was treated with saturated aqueous Na_2CO_3. Extraction of the basified solution with CH_2Cl_2 followed by drying over anhydrous $MgSO_4$ and removal of the CH_2Cl_2 gave (78%) **8** as a tan solid: 950 mg; mp 146–150 °C; ^1H NMR δ 4.08 (s, CH_3, 3 H), 7.59 (dd, 6-nap*H*, $J_{5,6}$ = 8.2, $J_{6,7}$ = 4.2 Hz, 1 H), 8.26 (d, 3-nap*H*, $J_{3,4}$ = 9.8 Hz, 1 H), 8.27 (dd, 5-nap*H*, $J_{5,6}$ = 8.2, $J_{5,7}$ = 2.0 Hz, 1 H), 8.40 (d, 4-nap*H*, $J_{3,4}$ = 9.8 Hz, 1 H), 9.24 (dd, 7-nap*H*, $J_{6,7}$ = 4.2, $J_{5,7}$ = 2.0 Hz, 1 H); ^{13}C NMR δ 52.6 (CH_3), 121.6 (C6), 123.4 (C3), 124.0 (C4a), 136.6 (C5), 138.5 (C4), 150.6 (C8a), 154.6 (C7), 155.0 (C2), 165.4 (CO); MS *m/e* 158 (22), 130 (100), 129 (40); IR (KBr) 1709, 1601, 1451, 1318, 1235, 1140, 870, 801, 774 cm^{-1}. Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.28; N, 14.89. Found: C, 63.64; H, 4.41; N, 14.69.

2-(Hydroxymethyl)-1,8-naphthyridine (9). A solution of sodium trimethoxyborohydride (379 mg, 2.97 mmol) in THF (10 mL) was added to a stirred solution of ester **8** (184 mg, 979 μmol) in CH_2Cl_2 (10 mL). The solution was maintained at 25 °C for 1 h, and the solvents were removed in vacuo. The remaining solid was dissolved in saturated aqueous $NaHCO_3$ (10 mL), and the water was removed in vacuo. The resulting solid was then extracted with hot EtOH (3 × 20 mL), and the combined EtOH extract was concentrated in vacuo to give a solid, which was purified by dry-flash chromatography [EtOAc, then EtOAc–EtOH (3:2)] to give (59%) alcohol **9**: 93 mg; mp 99–100 °C (C_6H_6–$CHCl_3$); ^1H NMR δ 4.40 (br, OH, 1 H), 5.01 (s, CH_2, 2 H), 7.46 (d, 3-nap*H*, $J_{3,4}$ = 8.4 Hz, 1 H), 7.51 (dd, 6-nap*H*, $J_{5,6}$ = 8.1, $J_{6,7}$ = 4.3 Hz, 1 H), 8.20 (d, 4-nap*H*, $J_{3,4}$ = 8.4 Hz, 1 H), 8.22 (dd, 5-nap*H*, $J_{5,6}$ = 8.1, $J_{5,7}$ = 2.0 Hz, 1 H), 9.10 (dd, 7-nap*H*, $J_{6,7}$ = 4.3, $J_{5,7}$ = 2.0 Hz, 1 H); ^{13}C NMR δ 64.5 (CH_2), 119.7 (C3), 122.2 (C6), 137.2, 137.9 (C4, C5), 153.7 (C7), 163.9 (C2) (C4a and C8a were not observed with a 4-s delay); IR (KBr) 3412, 1607, 1499, 1080, 848, 808, 777 cm^{-1}. Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.25; H, 5.16; N, 17.30.

Reaction of 2,7-Bis(trichloromethyl)-1,8-naphthyridine (2) with KOH in EtOH. A stirred solution of **2** (254 mg, 696 μmol) and KOH (474 mg, 8.46 mmol) in EtOH (35 mL) was refluxed for 3 h. The EtOH was then removed in vacuo, and aqueous saturated $NaHCO_3$ (10 mL) was added. The aqueous solution was extracted with $CHCl_3$ (3 × 15 mL), the combined organic solution was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed in vacuo to give a brown solid, which was purified by dry-flash chromatography [$CHCl_3$, then $CHCl_3$–EtOAc (1:1)] to give two fractions:

Fraction 1, 7-(trichloromethyl)-1,8-naphthyridin-2-one (11): 73 mg; 40%; mp 201–202 °C dec; ^1H NMR δ 6.79 (d, 3-nap*H*, $J_{3,4}$ = 9.6 Hz, 1 H), 7.74 (d, 4-nap*H*, $J_{3,4}$ = 9.6 Hz, 1 H), 7.86 (d, 6-nap*H*, $J_{5,6}$ = 8.2 Hz, 1 H), 8.03 (d, 5-napH, $J_{5,6}$ = 8.2 Hz, 1 H), 9.56 (br s, OH, 1 H); ^{13}C NMR (Me_2SO-d_6) δ 96.8 (CCl_3), 113.4 (C6), 115.8 (C4a), 125.3 (C3), 138.2 (C4), 138.9 (C5), 148.9 (C8a), 157.1 (C7), 163.0 (C2); MS *m/e* 264 (11), 262 (10), 229 (71), 227 (100); IR (KBr) 3434, 1663, 1597, 1547, 870, 824, 762 cm^{-1}. Anal. Calcd for $C_9H_5N_2Cl_3O$: C, 41.02; H, 1.91; N, 10.63; Cl, 40.36. Found: C, 41.20; H, 1.87; N, 10.31; Cl, 40.41.

