**	--	22
		$BF_3{\cdot}OEt_2$	80
 **15** R = C_6H_{11}	**16** R = C_6H_{11}	--	56
		$BF_3{\cdot}OEt_2$	78

[a] Reactions were run at 0 °C in the presence of BF_3OEt_2 or were allowed to warm to rt prior to quenching in the absence of $BF_3{\cdot}OEt_2$. [b] In this case, 1.5 equiv of the Grignard reagent was employed, in all other cases, 5 equiv was used.

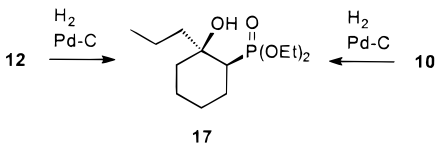
parallel process, allylation of β-keto amides and β-keto esters,[11] has been accomplished with magnesium and/or zinc reagents even in cases where the α carbon was unsubstituted and proton transfer from the activated methylene position was possible. In part because of this precedent and in part because the allyl group can be easily converted to a variety of other functional groups,[12] we began this survey by examining the reactions of several representative β-keto phosphonates with allyl Grignard reagents.[13]

In the first experiment, a slight excess of allylmagnesium chloride in THF was added to phosphonate **7** (Table 1) at 0 °C, and the reaction was allowed to warm to room temperature over several hours. The desired hydroxy phosphonate (**8**) was obtained, albeit in low yield (18%). Reaction with excess Grignard reagent significantly improved the yield (61%), and only a single product was observed by ^{31}P NMR. When the reaction was attempted at reflux, none of the desired product was observed.

To gauge the scope of this reaction, a number of cyclic and acyclic β-keto phosphonates were subjected to reaction with allylmagnesium chloride under identical reaction conditions. Unfortunately, the results varied dramatically depending upon the β-keto phosphonate utilized. The six-membered ring phosphonates (**9** and **11**) gave only moderate yields of adducts **10** and **12**, and varied results were obtained with acyclic examples **13** and **15**.

It is well-known that addition of cerium chloride will improve the reaction of Grignard reagents with readily enolizable ketones,[14] but when $CeCl_3$ was added to these reactions at a variety of temperatures the yields were not significantly improved. However, in the presence of boron trifluoride etherate the allylation of each of these phosphonates was greatly improved. For example, allyl addition to diethyl 2-oxopropylphosphonate (**13**) had resulted in only a 22% yield of the desired hydroxy phosphonate in the absence of $BF_3{\cdot}OEt_2$, but in the presence of this Lewis acid the yield increased to 80%. The more enolizable phosphonates still gave moderate yields, but even these were improved relative to the parallel reactions conducted in the absence of the Lewis acid.

Although diastereomers might be formed in additions to phosphonates **7**, **9**, and **11**, in each case one major product could be detected by ^{31}P NMR analysis of the reaction mixtures. Detailed analysis of the spectra of the major diastereomer of phosphonate **10** suggested that this product was the cis isomer as shown. The observed couplings of the α hydrogen (δ 1.85, J_{HP} = 19.4 Hz; J_{HH} = 11.6, 4.1 Hz) indicated a conformation in which this hydrogen was in an axial orientation with the phosphoryl group equatorial. Observation of NOE between the α hydrogen and an allylic hydrogen and between the α hydrogen and the vinylic methine suggested that the allyl group was an equatorial substituent on the adjacent carbon. Whether this outcome is the result of a mechanism involving complexation and delivery or whether the product stereochemistry is governed by the steric bulk of the phosphoryl group is not yet clear. Because phosphonates **7** and **11** gave only a single diastereomer as the product, it would be reasonable to assume formation of cis products **8** and **12** in these cases as well. This was confirmed in the case of phosphonate **12** when catalytic hydrogenation gave phosphonate **17**, identical with material prepared by hydrogenation of phosphonate **10**.



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Nucleophilic additions of other types of Grignard reagents were not as successful under these reactions conditions. For example, addition of phenylmagnesium chloride to a solution of phosphonate **7** in THF did not afford the desired β-hydroxy phosphonate. Use of PhMgBr in ether gave the hydroxy phosphonate, but only in low yield. At this time, parallel reactions attempted with methylmagnesium halides and vinylmagnesium halides have resulted in just minor amounts of the desired products, even in the presence of Lewis acids.

Grignard reagents more closely related to allylmagnesium chloride showed better reactivity (Table 2). For example, benzylmagnesium bromide undergoes addition to phosphonate **7** under these reaction conditions to afford β-hydroxy phosphonate **18** in modest yield. Other representative β-keto phosphonates (**9**, **13**, and **15**) subjected to the same reaction conditions also gave the benzylated products in moderate yields, with acyclic

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Table 2. Reaction of Benzyl- and Crotylmagnesium Halides with β-Keto Phosphonates

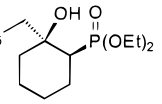
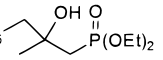
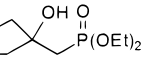
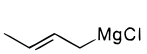
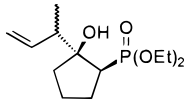
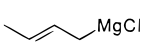
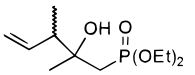
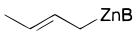
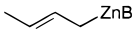
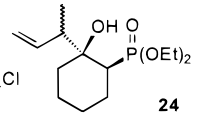
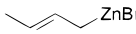
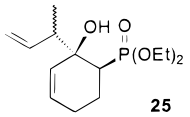
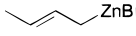
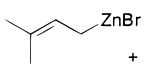
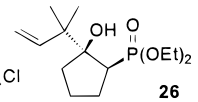
Substrate	RMgX	Product	% Yield
7	$C_6H_5CH_2MgBr$		33
	$C_6H_5CH_2MgBr$ $BF_3{\cdot}OEt_2$	**18**	37
9	$C_6H_5CH_2MgBr$		29
		19	
13	$C_6H_5CH_2MgBr$		53
		20	
15	$C_6H_5CH_2MgBr$		25
		21 R = C_6H_{11}	
7			33
		22	
13			59
		23	

Table 3. Reaction of Organozinc Reagents with β-Keto Phosphonates

Substrate	RZnX	Product	% Yield
7		**8**	83
9		**10**	58
9	" + NH_4Cl	**10**	73
11		**12**	72
13		**14**	99
15		**16**	74
7		**22**	78
9			40
	" + NH_4Cl	**24**	52
11			75
		25	
13		**23**	98
7	 + NH_4Cl		77
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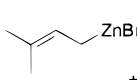
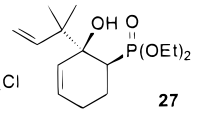
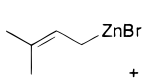
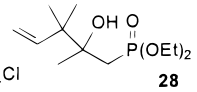
11	 + NH_4Cl		86
		27	
13	 + NH_4Cl		86
		28	

phosphonate **13** affording the best yield of the desired adduct (53%). However, addition of Lewis acids did not significantly improve the yields of these reactions. For example, reaction of phosphonate **7** with benzylmagnesium bromide in the presence of $BF_3{\cdot}OEt_2$ gave virtually the same yield observed in the absence of this Lewis acid. Addition of crotyl substituents was examined primarily to explore the special reactivity of allyl Grignard reagents with this class of compounds. Reaction of crotylmagnesium chloride with phosphonates **7** and **13** resulted in addition with complete allylic transposition to afford hydroxy phosphonates **22** and **23** in 33% and 59% yield, respectively.