Fraction 2, 7-(ethoxycarbonyl)-1,8-naphthyridin-2-one (12): 26 mg; 17%; mp 207–208 °C dec; ^1H NMR δ 1.45 (t, CH_3, J = 7.1 Hz, 3 H), 4.50 (q, CH_2, J = 7.1 Hz, 2 H), 6.79 (d, 3-nap*H*, $J_{3,4}$ = 9.6 Hz, 1 H), 7.74 (d, 4-napH, $J_{3,4}$ = 9.6 Hz, 1 H), 7.99 (s, 5,6-nap*H*, 2 H), 9.48 (br s, OH, 1 H); ^{13}C NMR (Me_2SO-d_6) δ 14.0 (CH_3), 61.4 (CH_2), 117.1 (C4a), 118.8 (C6), 125.4 (C3), 137.8 (C5), 138.4 (C4), 147.4 (C8a), 149.8 (C7), 163.0 (C2), 164.4 (CO); MS *m/e* 218 (30), 173 (7), 146 (100), 145 (30); IR (KBr) 3425, 1730, 1659, 1595, 1547, 1287, 1154, 764 cm^{-1}. Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.53; H, 4.74; N, 12.71.

When the reaction was conducted at 25 °C for 36 h, the formation of **11** was increased (79%) and very little **12** was formed.

Reaction of 2-(Trichloromethyl)-1,8-naphthyridine (6) with KOH in EtOH. A stirred solution of **6** (268 mg, 1.08 mmol) and KOH (623 mg, 11.1 mmol) in absolute EtOH (20 mL) was refluxed for 3 h and worked up as described above for **2** to give (61%) **1,8-naphthyridin-2-one (10)**: 96 mg; mp 198–201.5 °C (lit.[31] mp 198–199 °C); ^{13}C NMR δ 115.0 (C4a), 118.6 (C6), 123.8 (C3), 136.4 (C5), 138.8 (C4), 150.0 (C8a), 150.6 (C7), 164.0 (C2). Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.59; H, 4.23; N, 19.10.

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Registry No. **1**, 125902-19-4; **2**, 125902-20-7; **3**, 125902-21-8; **4**, 125902-22-9; **5**, 125902-23-0; **6**, 125902-24-1; **7**, 125902-25-2; **8**, 125902-26-3; **9**, 125902-27-4; **10**, 15936-09-1; **11**, 125902-28-5; **12**, 125902-29-6; 2-methyl-1,8-naphthyridine, 1569-16-0; 2,7-dimethyl-1,8-naphthyridine, 14903-78-7.

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Regiochemistry of the Rearrangement of Cyclohexenyl and Cyclohexadienyl Phosphates to β-Keto Phosphonates

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Diethyl vinyl phosphates derived from substituted cyclohexanones are known to rearrange to β-keto phosphonates upon treatment with excess LDA. To develop strategies for the regiocontrol of this rearrangement, the effect of regiospecific preparation of the vinyl phosphate has been tested and the use of dienyl phosphates has been studied. With 3-methylcyclohexanone both phosphonate regioisomers are formed in a ratio independent of the regiochemistry of the vinyl phosphate. However, regiocontrol is observed in rearrangements of dienyl phosphates derived from methyl-substituted cyclohexenones. In this series, formation of the kinetic enolate, reaction with diethyl phosphorochloridate, and in situ treatment of the intermediate vinyl phosphate with LDA result in the phosphono ketone, with C–P bond formation at the site corresponding to the original kinetic enolate. Catalytic hydrogenation of the phosphono enone then can be used to obtain a phosphono ketone. In contrast to the course of this rearrangement with cyclohexenones, the diethyl vinyl phosphate derivative of cycloheptenone undergoes a 1,2-rearrangement yielding a hydroxy phosphonate.

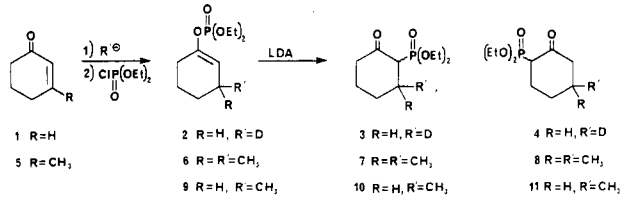
We recently reported that dialkyl vinyl phosphate derivatives of five- and six-membered-ring ketones undergo rearrangement to β-keto phosphonates upon treatment with base.[2,3] This reaction represents a convenient method for the synthesis of some β-keto phosphonates that cannot

(1) Fellow of the Alfred P. Sloan Foundation, 1985–1989.