In cases where moderate yields of addition products were observed, analysis of the reaction mixture by ^{31}P NMR immediately after workup generally indicated the presence of only two phosphorus-containing materials, the desired product and some of the starting β-keto phosphonate. Because the presence of the starting β-keto phosphonate may reflect proton transfer to the Grignard reagent followed by protonation upon workup, we chose to examine some organometallic reagents likely to be less reactive.[15] Zinc reagents, especially allylzinc reagents, are readily accessible and are known to add to carbonyl groups, often with high stereoselectivity.[11,16] The reaction of allylzinc bromide with phosphonate **7** provided hydroxy phosphonate **8** in 83% yield as a single product by ^{31}P NMR (Table 3). The zinc reagent appeared to be advantageous relative to the allylmagnesium chloride−$BF_3{\cdot}OEt_2$ system. Addition of allylzinc bromide to our selection of keto phosphonates gave the corresponding β-hydroxy phosphonates in yields that were generally improved relative to those obtained using Grignard reagents. Additions of crotyl and prenyl groups through the corresponding zinc reagents proceeded with complete allylic transposition and generally in attractive yields. With prenyl bromide and phosphonate **13**, the reaction gave far better yield when conducted in the presence of NH_4Cl than in its absence (86% vs 28%). Therefore, reactions with phosphonates **7** and **11** also were conducted in the presence of NH_4Cl, and comparable yields were obtained (77% and 86%, respectively). These conditions also gave an improved yield for reaction of phosphonate **9** with allylzinc bromide (73%) and crotylzinc bromide (52%).

The β-hydroxy phosphonates produced as the initial products of nucleophilic addition to β-keto phosphonates offer a number of opportunities for further reactions, some based on the functionality of the newly introduced allyl group and others that are not. For example, treatment of phosphonate **12** with Jones reagent resulted in oxidation with allylic transposition[17] and gave rise to the "vinylogous β-keto phosphonate" **29**. On the basis of the

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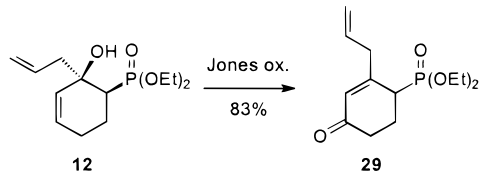
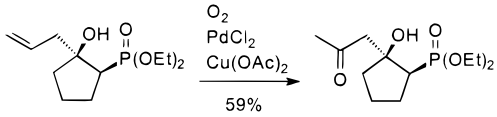


12 **29**

known reactivity of γ-phosphono crotonates,[18] it would be reasonable to expect compounds such as **29** to undergo Horner−Wadsworth−Emmons condensations under standard conditions. Treatment of phosphonate **8** with O_2 in the presence of $PdCl_2$ and $Cu(OAc)_2$[19] resulted in oxidation of the allyl group to the corresponding ketone **30**, providing a product with multiple sites for further reactivity.



8 **30**

In conclusion, despite the acidity of β-keto phosphonates, allyl organometallic reagents add efficiently to the carbonyl group. Addition of allyl Grignard reagents is facilitated by BF_3, but in several cases the corresponding allylzinc reagents give the carbonyl addition products in higher yield even in the absence of added Lewis acids. The products of allyl addition reactions have been shown to undergo several additional transformations, further expanding the range of phosphonates accessible through this strategy. Future work will focus on extension of these carbonyl addition reactions to other β-keto phosphonates and organometallic reagents, as well as other transformations of the resultant β-hydroxy phosphonates.

Experimental Section

Tetrahydrofuran (THF) and diethyl ether were distilled from sodium/benzophenone immediately prior to use. All nonaqueous reactions were conducted in oven-dried glassware, under an atomosphere of argon, and with magnetic stirring. Zinc dust was activated by washing several times with 1 M HCl followed by successive washings with water, methanol, and ether. After vacuum-drying, the zinc was stored under argon until used. Flash chromatography was carried out on silica gel with 40 μm average particle diameter. NMR spectra were recorded at 360 MHz for ^{1}H with $CDCl_3$ as solvent and $(CH_3)_4Si$ (^{1}H) or $CDCl_3$ (^{13}C, 77.0 ppm) as internal standards unless otherwise noted. ^{31}P NMR chemical shifts are reported in ppm relative to 85% H_3PO_4 (external standard). High resolution and FAB mass spectra were obtained at the University of Iowa Mass Spectrometry Facility. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

Diethyl [2-Hydroxy-2-(2-propenyl)cyclopentyl]phosphonate (8). Method A. A solution of diethyl (2-oxocyclopentyl)phosphonate[7d] (**7**, 151 mg, 0.69 mmol) in THF (2 mL) was added dropwise via cannula to a stirred solution of allylmagnesium chloride (1.8 mL, 2.0 M in THF) in THF (1.5 mL) at 0 °C. After the reaction mixture was stirred at 0 °C for 1.5 h, it was allowed to warm to room temperature and quenched by slow addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with ether, and the combined organic extracts were dried over Na_2SO_4 and then concentrated in vacuo. Purification of the residue by flash column chromatography (80% ethyl acetate, 20% hexanes) gave hydroxy phosphonate **8** (109 mg, 61%) as a clear oil.

Method B. Boron trifluoride etherate (0.3 mL, 2.3 mmol) was added to a stirred solution of allylmagnesium chloride (1.1 mL, 2.0 M in THF) in THF (10 mL) at 0 °C. After 20 min, a solution of phosphonate **7** (100 mg, 0.45 mmol) in THF (2 mL) was added. After stirring for 2 h at 0 °C, the reaction was quenched by addition of 3 M NaOH, and the mixture was stirred for 1 h at room temperature. Brine was added to the reaction mixture, and the layers were separated. The aqueous layer was washed with ether, and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash column chromatography gave hydroxy phosphonate **8** (93 mg, 78%).

Method C. Allyl bromide (0.24 mL, 2.8 mmol) was added to a suspension of zinc dust (180 mg, 2.8 mmol) in THF (6 mL). The mixture was allowed to stir at room temperature until a yellow-gray color was observed. After the resulting allylzinc bromide was cooled to −78 °C, a solution of phosphonate **7** (197 mg, 0.89 mmol) in THF (4 mL) was added via cannula, and the reaction was stirred at −78 °C for 1 h. The reaction mixture was added to 1 M HCl (20 mL), the aqueous layer was extracted with ether, and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash column chromatography gave hydroxy phosphonate **8** (196 mg, 83%): ^{1}H NMR δ 5.95−5.84 (m, 1H), 5.15−5.10 (m, 2H), 4.22−4.08 (m, 4H), 3.78 (s, 1H, exchanges in D_2O), 2.63 (dd, J = 13.8, 7.0 Hz, 1H), 2.38 (dd, J = 13.8, 7.7 Hz, 1H), 2.21−2.05 (m, 2H), 1.98−1.85 (m, 2H), 1.79−1.55 (m, 3H), 1.34 (dt, J_{HP} = 6.7 Hz, J = 6.8 Hz, 6H); ^{31}P NMR 32.3; ^{13}C NMR δ 134.1, 118.1, 81.7 (d, J_{CP} = 3.7 Hz), 62.2 (d, J_{CP} = 6.6 Hz), 61.4 (d, J_{CP} = 6.5 Hz), 45.1, 44.1 (d, J_{CP} = 141.6 Hz), 38.7 (d, J_{CP} = 13.1 Hz), 26.2, 22.4 (d, J_{CP} = 14.5 Hz), 16.3 (d, J_{CP} = 6.6 Hz), 16.3 (d, J_{CP} = 5.8 Hz); HRMS calcd for $C_{12}H_{23}O_4P$ 262.1333, found 262.1316.

Diethyl [2-Hydroxy-2-(2-propenyl)cyclohexyl]phosphonate (10). According to general procedure A, diethyl (2-oxocyclohexyl)phosphonate[7d] (**9**, 110 mg, 0.47 mmol) was added to allylmagnesium chloride (1.2 mL, 2.0 M in THF) at 0 °C. The reaction was stirred for 30 min at 0 °C and then allowed to warm to room temperature. Standard workup and purification by flash column chromatography (60% hexanes, 40% ethyl acetate) yielded hydroxy phosphonate **10** (47 mg, 36%) as a 2.5:1 mixture of diastereomers.