(2) Hammond, G. B.; Calogeropoulou, T.; Wiemer, D. F. *Tetrahedron Lett.* **1986**, *27*, 4265.

0022-3263/90/1955-2842$02.50/0

Scheme I



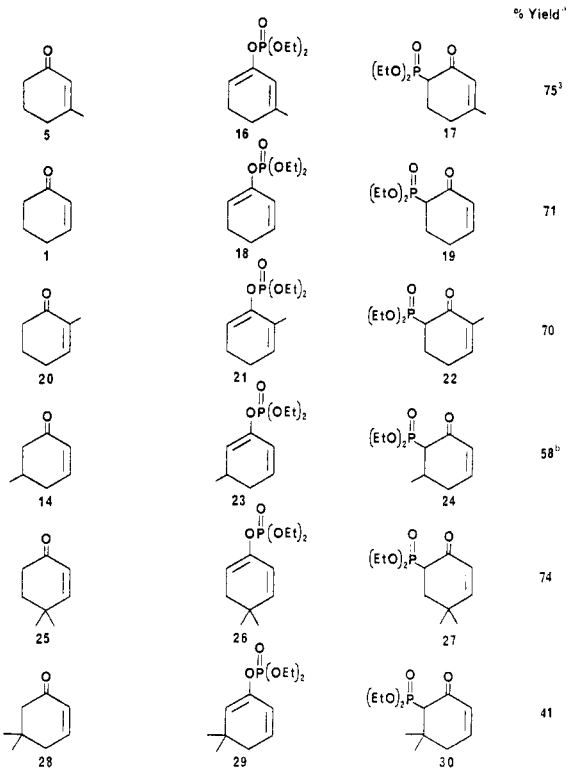
1 R=H
5 R=CH_3
2 R=H, R'=D
6 R=R'=CH_3
9 R=H, R'=CH_3
3 R=H, R'=D
7 R=R'=CH_3
10 R=H, R'=CH_3
4 R=H, R'=D
8 R=R'=CH_3
11 R=H, R'=CH_3

be prepared by the traditional Arbuzov reaction of α-halo ketones. It is especially attractive when the vinyl phosphates can be prepared in situ from the parent ketone and a dialkyl phosphorochloridate, for then the overall transformation from ketone to keto phosphonate can be accomplished in high yield in a one-flask procedure. However, before this sequence could be incorporated into any lengthy synthetic plan, the factors controlling the rearrangement's regiochemistry in unsymmetrical ketones must be clarified, and methods for obtaining specific regioisomers must be developed.

Our studies of vinyl phosphate to keto phosphonate rearrangements have delineated two general types: those best explained by an intermediate *allyl* anion formed through abstraction of a β'-proton,[3] and those where formation of a *vinyl* anion occurs for lack of acidic β'-hydrogens.[3,4] When a vinyl anion is formed, the rearrangement only gives one regioisomer, but when an unsymmetrical allyl anion is involved, different phosphonates result from rearrangement to either allylic terminus. Examples involving unsymmetrical allyl anions include the vinyl phosphates **2** and **6**, prepared through conjugate additions to cyclohexenone (**1**) and 3-methylcyclohexenone (**5**).[3] As might be expected, treatment of compound **2** with LDA afforded a nearly 50:50 ratio of regioisomers **3** and **4**, but similar treatment of vinyl phosphate **6** provided β-keto phosphonate **8**, with no trace of the isomeric phosphonate **7**. Both results are consistent with formation of an intermediate allyl anion, followed by migration of phosphorus to an allylic terminus governed by the degree of steric hindrance within the substrate. However, this simple rationalization of the product ratios began to unravel with the present studies of methyl-substituted cyclohexenyl phosphates.

Treatment of compound **1** with lithium dimethylcuprate, followed by quenching of the resulting enolate with diethyl phosphorochloridate, gave vinyl phosphate **9**. If the analogous rearrangements of compounds **2** and **6** are viewed as limiting cases, then rearrangement of compound **9** might be expected to give equal amounts of both regioisomers **10** and **11** or to favor formation of the 2,5-substituted product **11**. Indeed, when phosphate **9** was treated with LDA under the standard conditions, a mixture of the two regioisomeric keto phosphonates **10** and **11** was obtained. After separation of the regioisomers by column chromatography and assignment of the sets of peaks in the ^{31}P NMR spectra,[5] the relative ratio of these isomers was

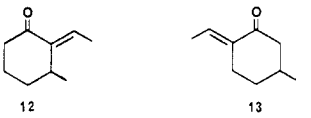
Table I. Synthesis of Enone Phosphonates



			% Yield[a]
5	16	17	75[3]
1	18	19	71
20	21	22	70
14	23	24	58[b]
25	26	27	74
28	29	30	41

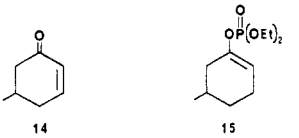
[a] Isolated yield from enone to phosphono enone. [b] Isolated as a mixture of diastereomers.

calculated to be approximately 64:36 from an NOE-suppressed ^{31}P NMR spectrum of the quenched reaction mixture. However, the major regioisomer appeared to be compound **10** on the basis of its spectral data. This unexpected result was verified by a Wadsworth–Horner–Emmons reaction of these phosphonates and acetaldehyde, which gave the known products **12**[6] and **13**.[7] It was later confirmed by independent syntheses of compounds **10** and **11** (vide infra).



12 13

While the basis for this ratio of β-keto phosphonate regioisomers is not yet clear, it does not appear to be related to the regiochemistry of the intermediate vinyl phosphate. Essentially the same product ratio was observed when the mixture of vinyl phosphates derived from 3-methylcyclohexanone by treatment with LDA (i.e., compounds **9** and **15**), or the single regioisomer (**15**) derived from conjugate addition of hydride to 5-methylcyclohexenone (**14**), was treated under the same reaction conditions. Together these results indicate that the regio-



14 15

chemical outcome of the rearrangement is a function of substrate structure in these cyclohexenyl phosphates. While this type of regiocontrol could be of value in a

(3) Calogeropoulou, T.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1987**, *52*, 4185.
(4) For preparation of α-phosphono lactones and esters by an analogous procedure, cf.: Jackson, J. A.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1989**, *54*, 4750.
(5) The ^{31}P NMR spectrum of the quenched reaction mixture was complex, containing six peaks of differing intensities between 20 and 30 ppm. Comparison with spectra of the purified keto phosphonates established that each regioisomer consists of two epimers and an enolic form. Converting one regioisomeric set to the corresponding anion with NaOEt simplifies the spectrum from three resonances (at +22.4, +22.8, and +28.7 ppm) to a single peak (at +34.6 ppm). The signals of the other regioisomeric keto phosphonate (+23.3, +24.5, and +27.5 ppm) also merge to a single resonance (at +33.6 ppm) under the same conditions. Ultimately, these assignments were confirmed by independent syntheses.
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synthetic sequence, a variation on this methodology was sought to obtain a more predictable route to specific keto phosphonate regioisomers.

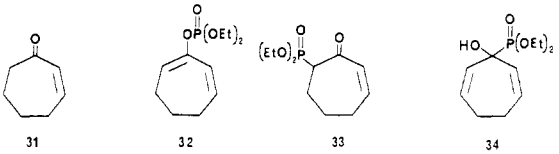
In an earlier study,[2,3] we had observed that the diethyl vinyl phosphate (**16**) derived from the kinetic enolate of 3-methylcyclohexenone (**5**) undergoes base-induced phosphorus migration to give only keto phosphonate **17**. To explore the extent of regiocontrol in cyclohexadienyl phosphate rearrangements, studies were continued with cylohexenone (**1**), 2-methylcyclohexenone (**20**), 5-methylcyclohexenone (**14**), 4,4-dimethylcyclohexenone (**25**), and 5,5-dimethylcyclohexenone (**28**) (Table I). In each case, treatment of the enone with LDA under conditions of kinetic control and subsequent reaction of the enolate with diethyl phosphorochloridate gave a single dienyl phosphate. After the regiochemistry of the dienyl phosphates formed under these conditions was established (as compounds **18**, **21**, **23**, **26**, and **29**, respectively), the reactions were repeated and the vinyl phosphates were treated in situ with additional LDA. In most cases a single phosphonate is formed, the regioisomer with a C–P bond at the α'-position of the resulting α,β-unsaturated ketone. In those five cases where the rearrangement worked well (cyclohexenone, 2-, 3-, and 5-methylcyclohexenone, and 4,4-dimethylcyclohexenone), the respective phosphonates were isolated in an average yield of 70%. With 5,5-dimethylcyclohexenone, we obtained the expected phosphonate in a lower yield and it was accompanied by a trace of the vinyl phosphonate (i.e., the α-phosphono α,β-unsaturated isomer).

Within this series of dienyl phosphates, reaction with LDA could result in proton abstraction from a variety of sites, often including vinylic carbon adjacent to the phosphate group (i.e., terminal or internal vinyl positions) and allylic positions proximal or distal to the phosphate. However, the general pattern of rearrangement regiochemistry can be explained only through removal of the terminal vinylic proton or a distal allylic proton, for only removal of these protons places significant electron density at the site ultimately occupied by phosphorus. With the vinyl phosphate of 4,4-dimethylcyclohexenone (**26**), where abstraction of a distal allylic proton is not possible, rearrangement takes place readily and in high yield. Formation of a vinyl anion is necessary to explain the observed regiochemistry in this case, implicating formation of analogous vinyl anions in rearrangement of the other dienyl phosphates. With phosphate **29**, removal of the terminal vinylic proton may be hindered, which could explain the lower yield in this case.