According to general procedure B, $BF_3{\cdot}OEt_2$ (0.27 mL, 2.1 mmol) was added to allylmagnesium chloride (1.1 mL, 2.0 M in THF) in THF (10 mL) at 0 °C and allowed to stir for 25 min. Phosphonate **9** (70 mg, 0.3 mmol in 2 mL THF) was added, and the reaction was stirred for 2 h. Standard workup and purification by flash column chromatography afforded hydroxy phosphonate **10** (42 mg, 51%) as a 17.5:1 mixture of diastereomers.

According to general procedure C, phosphonate **9** (51 mg, 0.22 mmol in 2 mL THF) was added to allylzinc bromide (1.0 mmol in 3 mL THF) via cannula at −78 °C. The reaction was quenched after 30 min by addition to 1 M HCl (20 mL). Standard workup and purification by flash column chromatography gave hydroxy phosphonate **10** (35 mg, 58%) as a 12:1 mixture of diastereomers. HRMS calcd for $C_{13}H_{25}O_4P$ 276.1490, found 276.1488. Anal. Calcd for $C_{13}H_{25}O_4P$: C, 56.51; H, 9.12. Found: C, 56.54; H, 9.07.

For the major diastereomer: ^{1}H NMR (600 MHz) ($(CD_3)_2$SO) δ 5.87−5.80 (m, 1H), 5.06−5.02 (m, 2H), 4.31 (s, 1H), 4.03−3.93 (m, 4H), 2.59 (dd, J = 13.5, 7.4 Hz, 1H), 2.36 (dd, J = 13.6, 8.0 Hz, 1H), 1.85 (ddd, J_{HP} = 19.4 Hz, J = 11.6, 4.1 Hz, 1H), 1.71−1.60 (m, 3H), 1.57−1.48 (m, 2H), 1.38−1.35 (m, 1H), 1.26 (tm, J = 13.0 Hz, 1H), 1.21 (dt, J_{HP} = 1.5 Hz, J = 7.0 Hz, 6H), 1.14−1.08 (m, 1H); ^{31}P NMR 33.4; ^{13}C NMR δ 135.0, 117.5, 70.6 (d, J_{CP} = 5.1 Hz), 61.3 (d, J_{CP} = 6.5 Hz), 60.2 (d, J_{CP} = 6.5 Hz), 46.6, 41.7 (d, J_{CP} = 133.7 Hz), 36.4 (d, J_{CP} = 12.4 Hz), 24.8 (d, J_{CP} = 13.8 Hz), 22.9, 20.7, 16.2 (d, J_{CP} = 5.8 Hz), 16.2 (d, J_{CP} = 5.8 Hz).

For the minor diastereomer: ^{1}H NMR (600 MHz) ($(CD_3)_2$SO) δ 5.89−5.82 (m, 1H), 5.06−5.02 (m, 2H), 4.43 (s, 1H), 4.04−3.95 (m, 4H), 2.43 (dd, J = 14.4, 9.1 Hz, 1H), 2.37 (dd, J

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= 14.5, 4.8 Hz, 1H), 1.94 (ddd, J_{HP} = 19.6 Hz, J = 10.9, 3.8 Hz, 1H), 1.83−1.77 (m, 1H), 1.74−1.70 (m, 1H), 1.63−1.60 (m, 1H), 1.57−1.49 (m, 2H), 1.24−1.10 (m, 3H), 1.21 (dt, J_{HP} = 1.5 Hz, J = 7.0 Hz, 6H); ^{31}P NMR 32.0; ^{13}C NMR δ 134.5, 117.0, 71.2 (d, J_{CP} = 2.2 Hz), 61.2 (d, J_{CP} = 6.6 Hz), 60.8 (d, J_{CP} = 7.3 Hz), 45.7 (d, J_{CP} = 133.7 Hz), 39.0, 35.7 (d, J_{CP} = 11.7 Hz), 24.4 (d, J_{CP} = 12.3 Hz), 23.8, 21.7, 16.2 (d, J_{CP} = 5.8 Hz), 16.2 (d, J_{CP} = 5.8 Hz).

Diethyl [2-Hydroxy-2-(2-propenyl)cylohex-3-enyl]phosphonate (12). According to general procedure C, phosphonate **11**[7e] (94 mg, 0.41 mmol in 2 mL THF) was added to allylzinc bromide (1.4 mmol in 3 mL THF) via cannula at −78 °C. The reaction was quenched after 35 min by addition to 1 M HCl (20 mL). Standard workup and purification by flash column chromatography (3:1 $CHCl_3$/EtOAc) gave hydroxy phosphonate **12** (80 mg, 72%): ^{1}H NMR δ 5.90−5.85 (m, 1H), 5.82−5.68 (m, 1H), 5.65−5.60 (m, 1H), 5.17−5.09 (m, 2H), 4.20−4.10 (m, 4H), 3.69 (s, 1H), 2.73 (dd, J = 13.7, 8.4 Hz, 1H), 2.56 (dd, J = 13.7, 6.1 Hz, 1H), 2.22−2.10 (m, 2H), 1.98−1.89 (m, 3H), 1.34 (dt, J_{HP} = 3.6 Hz, J = 7.1 Hz, 6H); ^{31}P NMR 32.1; ^{13}C NMR δ 133.8, 132.0 (d, J_{CP} = 10.9 Hz), 129.2, 118.4, 69.8 (d, J_{CP} = 4.3 Hz), 62.2 (d, J_{CP} = 6.5 Hz), 61.2 (d, J_{CP} = 6.5 Hz), 46.1 (d, J_{CP} = 1.5 Hz), 40.7 (d, J_{CP} = 138.8 Hz), 24.6 (d, J_{CP} = 13.1 Hz), 20.0 (d, J_{CP} = 3.6 Hz), 16.3 (d, J_{CP} = 6.6 Hz), 16.3 (d, J_{CP} = 6.5 Hz); HRFABMS calcd for $C_{13}H_{23}O_4P$ $(M + Na)^+$ 297.1232, found 297.1228.

Diethyl (2-Hydroxy-2-methyl-4-pentenyl)phosphonate (14). According to general procedure C, phosphonate **13** (96 mg, 0.49 mmol in 2 mL THF) was added to allylzinc bromide (1.6 mmol in 3 mL THF) via cannula at −78 °C. The reaction was quenched after 30 min by addition to 1 M HCl. Standard workup and purification by flash column chromatography (50% ethyl acetate, 50% hexanes) gave hydroxy phosphonate **14** (116 mg, 99%): ^{1}H NMR δ 5.94−5.80 (m, 1H), 5.15−5.08 (m, 2H), 4.19−4.06 (m, 4H), 3.75 (s, 1H), 2.35 (d, J = 7.3 Hz, 2H), 2.11−1.90 (m, 2H), 1.34 (t, J = 7.2 Hz, 6H), 1.34 (s, 3H); ^{31}P NMR 31.1; ^{13}C NMR δ 133.8, 118.5, 70.2 (d, J_{CP} = 4.6 Hz), 61.6 (d, J_{CP} = 4.5 Hz), 61.5 (d, J_{CP} = 4.5 Hz), 47.9 (d, J_{CP} = 11.9 Hz), 36.7 (d, J_{CP} = 135.8 Hz), 28.0 (d, J_{CP} = 8.5 Hz), 16.3 (d, J_{CP} = 6.1 Hz, 2C); HRFABMS calcd for $C_{10}H_{21}O_4P$ $(M + Na)^+$ 259.1075, found 259.1095.