A high kinetic acidity for the terminal vinyl proton of these dienyl phosphates could be explained in several ways.[8] Because heteroatom-assisted lithiations are well precedented, it is possible that complexation between the lithium counterion and the phosphate group enhances proton abstraction from this site.[9]

The regioselectivity observed in these rearrangements of cyclohexadienyl phosphates can be used to advantage in the preparation of phosphono ketones that are difficult to prepare directly. For example, phosphono enone **17** was subjected to catalytic hydrogenation[10] to obtain phosphonate **11** in good overall yield. Through a similar sequence, the phosphonate derived from 5-methylcyclohexenone (i.e., **24**) undergoes catalytic hydrogenation to afford keto phosphonate **10**. While preparation of phosphonates **11** and **10** from their respective enones rather than from 3-methylcyclohexanone requires an additional step, the slightly longer approach avoids a tedious separation and makes both regioisomers readily available. Presumably, conversion of enone phosphonates to keto phosphonates by catalytic hydrogenation is a general process.[10]

The success of this rearrangement in providing a series of cyclohexenone phosphonates encouraged exploration of this process in larger ring systems. Although the vinyl phosphate derivative of cycloheptanone undergoes phosphate elimination when treated with base,[3] an analogous loss of phosphate from a cycloheptenone derivative would afford a highly strained system. Therefore, cycloheptenone (**31**) was treated with LDA and diethyl phosphoro-



31 32 33 34

chloridate to obtain the vinyl phosphate **32**. Upon reaction with LDA, this vinyl phosphate gave a mixture of products. A major product (ca. 20%) was isolated, but the high degree of symmetry in its ^1H and ^{13}C NMR data ruled out assignment as the desired β-keto phosphonate **33**. Rather, this product was assigned structure **34**, the result of a 1,2-phosphorus migration. Although there are precedents for 1,2-rearrangements of benzylic[11] and allylic[12] phosphates, this process has not been reported in a vinyl or dienyl system. Presumably, this product implicates formation of a symmetrical pentadienyl anion by abstraction of a proximal allylic proton, followed by a 1,2-phosphorus shift.[13]

In summary, while the 1,3-migration of phosphorus from oxygen to carbon is useful for preparation of β-keto phosphonate derivatives of five- and six-membered-ring ketones, when unsymmetrical allyl anions are involved, the regiochemistry may be difficult to predict. By taking advantage of the regioselectivity of this rearrangement with dienyl phosphates, this method becomes a more predictable tool for the construction of specific β-keto phosphonates. Studies of this reaction in more highly functionalized systems are in progress and will be reported in due course.

Experimental Section

Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use, and all reactions in this solvent were conducted under a positive pressure of an inert gas. Column chromatography was done on Merck grade 62 silica gel (60–200 mesh), while radial chromatography was performed with a Chromatotron apparatus and Merck PF254 silica gel with $CaSO_4 \cdot 0.5H_2O$. NMR spectra (^1H, ^{13}C, and ^{31}P) were recorded on either a JEOL FX-90Q or a Bruker WM-360 spectrometer, with $CDCl_3$ as solvent. The ^1H and ^{13}C chemical shifts are reported in parts per million downfield from $(CH_3)_4Si$, while the ^{31}P chemical shifts are reported in parts per million relative to H_3PO_4 (external standard). Low-resolution electron impact (EI) mass spectra were recorded with a Hewlett-Packard 5985B instrument operating at 70 eV; only selected ions are reported here. High-resolution mass spectra were recorded on a VG Instruments ZAB-HF spectrometer at the University of Iowa Mass Spec-

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(13) Because our objective is preparation of β-keto phosphonates, conditions have not been optimized to favor this 1,2-rearrangement.

trometry Facility. Microanalyses were conducted by Galbraith Laboratories, Knoxville, TN, or by Desert Analytics, Tucson, AZ.