Diethyl (3-Cyclohexyl-2-oxopropyl)phosphonate (15). *n*-Butyllithium (2.42 M in hexanes, 2.75 mL, 6.7 mmol) was added dropwise to a solution of diethyl methylphosphonate (1.01 g, 6.6 mmol) in THF (7 mL) at −78 °C.[20] The resulting solution was stirred for 30 min at −78 °C followed by slow addition of ethyl cyclohexylacetate (0.70 g, 4.1 mmol in 1.5 mL THF). The reaction was allowed to warm to room temperature and then quenched by addition of saturated aqueous NH_4Cl. The layers were separated, and the aqueous portion was extracted with ether. The organic extracts were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash column chromatography (3:1 ethyl acetate/hexanes) gave β-keto phosphonate **15** as a clear oil (0.59 g, 52%): ^{1}H NMR δ 4.19−4.10 (m, 4H), 3.06 (d, J_{HP} = 22.8 Hz, 2H), 2.50 (d, J = 6.7 Hz, 2H), 1.91−1.78 (m, 1H), 1.73−1.62 (m, 5H), 1.34 (t, J = 7.1 Hz, 6H), 1.30−1.06 (m, 3H), 1.00−0.88 (m, 2H); ^{31}P NMR 20.7; ^{13}C NMR δ 201.7 (d, J_{CP} = 5.8 Hz), 62.4 (d, J_{CP} = 6.5 Hz, 2C), 51.6, 42.7 (d, J_{CP} = 126.4 Hz), 33.3, 32.9 (2C), 26.1, 25.9 (2C), 16.2 (d, J_{CP} = 5.9 Hz, 2C); HRFABMS calcd for $C_{13}H_{25}O_4P$ $(M + H)^+$ 277.1569, found 277.1569.

Diethyl (2-Cyclohexylmethyl-2-hydroxy-4-pentenyl)-phosphonate (16). According to general procedure B, BF_3·OEt_2 (0.22 mL, 1.7 mmol) was added to allylmagnesium chloride (0.86 mL, 2.0 M in THF) in THF (10 mL) at 0 °C, and the mixture was allowed to stir for 20 min. Phosphonate **15** (96 mg, 0.35 mmol in 2 mL THF) was added, and the reaction was stirred for 2 h. Standard workup and purification by flash column chromatography (50% ethyl acetate, 50% hexanes) yielded hydroxy phosphonate **16** (86 mg, 78%) as a clear oil.

(20) Wilson, J. M. PhD Thesis, University of Iowa, December, 1998.

According to general procedure C, phosphonate **15** (92 mg, 0.33 mmol in 2 mL THF) was added to allylzinc bromide (1.1 mmol in 3 mL THF) via cannula at −78 °C. The reaction was quenched after 1 h by addition to 1 M HCl (20 mL). Standard workup and purification by flash column chromatography (30% ethyl acetate, 70% hexanes) gave hydroxy phosphonate **16** (78 mg, 74%): ^{1}H NMR (600 MHz) δ 5.89−5.77 (m, 1H), 5.13−5.08 (m, 2H), 4.17−4.06 (m, 4H), 3.84 (s, 1H), 2.42 (dd, J = 7.4, 1.2 Hz, 2H), 2.01 (dd, J_{HP} = 23.7 Hz, J = 15.8 Hz, 1H), 1.98 (dd, J_{HP} = 23.8 Hz, J = 15.8 Hz, 1H), 1.88 (br d, J = 12.7 Hz, 1H), 1.74 (br d, J = 12.9 Hz, 1H), 1.68−1.60 (m, 3H), 1.56−1.49 (m, 2H), 1.45−1.41 (m, 1H), 1.34 (dt, J_{HP} = 1.4 Hz, J = 7.0 Hz, 6H), 1.29−1.20 (m, 2H), 1.17−1.10 (m, 1H), 1.02−0.95 (m, 2H); ^{31}P NMR 31.1; ^{13}C NMR δ 134.0, 118.5, 72.9 (d, J_{CP} = 5.1 Hz), 61.6 (d, J_{CP} = 6.5 Hz), 61.6 (d, J_{CP} = 6.5 Hz), 47.5 (d, J_{CP} = 9.4 Hz), 45.2 (d, J_{CP} = 9.5 Hz), 35.7 (d, J_{CP} = 135.8 Hz), 35.1, 34.9, 33.3, 26.4, 26.3, 26.2, 16.3 (d, J_{CP} = 6.5 Hz, 2C). Anal. Calcd for $C_{16}H_{31}O_4P$: C, 60.36; H, 9.81. Found: C, 60.28; H, 9.76.

Hydrogenation of Phosphonate 12. A solution of hydroxy phosphonate **12** (32 mg, 0.12 mmol) in MeOH (3 mL) was hydrogenated at 50 psi in the presence of 10% Pd on activated carbon (∼20 mg) at room temperature for 8 h. The catalyst was removed by filtration, and the solvent was removed in vacuo. Purification of the residue by flash column chromatography (60% hexanes, 40% ethyl acetate) gave compound **17** (30 mg, 92%) as a clear oil: ^{1}H NMR δ 4.21−4.01 (m, 4H), 3.80 (d, J = 2.2 Hz, 1H), 1.95−1.66 (m, 8H), 1.50−1.44 (m, 1H), 1.42−1.31 (m, 2H), 1.34 (dt, J_{HP} = 4.1 Hz, J = 7.0 Hz, 6H), 1.27−1.13 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{31}P NMR 33.7; ^{13}C NMR δ 71.4 (J_{CP} = 5.1 Hz), 62.5 (d, J_{CP} = 6.5 Hz), 60.9 (d, J_{CP} = 8.0 Hz), 45.8 (J_{CP} = 2.2 Hz), 42.2 (J_{CP} = 132.9 Hz), 35.9 (J_{CP} = 13.8 Hz), 25.8 (J_{CP} = 15.2 Hz), 22.6, 20.9, 17.1, 16.5 (J_{CP} = 5.8 Hz), 16.3 (J_{CP} = 6.6 Hz), 14.6; HRMS calcd for $C_{13}H_{27}O_4P$ 278.1647, found 278.1631.

Hydrogenation of a sample of phosphonate **10**, a 2.5:1 mixture of diastereomers, gave a mixture of the two saturated diastereomers. The major diastereomer was identical to the product obtained by hydrogenation of compound **12** (by ^{13}C and ^{31}P NMR). For the minor diastereomer: ^{31}P NMR 32.2; ^{13}C NMR δ 72.2 (J_{CP} = 4.3 Hz), 61.7 (J_{CP} = 6.5 Hz), 61.3 (J_{CP} = 7.9 Hz), 47.7 (J_{CP} = 134.5 Hz), 36.5 (J_{CP} = 2.2 Hz), 35.7 (J_{CP} = 16.0 Hz), 25.8 (J_{CP} = 14.5 Hz), 24.5 (J_{CP} = 5.8 Hz), 22.7, 16.4 (J_{CP} = 5.1 Hz), 16.3 (J_{CP} = 5.8 Hz), 15.7, 14.6.