3-Methyl-1-[(diethoxyphosphinyl)oxy]-1-cyclohexene (9). A solution of enone **1** (0.39 mL, 4.0 mmol) in ether (53 mL) was added dropwise to a solution of lithium dimethylcuprate [prepared in situ from copper(I) iodide (1.016 g, 5.3 mmol) and MeLi (10.6 mmol)] in ether (53 mL) at 0 °C. The reaction mixture was stirred for 1 h at room temperature and then cooled to 0 °C, and a mixture of diethyl phosphorochloridate (4.5 mL, 30.6 mmol) and anhydrous triethylamine (10.6 mL, 71.0 mmol) was added. After the reaction warmed to room temperature, it was stirred for an additional 1.75 h and then quenched by addition of saturated $NaHCO_3$. The organic layer was washed with cold 1 M NH_4OH and water and then dried over $MgSO_4$. Concentration in vacuo and purification of the resulting oil by flash chromatography (silica gel; 70% hexane, 30% EtOAc) gave phosphate **9** (0.78 g, 79%): ^1H NMR δ 5.35 (br s, 1), 4.19–4.11 (m, 4), 2.33–2.30 (m, 1), 2.21–2.16 (m, 2), 1.86–1.56 (m, 3), 1.35 (t, 6, J = 7.2 Hz), 1.17–1.07 (m, 1), 0.99 (d, 3, J = 7.0 Hz); ^{13}C NMR δ 147.35 (d, J_{CP} = 9.4 Hz), 116.5 (d, J_{CP} = 5.6 Hz), 63.9 (d, J_{CP} = 5.6 Hz, 2), 30.3, 29.3, 27.5 (d, J_{CP} = 3.0 Hz), 21.6, 21.3, 16.0 (d, J_{CP} = 6.8 Hz, 2); ^{31}P NMR –6.2; EIMS m/z (relative intensity) 248 (M^+, 11), 233 (10), 155 (54), 127 (72), 99 (100), 94 (28), 79 (46).

3-Methyl-2-(diethoxyphosphinyl)cyclohexanone (10) and 3-Methyl-6-(diethoxyphosphinyl)cyclohexanone (11). Vinyl phosphate **9** (2.01 g, 8.1 mmol) in THF (5 mL) was added dropwise to a solution of LDA (2.4 equiv) in 70 mL of THF at –85 °C, and the resulting mixture was stirred at –90 to –85 °C for 12.5 h. The reaction was quenched by addition of 1 M acetic acid in ether, and the resulting oil was purified by column chromatography (silica gel; 80% $CHCl_3$, 20% EtOAc) to obtain phosphonates **10** and **11** (1.62 g, 81% total) in a 64:36 ratio by ^{31}P NMR.

Phosphonate **10**: ^1H NMR ($CDCl_3/CD_3OD/CD_3ONa$) δ 4.03–3.81 (m, 4), 2.64–2.48 (m, 1), 1.85–1.73 (m, 1), 1.69–1.53 (m, 2), 1.51–1.40 (m, 1), 1.35–1.21 (m, 1), 1.27 (t, 6, J = 7.1 Hz), 1.07 (d, 3, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 206.6 (d, J_{CP} = 2.6 Hz), 206.4 (d, J_{CP} = 3.0 Hz), 62.5 (d, J_{CP} = 7.3 Hz), 62.4 (d, J_{CP} = 7.2 Hz), 57.5 (d, J_{CP} = 124.8 Hz), 56.9 (d, J_{CP} = 130.8 Hz), 40.9, 40.8, 36.0 (d, J_{CP} = 4.4 Hz), 32.5 (d, J_{CP} = 4.3 Hz), 30.1 (d, J_{CP} = 5.7 Hz), 28.1 (d, J_{CP} = 2.4 Hz), 24.9, 21.5, 21.0, 20.8, 16.31 (d, J_{CP} = 5.8 Hz), 16.30 (d, J_{CP} = 5.9 Hz); ^{31}P NMR ($CDCl_3$) +22.4, +22.8 (cis, trans isomers), +28.7 (enol tautomer); EIMS m/z (relative intensity) 248 (M^+, 19), 233 (53), 220 (27), 177 (80), 138 (67), 123 (90), 111 (76), 109 (49), 81 (100), 41 (96). Anal. Calcd for $C_{11}H_{21}O_4P$: C, 53.22; H, 8.53. Found: C, 52.96; H, 8.69.

Phosphonate **11**: ^1H NMR ($CDCl_3/CD_3OD/CD_3ONa$) δ 4.00–3.86 (m, 4), 2.25–2.09 (m, 2), 1.75–1.65 (m, 2), 1.27 (t, 6, J = 7.1 Hz), 1.26 (m, 1), 1.19–1.07 (m, 1), 0.96 (d, 3, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 206.0 (d, J_{CP} = 2.8 Hz), 205.8 (d, J_{CP} = 5.8 Hz), 62.5 (d, J_{CP} = 6.7 Hz), 62.2 (d, J_{CP} = 6.7 Hz), 50.0, 49.6 (d, J_{CP} = 143.9 Hz), 49.4 (d, J_{CP} = 131.8 Hz), 49.2, 33.84, 33.78, 29.9, 28.5, 26.6 (d, J_{CP} = 3.6 Hz), 26.2 (d, J_{CP} = 5.7 Hz), 22.0, 21.6, 16.4 (d, J_{CP} = 6.5 Hz), 16.3 (d, J_{CP} = 6.6 Hz); ^{31}P NMR ($CDCl_3$) +23.3, +24.5 (cis, trans isomers), +27.5 (enol tautomer); EIMS m/z (relative intensity) 248 (38), 233 (44), 220 (54), 178 (73), 138 (98), 122 (55), 111 (81), 109 (100), 81 (88). Anal. Calcd for $C_{11}H_{21}O_4P$: C, 53.22; H, 8.53. Found: C, 52.99; H, 8.52.