Diethyl (2-Hydroxy-2-phenylmethylcyclopentyl)phosphonate (18). A three-neck flask equipped with an addition funnel, condenser, and magnesium turnings (60 mg, 2.5 mmol) was flame-dried and purged with argon. After the apparatus had cooled, ether (1 mL) and one-third of the benzyl bromide (0.08 mL, 0.67 mmol) were added to the vigorously stirred magnesium. Once the reaction began to reflux, a solution of the remaining benzyl bromide (0.20 mL, 1.7 mmol) in ether (5 mL) was added slowly to maintain reflux. After the benzyl bromide addition was complete, the reaction was heated at reflux for an additional hour and then allowed to cool to room temperature. A solution of phosphonate **7** (105 mg, 0.48 mmol) in ether (2 mL) was added dropwise to the Grignard reagent. The reaction was allowed to stir at room temperature for 5 h and then quenched by addition of 2 N HCl. The layers were separated, and the aqueous layer was washed with ether. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (80% hexanes, 20% ethyl acetate) gave hydroxy phosphonate **18** (49 mg, 33%): ^{1}H NMR δ 7.32−7.20 (m, 5H), 4.28−4.10 (m, 4H), 3.88 (br s, 1H), 3.18 (d, J = 13.5 Hz, 1H), 2.94 (d, J = 13.5 Hz, 1H), 2.23−2.09 (m, 2H), 1.94−1.79 (m, 2H), 1.66−1.50 (m, 3H), 1.36 (dt, J_{HP} = 16.2 Hz, J = 7.1 Hz, 6H); ^{31}P NMR 32.5; ^{13}C NMR δ 138.0, 130.4 (2C), 128.0 (2C), 126.3, 82.5 (d, J_{CP} = 3.7 Hz), 62.2 (d, J_{CP} = 6.5 Hz), 61.4 (d, J_{CP} = 7.3 Hz), 46.4, 43.9 (d, J_{CP} = 141.0 Hz), 38.6 (d, J_{CP} = 14.5 Hz), 25.9, 22.0 (d, J_{CP} = 13.8 Hz), 16.5 (d, J_{CP} = 3.6 Hz), 16.4 (d, J_{CP} = 3.7 Hz); HRFABMS calcd for $C_{16}H_{25}O_4P$ $(M + H)^+$ 313.1569, found 313.1576. Anal. Calcd for $C_{16}H_{25}O_4P$: C, 61.53; H, 8.07. Found: C, 61.65; H, 8.20.

Diethyl (2-Hydroxy-2-phenylmethylcyclohexyl)phosphonate (19). According to the procedure used for preparation of compound **18**, phosphonate **9** (92 mg, 0.39 mmol in 2 mL ether) was treated with benzylmagnesium bromide prepared in situ from benzyl bromide (0.23 mL, 1.9 mmol) and magnesium (50 mg, 2.1 mmol) in ether (3 mL). After 3 h at room temperature, the reaction was quenched by addition of 2 N HCl. Standard workup and purification by flash column chromatography (50% hexanes, 50% ethyl acetate) gave hydroxy phosphonate **19** (37 mg, 29%): ^{1}H NMR δ 7.31−7.19 (m, 5H), 4.25−4.09 (m, 4H), 4.00 (d, J = 2.0 Hz, 1H, exchanges in D_2O), 3.28 (d, J = 13.6 Hz, 1H), 2.81 (d, J = 13.7 Hz, 1H), 2.04−1.72 (m, 4H), 1.64−1.48 (m, 2H), 1.42−1.34 (m, 1H), 1.36 (t, J = 7.0 Hz, 6H), 1.23−1.04 (m, 2H); ^{31}P NMR 33.5; ^{13}C NMR δ 137.5, 130.7 (2C), 127.8 (2C), 126.1, 71.5 (d, J_{CP} = 4.4 Hz), 62.7 (d, J_{CP} = 7.3 Hz), 61.2 (d, J_{CP} = 7.3 Hz), 48.7, 43.7 (d, J_{CP} = 133.7 Hz), 36.1 (d, J_{CP} = 13.1 Hz), 25.5 (d, J_{CP} = 15.2 Hz), 22.9, 20.8, 16.5 (d, J_{CP} = 5.0 Hz), 16.3 (d, J_{CP} = 6.5 Hz); HRFABMS calcd for $C_{17}H_{27}O_4P$ (M + Na)$^+$ 349.1545, found 349.1540.

Diethyl (2-Hydroxy-2-methyl-3-phenylpropyl)phosphonate (20). According to the procedure for preparation of compound **18**, phosphonate **13** (100 mg, 0.51 mmol in 2 mL ether) was treated with benzylmagnesium bromide prepared in situ from benzyl bromide (0.31 mL, 2.6 mmol) and magnesium (62 mg, 2.6 mmol) in ether (30 mL). After 5 h at room temperature, the reaction was quenched by addition of 2 N HCl. Standard workup and purification by flash column chromatography (80% hexanes, 20% ethyl acetate) gave hydroxy phosphonate **20** (78 mg, 53%): ^{1}H NMR δ 7.33−7.22 (m, 5H), 4.18−4.05 (m, 4H), 3.90 (br s, 1H), 2.94−2.84 (m, 2H), 2.10−1.90 (m, 2H), 1.33 (s, 3H), 1.33 (t, J = 7.1 Hz, 6H); ^{31}P NMR 30.7; ^{13}C NMR δ 137.2, 130.6 (2C), 128.0 (2C), 126.5, 70.8 (d, J_{CP} = 4.3 Hz), 61.7 (d, J_{CP} = 6.7 Hz), 61.6 (d, J_{CP} = 6.8 Hz), 49.5 (d, J_{CP} = 12.9 Hz), 37.0 (d, J_{CP} = 136.1 Hz), 28.1 (d, J_{CP} = 6.7 Hz), 16.3 (d, J_{CP} = 6.1 Hz, 2C). Anal. Calcd for $C_{14}H_{23}O_4P$: C, 58.73; H, 8.10. Found: C, 58.48; H, 8.20.

Diethyl (2-Cyclohexylmethyl-2-hydroxy-3-phenylpropyl)phosphonate (21). According to the usual procedure, phosphonate **15** (106 mg, 0.38 mmol) was treated with benzylmagnesium bromide prepared in situ from benzyl bromide (0.22 mL, 1.9 mmol) and magnesium (50 mg, 2.1 mmol) in 3 mL ether. After 4 h at room temperature, the reaction was quenched by addition of 2 N HCl. Standard workup and purification by flash column chromatography (50% hexanes, 50% ethyl acetate) gave hydroxy phosphonate **21** (40 mg, 28%): ^{1}H NMR δ 7.31−7.21 (m, 5H), 4.17−4.03 (m, 4H), 3.70 (s, 1H), 2.97 (dd, J = 13.6, 2.2 Hz, 1H), 2.92 (d, J = 13.6 Hz, 1H), 1.96 (d, J_{HP} = 18.4 Hz, 2H), 1.88 (dm, J = 12.7 Hz, 1H), 1.79 (dm, J = 13.0 Hz, 1H), 1.70−1.52 (m, 5H), 1.43 (ddd, J = 14.3, 4.8, 1.7 Hz, 1H), 1.36−1.23 (m, 2H), 1.32 (dt, J_{HP} = 11.5 Hz, J = 7.1 Hz, 6H), 1.20−1.11 (m, 1H), 1.03−0.93 (m, 2H); ^{31}P NMR 31.0; ^{13}C NMR δ 137.4, 130.8 (2C), 128.0 (2C), 126.3, 73.5 (d, J_{CP} = 4.4 Hz), 61.6 (d, J_{CP} = 6.6 Hz), 61.6 (d, J_{CP} = 6.6 Hz), 47.6 (d, J_{CP} = 8.0 Hz), 46.9 (d, J_{CP} = 10.2 Hz), 35.6 (d, J_{CP} = 135.9 Hz), 35.1, 35.1, 33.5, 26.5, 26.4, 26.3, 16.3 (d, J_{CP} = 5.9 Hz), 16.3 (d, J_{CP} = 5.8 Hz). Anal. Calcd for $C_{20}H_{33}O_4P$: C, 65.20; H, 9.03. Found: C, 65.04; H, 9.05.

Diethyl [2-Hydroxy-2-(1-methyl-2-propenyl)cyclopentyl]phosphonate (22). Method A. A two-neck flask equipped with an addition funnel, condenser, and magnesium turnings (60 mg, 2.5 mmol) was flame-dried and purged with argon. After the apparatus had cooled, ether (1 mL) and one-third of the crotyl chloride (0.07 mL, 0.72 mmol) were added to the vigorously stirred magnesium. Once the reaction began to reflux, a solution of the remaining crotyl chloride (0.15 mL, 1.5 mmol) in ether (2 mL) was added slowly to maintain reflux. After the crotyl chloride was added, the reaction was heated at reflux for an additional hour and then cooled to room temperature. A solution of phosphonate **7** (96 mg, 0.43 mmol) in ether (2 mL) was added dropwise to the Grignard reagent. The reaction was allowed to stir at room temperature for 4 h and then quenched by addition of 2 N HCl. The layers were separated, and the aqueous layer was washed with ether. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (50% ethyl acetate, 50% hexanes) gave hydroxy phosphonate **22** (40 mg, 33%) as a 2:1 mixture of diastereomers.

Method C. Crotyl bromide (0.24 mL, 2.3 mmol) was added to a suspension of zinc dust (150 mg, 2.3 mmol) in THF (3 mL). The mixture was allowed to stir at room temperature until a yellow-gray color was observed. After the crotylzinc bromide was cooled to −78 °C, a solution of phosphonate **7** (93 mg, 0.42 mmol) in THF (2 mL) was added slowly via cannula. After stirring for 1 h at −78 °C, the reaction was quenched by addition to 1 M HCl (20 mL). The aqueous layer was extracted with ether, and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography yielded hydroxy phosphonate **22** (91 mg, 78%) as a 1:5.8 mixture of diastereomers: HRFABMS calcd for $C_{13}H_{25}O_4P$ (M + Na)$^+$ 299.1388, found 299.1388.

For the major diastereomer from the zinc reaction: ^{1}H NMR δ 5.99 (ddd, J = 17.5, 9.9, 7.7 Hz, 1H), 5.17−5.05 (m, 2H), 4.19−4.06 (m, 4H), 3.68 (s, 1H), 2.58 (dq, J = 7.0, 6.9 Hz, 1H), 2.39−2.26 (m, 1H), 2.20−2.04 (m, 1H), 1.95−1.81 (m, 2H), 1.75−1.51 (m, 3H), 1.34 (dt, J_{HP} = 7.0 Hz, J = 3.6 Hz, 6H), 1.06 (d, J = 6.9 Hz, 3H); ^{31}P NMR 32.4; ^{13}C NMR δ 140.5, 115.1, 84.3 (d, J_{CP} = 3.6 Hz), 62.1 (d, J_{CP} = 4.4 Hz), 61.2 (d, J_{CP} = 7.2 Hz), 46.1, 42.6 (d, J_{CP} = 141.0 Hz), 35.7 (d, J_{CP} = 12.3 Hz), 26.7, 22.6 (d, J_{CP} = 13.8 Hz), 16.4 (d, J_{CP} = 5.9 Hz), 16.3 (d, J_{CP} = 5.8 Hz), 15.0.

For the minor diastereomer from the zinc reaction: ^{1}H NMR δ 5.76 (ddd, J = 17.3, 10.3, 8.5 Hz, 1H), 5.17−5.05 (m, 2H), 4.19−4.06 (m, 4H), 3.81 (s, 1H), 2.65 (dq, J = 7.5, 7.3 Hz, 1H), 2.39−2.26 (m, 1H), 2.20−2.04 (m, 1H), 1.95−1.81 (m, 2H), 1.75−1.51 (m, 3H), 1.34 (dt, J_{HP} = 7.0 Hz, J = 3.6 Hz, 6H), 1.13 (d, J = 6.8 Hz, 3H); ^{31}P NMR 32.8; ^{13}C NMR δ 140.4, 116.2, 84.5 (d, J_{CP} = 2.9 Hz), 62.1 (d, J_{CP} = 6.5 Hz), 61.2 (d, J_{CP} = 7.3 Hz), 46.2, 42.8 (d, J_{CP} = 140.2 Hz), 34.4 (d, J_{CP} = 13.8 Hz), 26.4, 22.5 (d, J_{CP} = 14.5 Hz), 16.4 (d, J_{CP} = 5.9 Hz), 16.3 (d, J_{CP} = 5.8 Hz), 15.2.

Diethyl (2-Hydroxy-2,3-dimethyl-4-pentenyl)phosphonate (23). According to general procedure C, phosphonate **13** (108 mg, 0.55 mmol in 2 mL THF) was added to crotylzinc bromide (2.5 mmol in 3 mL THF) via cannula at −78 °C. The reaction was quenched after 1 h by addition to 1 M HCl. Standard workup and purification by flash column chromatography (50% hexanes, 50% ethyl acetate) afforded hydroxy phosphonate **23** (136 mg, 98%) as a 1.3:1 mixture of diastereomers. HRFABMS calcd for $C_{11}H_{23}O_4P$ (M + Na)$^+$ 273.1232, found 273.1247.

For the major diastereomer: ^{1}H NMR δ 5.79 (ddd, J = 17.2, 10.4, 8.2 Hz, 1H), 5.12−5.06 (m, 2H), 4.21−4.12 (m, 4H), 3.83 (s, 1H), 2.44−2.31 (m, 1H), 2.22−1.91 (m, 2H), 1.35 (t, J = 7.1 Hz, 6H), 1.30 (s, 3H), 1.06 (d, J = 6.9 Hz, 3H); ^{31}P NMR 31.6; ^{13}C NMR δ 139.9, 116.2, 72.1, 62.3 (d, J_{CP} = 6.5 Hz, 2C), 49.0 (d, J_{CP} = 13.1 Hz), 35.9 (d, J_{CP} = 138.1 Hz), 24.1 (d, J_{CP} = 6.5 Hz), 16.3 (d, J_{CP} = 5.8 Hz, 2C), 14.0.

For the minor diastereomer: ^{1}H NMR δ 5.89 (ddd, J = 16.6, 11.0, 7.8 Hz, 1H), 5.12−5.06 (m, 2H), 4.21−4.12 (m, 4H), 3.72 (s, 1H), 2.44−2.31 (m, 1H), 2.22−1.91 (m, 2H), 1.35 (t, J = 7.1 Hz, 6H), 1.30 (s, 3H), 1.05 (d, J = 6.9 Hz, 3H); ^{31}P NMR 31.6; ^{13}C NMR δ 139.6, 116.1, 72.1, 62.3 (d, J_{CP} = 7.3 Hz, 2C), 48.7 (d, J_{CP} = 13.8 Hz), 35.1 (d, J_{CP} = 138.8 Hz), 25.4 (d, J_{CP} = 5.8 Hz), 16.3 (d, J_{CP} = 5.8 Hz, 2C), 14.3.

Diethyl [2-Hydroxy-2-(1-methyl-2-propenyl)cyclohexyl]phosphonate (24). According to procedure C, phosphonate **9** (55 mg, 0.24 mmol in 2 mL THF) was added to crotylzinc bromide (1.1 mmol in 2 mL THF) via cannula at −78 °C. The reaction was quenched after 1 h by addition to 1 M HCl (20 mL). Standard workup and purification by flash column chromatography (60% hexanes, 40% ethyl acetate) gave hydroxy phosphonate **24** (27 mg, 40%) as a 1.1:1.0 mixture of diastereomers. HRFABMS calcd for $C_{14}H_{27}O_4P$ (M + Na)$^+$ 313.1545, found 313.1548.

For the major diastereomer: ^{1}H NMR δ 5.91 (ddd, J = 17.5, 10.4, 6.9 Hz, 1H), 5.18−5.02 (m, 2H), 4.22−4.04 (m, 4H), 3.96 (d, J = 2.4 Hz, 1H, exchanges in D_2O), 2.90−2.77 (m, 1H), 2.14 (ddd, J_{HP} = 19.7 Hz, J = 12.3, 4.4 Hz, 1H), 1.94−1.57 (m, 5H),

1.53−1.44 (m, 1H), 1.34 (dt, J_{HP} = 3.4 Hz, J = 7.1 Hz, 6H), 1.21−1.10 (m, 2H), 1.10 (d, J = 6.9 Hz, 3H); ^{31}P NMR 34.0; ^{13}C NMR δ 140.3, 115.5, 73.5 (d, J_{CP} = 4.3 Hz), 62.7 (d, J_{CP} = 7.3 Hz), 61.0 (d, J_{CP} = 7.3 Hz), 45.7 (d, J_{CP} = 3.0 Hz), 41.2 (d, J_{CP} = 132.2 Hz), 29.9 (d, J_{CP} = 13.0 Hz), 25.8 (d, J_{CP} = 15.3 Hz), 23.2 (d, J_{CP} = 2.9 Hz), 20.5, 16.5 (d, J_{CP} = 5.1 Hz), 16.2 (d, J_{CP} = 6.6 Hz), 12.9.