(*E*)-2-Ethylidene-3-methylcyclohexanone (12) and (*E*)-2-Ethylidene-5-methylcyclohexanone (13). An equimolar mixture of phosphonates **10** and **11** in DME (2 mL) was added at room temperature to a slurry of NaH [26.6 mg, 0.665 mmol, 60% dispersion in mineral oil, washed with pentane (3 × 3 mL)] in DME (2 mL). After the resulting solution was stirred for 1.5 h, it was cooled to 0 °C and acetaldehyde (2.0 mL, 35.8 mmol) was added. The reaction mixture was stirred at 0 °C for an additional 2 h and then allowed to warm to room temperature over the course of 2 h. After addition of water, the aqueous layer was extracted with ether, the combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated in vacuo to afford a brown oil. Purification by column chromatography (silica gel; 89% hexane, 11% EtOAc) gave compounds **13**[7] and **12**[6] (47 mg, 90% based on recovered phosphonate), identified by MS data and by comparison with known ^1H NMR[7] and ^1H and ^{13}C NMR[6] data, respectively.

6-(Diethoxyphosphinyl)cyclohex-2-en-1-one (19). Addition of compound **1** (0.5 g, 5.21 mmol) in 15 mL of THF to LDA (1.1 equiv in 40 mL of THF) at –65 °C followed by addition of diethyl phosphorochloridate (0.83 mL, 5.73 mmol, 1.1 equiv) gave dienyl phosphate **18**. The resulting solution (ca. 5.2 mmol) was added to a solution of 2.3 equiv of LDA at –70 °C. After 5 min, TLC analysis indicated nearly complete reaction, but the mixture was allowed to stir for a total of 15 min before it was quenched by addition of acetic acid. The desired keto phosphonate **19** (861 mg, 71%) was obtained after standard workup and purification by flash chromatography (1:1 $CHCl_3$/EtOAc): ^1H NMR δ 7.05 (ddd, J = 10.2, 4.6, 1.2 Hz, 1), 6.06 (dd, J = 10.2, 1.5 Hz, 1), 4.16 (m, 4), 3.02 (dt, J_{HP} = 25.6, J = 5.6 Hz, 1), 2.70 (m, 1), 2.39 (m, 2), 2.32 (m, 1), 1.35 (t, J = 7.0 Hz, 3), 1.31 (t, J = 6.9 Hz, 3); ^{13}C NMR δ 192.7 (d, J_{CP} = 4.2 Hz), 150.6, 129.1 (d, J_{CP} = 1.5 Hz), 62.2 (d, J_{CP} = 7.3 Hz), 61.9 (d, J_{CP} = 7.3 Hz), 46.0 (d, J_{CP} = 132.2 Hz), 23.6 (d, J_{CP} = 5.9 Hz), 23.4 (d, J_{CP} = 4.5 Hz, 16.0 (d, J_{CP} = 5.9 Hz, 2); ^{31}P NMR +23.0; EIMS m/z (relative intensity) 232 (M^+, 12), 231 (9), 204 (9), 203 (8), 187 (15), 175 (40), 138 (100), 111 (50), 109 (48), 68 (80). Anal. Calcd for $C_{10}H_{17}O_4P{\cdot}0.5H_2O$: C, 49.79; H, 7.52. Found: C, 49.85; H, 7.41.

6-(Diethoxyphosphinyl)-2-methylcyclohex-2-en-1-one (22). Dienyl phosphate **21** was obtained upon treatment of enone **20** (125 mg, 1.13 mmol) with LDA (1.1 equiv) and diethyl phosphorochloridate (0.18 mL, 1.24 mmol) under the standard reaction conditions (cf. preparation of compound **19**). To this dienyl phosphate was added a solution of LDA (2.2 equiv in 15 mL of THF at –78 °C, and the resulting orange brown solution was stirred overnight and allowed to warm from –78 °C to room temperature. The reaction was quenched by addition of 1 M acetic acid (4.4 equiv) in ether, and the resulting mixture was filtered through a 1-cm layer of Florisil (60–120 mesh). Purification of the crude product by flash chromatography (silica gel, 50% EtOAc, 50% hexane) gave the desired keto phosphonate **22** (193 mg, 70%): ^1H NMR δ 6.75 (br s, 1), 4.18–4.06 (m, 4), 2.98 (dt, J_{HP} = 25.6, J = 5.9 Hz, 1), 2.71–2.56 (m, 1), 2.42–2.18 (m, 3), 1.78 (br s, 3), 1.35–1.25 (m, 6); ^{13}C NMR δ 193.6 (d, J_{CP} = 4.4 Hz), 145.8, 135.4 (d, J_{CP} = 2.9 Hz), 62.5 (d, J_{CP} = 6.5 Hz), 62.1 (d, J_{CP} = 6.2 Hz), 46.5 (d, J_{CP} = 132.9 Hz), 24.3 (s, d, 2), 16.3 (d, J_{CP} = 5.8 Hz), 16.2 (2); ^{31}P NMR +23.6; EIMS, m/z (relative intensity) 246 (M^+, 0.5), 138 (12), 111 (32), 109 (68), 108 (94), 82 (85), 81 (100), 77 (50), 65 (54), 53 (77). Anal. Calcd for $C_{11}H_{19}O_4P{\cdot}0.25H_2O$: C, 52.69; H, 7.84. Found: C, 52.36; H, 7.86.