For the minor diastereomer: ^{1}H NMR δ 6.12 (ddd, J = 17.2, 10.6, 6.6 Hz, 1H), 5.18−5.02 (m, 2H), 4.22−4.04 (m, 4H), 3.76 (d, J = 2.1 Hz, 1H, exchanges in D_2O), 2.90−2.77 (m, 1H), 2.14 (ddd, J_{HP} = 19.7 Hz, J = 12.3, 4.4 Hz, 1H), 1.94−1.57 (m, 5H), 1.53−1.44 (m, 1H), 1.34 (dt, J_{HP} = 3.4 Hz, J = 7.1 Hz, 6H), 1.21−1.10 (m, 2H), 1.04 (d, J = 6.9 Hz, 3H); ^{31}P NMR 33.3; ^{13}C NMR δ 140.1, 114.9, 73.8, 62.5 (d, J_{CP} = 7.3 Hz), 60.9 (d, J_{CP} = 5.1 Hz), 45.9 (d, J_{CP} = 2.9 Hz), 40.8 (d, J_{CP} = 133.7 Hz), 30.6 (d, J_{CP} = 13.1 Hz), 25.6 (d, J_{CP} = 14.5 Hz), 22.9 (d, J_{CP} = 2.9 Hz), 20.6, 16.5 (d, J_{CP} = 5.1 Hz), 16.2 (d, J_{CP} = 6.6 Hz), 14.2.

Diethyl [2-Hydroxy-2-(1-methyl-2-propenyl)cyclohex-3-enyl]phosphonate (25). According to procedure C, phosphonate **11** (99 mg, 0.43 mmol in 2 mL THF) was added to crotylzinc bromide (2.2 mmol in 3 mL THF) via cannula at −78 °C. The reaction was quenched after 1 h by addition to 1 M HCl (20 mL). Standard workup and purification by flash column chromatography (3:1 chloroform/ethyl acetate) afforded hydroxy phosphonate **25** (92 mg, 75%) as a 2:1 mixture of diastereomers. HRFABMS calcd for $C_{13}H_{25}O_4P$ $(M + Na)^+$ 311.1388, found 311.1390.

For the major diastereomer: ^{1}H NMR (600 MHz) δ 5.94 (ddd, J = 10.2, 5.9, 1.8 Hz, 1H), 5.74 (ddd, J = 10.2, 6.1, 2.4 Hz, 1H), 5.57 (ddd, J = 17.2, 10.3, 9.2 Hz, 1H), 5.17−5.09 (m, 1H), 5.00 (d, J = 10.3 Hz, 1H), 4.19−4.06 (m, 4H), 3.59 (s, 1H), 3.03 (dq, J = 9.2, 6.9 Hz, 1H), 2.39 (dm, J_{HP} = 23.3 Hz, 1H), 2.21−2.10 (m, 1H), 2.04−1.86 (m, 3H), 1.36−1.31 (m, 6H), 1.15 (d, J = 6.9 Hz, 3H); ^{31}P NMR 32.4; ^{13}C NMR δ 140.9, 130.4, 128.0 (d, J_{CP} = 10.9 Hz), 116.0, 71.5 (d, J_{CP} = 5.1 Hz), 62.2 (d, J_{CP} = 6.5 Hz), 61.1 (d, J_{CP} = 6.6 Hz), 46.9 (d, J_{CP} = 1.5 Hz), 40.8 (d, J_{CP} = 137.3 Hz), 24.9 (d, J_{CP} = 13.8 Hz), 20.5 (d, J_{CP} = 3.6 Hz), 16.4 (d, J_{CP} = 5.8 Hz), 16.3 (d, J_{CP} = 7.2 Hz), 14.4.

For the minor diastereomer: ^{1}H NMR (600 MHz) δ 6.09 (ddd, J = 17.3, 10.4, 7.6 Hz, 1H), 5.87 (dm, J = 10.2 Hz, 1H), 5.63 (dm, J = 10.3 Hz, 1H), 5.17−5.09 (m, 1H), 5.00 (d, J = 10.3 Hz, 1H), 4.19−4.06 (m, 4H), 3.66 (s, 1H), 2.92 (dq, J = 6.9, 6.9 Hz, 1H), 2.39 (dm, J_{HP} = 23.3 Hz, 1H), 2.21−2.10 (m, 1H), 2.04−1.86 (m, 3H), 1.36−1.31 (m, 6H), 0.99 (d, J = 6.8 Hz, 3H); ^{31}P NMR 32.1; ^{13}C NMR δ 139.7,129.8 (d, J_{CP} = 8.8 Hz),129.6, 116.1, 71.9 (d, J_{CP} = 5.1 Hz), 62.3 (d, J_{CP} = 7.3 Hz), 61.0 (d, J_{CP} = 7.2 Hz), 45.7 (d, J_{CP} = 3.6 Hz), 40.0 (d, J_{CP} = 139.2 Hz), 24.3 (d, J_{CP} = 12.3 Hz), 20.3 (d, J_{CP} = 4.4 Hz), 16.4 (d, J_{CP} = 5.8 Hz), 16.3 (d, J_{CP} = 7.2 Hz), 14.7.

Diethyl [2-Hydroxy-2-(1,1-dimethyl-2-propenyl)cyclopentyl]phosphonate (26). 4-Bromo-2-methyl-2-butene (0.26 mL, 2.3 mmol) and zinc dust (150 mg, 2.3 mmol) were added all at once to a stirred solution of phosphonate **7** (102 mg, 0.46 mmol) in THF (2 mL) and saturated aqueous NH_4Cl (3 mL). The reaction mixture was stirred for 1 h at room temperature and then diluted with ether. The aqueous layer was extracted with ether, and the combined organic layers were dried over Na_2SO_4 and then concentrated in vacuo. Purification of the residue by flash column chromatography (60% hexanes, 40% ethyl acetate) gave hydroxy phosphonate **26** (104 mg, 77%): ^{1}H NMR δ 6.02 (dd, J = 18.0, 10.2 Hz, 1H), 5.10−5.05 (m, 2H), 4.18−4.05 (m, 4H), 3.83 (s, 1H), 2.50 (ddd, J_{HP} = 20.7 Hz, J = 9.5, 4.5 Hz, 1H), 2.18−2.07 (m, 1H), 1.89−1.78 (m, 2H), 1.76−1.57 (m, 3H), 1.32 (t, J = 7.0 Hz, 6H), 1.12 (s, 3H), 1.08 (s, 3H); ^{31}P NMR 32.8; ^{13}C NMR δ 144.7, 113.4, 86.7 (d, J_{CP} = 5.0 Hz), 62.2 (d, J_{CP} = 6.5 Hz), 61.1 (d, J_{CP} = 6.5 Hz), 44.6, 42.4 (d, J_{CP} = 139.5 Hz), 37.8 (d, J_{CP} = 5.1 Hz), 29.8 (d, J_{CP} = 4.4 Hz), 24.6 (d, J_{CP} = 5.8 Hz), 22.7, 22.0, 16.4 (d, J_{CP} = 6.6 Hz), 16.2 (d, J_{CP} = 6.5 Hz); HRFABMS calcd for $C_{14}H_{27}O_4P$ $(M + Na)^+$ 313.1545, found 313.1543.

Diethyl [2-Hydroxy-2-(1,1-dimethyl-2-propenyl)cyclohex-3-enyl]phosphonate (27). According to the procedure shown for compound **26**, 4-bromo-2-methyl-2-butene (0.25 mL, 2.2 mmol) and zinc dust (140 mg, 2.2 mmol) were added to a stirred solution of phosphonate **11** (99 mg, 0.43 mmol) in THF (2 mL) and NH_4Cl (3 mL). After 1 h, the reaction mixture was diluted with ether. Standard workup and purification by flash column chromatography (50% ethyl acetate, 50% hexanes) afforded hydroxy phosphonate **27** (111 mg, 86%): ^{1}H NMR δ 6.08 (dd, J = 17.6, 10.9 Hz, 1H), 5.98 (dm, J = 10.2 Hz, 1H), 5.69 (d, J = 10.5 Hz, 1H), 5.06 (dd, J = 10.7, 1.3 Hz, 1H), 5.03 (dd, J = 17.5, 1.4 Hz, 1H), 4.17−4.07 (m, 4H), 3.77 (s, 1H), 2.71 (dm, J_{HP} = 23.5 Hz, 1H), 2.31−2.22 (m, 1H), 2.09−1.98 (m, 1H), 1.95−1.84 (m, 2H), 1.31 (dt, J_{HP} = 4.9 Hz, J = 7.1 Hz, 6H), 1.12 (s, 3H), 1.07 (s, 3H); ^{31}P NMR 31.9; ^{13}C NMR δ 145.1, 130.2, 129.4, 112.7, 73.2 (d, J_{CP} = 5.0 Hz), 62.0 (d, J_{CP} = 7.2 Hz, 2C), 46.0 (d, J_{CP} = 8.0 Hz), 39.1 (d, J_{CP} = 138.8 Hz), 23.3 (d, J_{CP} = 5.0 Hz), 23.1, 21.8 (d, J_{CP} = 4.3 Hz), 21.4, 16.3 (d, J_{CP} = 6.6 Hz, 2C); HRFABMS calcd for $C_{15}H_{27}O_4P$ $(M + Na)^+$ 325.1545, found 325.1538.

Diethyl (2-Hydroxy-2,3,3-trimethyl-4-pentenyl)phosphonate (28). According to the general procedure shown for compound **26**, 4-bromo-2-methyl-2-butene (0.3 mL, 2.6 mmol) and zinc dust (170 mg, 2.6 mmol) were added to a stirred solution of phosphonate **13** (100 mg, 0.5 mmol) in THF (2 mL) and NH_4Cl (3 mL). After 1 h, the reaction mixture was diluted with ether. Standard workup and purification by flash column chromatography (60% hexanes, 40% ethyl acetate) gave hydroxy phosphonate **28** (117 mg, 86%): ^{1}H NMR δ 6.09 (dd, J = 17.6, 10.9 Hz, 1H), 5.06 (dd, J = 10.8, 1.4 Hz, 1H), 5.02 (dd, J = 17.6, 1.5 Hz, 1H), 4.19−4.05 (m, 4H), 3.80 (s, 1H, exchanges in D_2O), 2.15 (ddd, J_{HP} = 18.2 Hz, J = 15.3, 1.0 Hz, 1H), 1.92 (dd, J_{HP} = 20.1 Hz, J = 15.3 Hz, 1H), 1.38 (s, 3H), 1.33 (dt, J_{HP} = 2.9 Hz, J = 7.1 Hz, 6H), 1.07 (s, 3H), 1.04 (s, 3H); ^{31}P NMR 32.6; ^{13}C NMR δ 144.8, 112.8, 73.6 (d, J_{CP} = 5.8 Hz), 61.8 (d, J_{CP} = 6.5 Hz), 61.4 (d, J_{CP} = 7.2 Hz), 44.6 (d, J_{CP} = 16.0 Hz), 33.2 (d, J_{CP} = 137.3 Hz), 23.6, 21.6 (2C), 16.3 (d, J_{CP} = 5.8 Hz, 2C). Anal. Calcd for $C_{12}H_{25}O_4P$: C, 54.53; H, 9.53. Found: C, 54.49; H, 9.63.

Phosphonate 29. A solution of hydroxy phosphonate **12** (60 mg, 0.22 mmol) in acetone (2.5 mL) was added dropwise via cannula to a stirred solution of chromium(VI) oxide (46 mg, 0.46 mmol) in acetic acid (1 mL) at 15 °C. The reaction mixture was stirred at 15 °C for 2 h and then concentrated in vacuo. The residue was diluted with CH_2Cl_2 and poured into aqueous saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried over Na_2SO_4 and then concentrated in vacuo. Purification of the residue by flash column chromatography (3:1 chloroform/ethyl acetate) yielded phosphonate **29** (50 mg, 83%): ^{1}H NMR δ 6.01 (d, J = 4.9 Hz, 1H), 5.79 (dddd, J = 16.8, 10.2, 7.5, 6.1 Hz, 1H), 5.21−5.14 (m, 2H), 4.20−4.08 (m, 4H), 3.28−3.14 (m, 2H), 2.92−2.74 (m, 2H), 2.51−2.41 (m, 1H), 2.36 (ddm, J_{HP} = 17.9 Hz, J = 5.0 Hz, 1H), 2.29−2.09 (m, 1H), 1.33 (dt, J_{HP} = 11.3 Hz, J = 7.1 Hz, 6H); ^{31}P NMR 26.1; ^{13}C NMR δ 198.3 (d, J_{CP} = 4.3 Hz), 158.3 (d, J_{CP} = 8.7 Hz), 133.1, 128.5 (d, J_{CP} = 10.2 Hz), 118.8, 63.0 (d, J_{CP} = 7.2 Hz), 62.1 (d, J_{CP} = 7.3 Hz), 41.2, 37.9 (d, J_{CP} = 134.4 Hz), 33.8, 24.2 (d, J_{CP} = 4.3 Hz), 16.4 (d, J_{CP} = 6.6 Hz), 16.3 (d, J_{CP} = 5.8 Hz); HRMS calcd for $C_{13}H_{21}O_4P$ 272.1177, found 272.1180.

Ketone 30. A suspension of hydroxy phosphonate **8** (30 mg, 0.11 mmol), $PdCl_2$ (2 mg, 0.01 mmol), and $Cu(OAc)\cdot H_2O$ (5 mg, 0.02 mmol) in *N*,*N*-dimethylacetamide (4 mL) and water (0.5 mL) was placed under an atmosphere of oxygen and stirred for 3 days. The mixture was diluted with ether and filtered through Celite. The ether filtrate was added to water and extracted with ether. The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (50% hexanes, 50% ethyl acetate) afforded ketone **30** (19 mg, 59%): ^{1}H NMR δ 4.18−4.00 (m, 5H), 3.33 (d, J = 16.7 Hz, 1H), 2.71 (d, J = 16.8 Hz, 1H), 2.26−2.14 (m, 1H), 2.20 (s, 3H), 2.13−2.06 (m, 1H), 1.98−1.87 (m, 3H), 1.76−1.65 (m, 2H), 1.32 (dt, J_{HP} = 2.1 Hz, J = 7.1 Hz, 6H); ^{31}P NMR 31.6; ^{13}C NMR δ 209.1, 80.2 (J_{CP} = 3.6 Hz), 62.3 (d, J_{CP} = 6.5 Hz), 61.0 (d, J_{CP} = 6.5 Hz), 52.1, 45.1 (d, J_{CP} = 142.4 Hz), 39.6 (J_{CP} = 14.6 Hz), 31.5, 25.6, 22.2 (d, J_{CP} = 14.6 Hz), 16.5 (d, J_{CP} = 5.8 Hz), 16.4 (d, J_{CP} = 6.5 Hz); HRMS calcd for $C_{12}H_{23}O_5P$ 278.1283, found 278.1269.

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Supporting Information Available: ^{1}H and/or ^{13}C NMR spectra for compounds **8**, **12**, **14**, **15**, **17**, **19**, **22**−**27**, **29**, and **30**. This material is available free of charge from the Internet at http://pubs.acs.org.

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