6-(Diethoxyphosphinyl)-5-methylcyclohex-2-en-1-one (24). Enone **14**[14] (0.2 g, 1.8 mmol) was added to LDA (1.1 equiv) at –70 °C, the resulting solution was stirred for 1.25 h at –65 to –50 °C, and diethyl phosphorochloridate was added. The reaction mixture was stirred for 2 h while it warmed to –20 °C. After cooling to –65 °C, the resulting solution of vinyl phosphate (**23**) was added to a solution of LDA (2.3 equiv) and stirred at –50 °C overnight. This reaction was quenched by addition of acetic acid in ether, and the crude products were purified by column chromatography. A mixture of keto phosphonate diastereomers was obtained (0.45 g, 58%) in a 3:2 ratio as a measured by ^1H or ^{31}P NMR. Major diastereomer (ca. 60%): ^1H NMR δ 6.89–6.83 (m, 1), 6.03–6.01 (br d, J = 10.3 Hz, 1), 4.16–4.01 (m, 4), 3.05–2.94 (m, 2), 2.88–2.77 (m, 1), 2.64 (d, J = 10 Hz, 1), 2.39–2.28 (m, 1), 2.09 (dd, J = 19.5, 5.8 Hz, 1), 1.34–1.21 (m, 4), 1.14 (dd, J = 7.1 Hz, 3). Minor diastereomer (ca. 40%): ^1H NMR δ 7.00–6.93 (m, 1), 6.04–6.02 (br d, J = 10.2 Hz, 1), 4.16–4.01 (m, 4), 3.05–2.94 (m, 2), 2.81 (d, J_{HP} = 26.6 Hz, 1), 2.71–2.60 (m, 1), 1.34–1.21 (m, 4), 1.14 (dd, J = 7.1 Hz, 3). ^{31}P NMR ($CHCl_3$) +21.5 (major), +21.9 (minor); (EtOH) +21.4 (major), +22.3 (minor). After addition of aqueous NaOH to an ethanol solution of this mixture, a single peak was observed (at +33.8 ppm). EIMS m/z (relative intensity) 247 (M^+ + H, 33), 246 (M^+, 51), 231 (34), 204 (13), 210 (26), 189 (15), 179 (100), 175 (89), 173 (20); HRMS, calcd for $C_{11}H_{19}O_4P$ 246.1021, found 246.1017. Anal. Calcd for $C_{11}H_{19}O_4P{\cdot}0.25H_2O$: C, 52.69; H, 7.84. Found: C, 52.47; H, 8.09.

6-(Diethoxyphosphinyl)-4,4-dimethylcyclohex-2-en-1-one (27). According to the standard procedure, enone **25** (0.53 mL, 4.03 mmol) in 10 mL of THF was added to a solution of LDA (1.1 equiv) in 40 mL of THF. After addition of diethyl phosphorochloridate (0.64 mL, 4.43 mmol), the resulting mixture was allowed to warm to 0 °C and added to LDA (2.3 equiv) at –70 °C. Al-

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though the reaction appeared to be complete within 20 min by TLC, it was stirred overnight at −40 °C to ensure complete reaction and then was quenched by addition of acetic acid. Standard workup and purification by flash chromatography (1:1 $CHCl_3$/EtOAc) gave keto phosphonate **27** (780 mg, 74%): ^1H NMR δ 6.68 (d, J = 10.1 Hz, 1), 5.87 (dd, J = 10.1, J_{HP} = 3.5 Hz, 1), 4.35–4.10 (m, 4), 3.08 (ddd, J_{HP} = 25.0, J = 12.2, 6.4 Hz, 1), 2.24–2.10 (m, 2), 1.34 (t, J = 7.1 Hz, 6), 1.21 (s, 3), 1.19 (s, 3); ^{13}C NMR δ 192.9 (d, J_{CP} = 6.3 Hz), 159.0, 126.8 (d, J_{CP} = 5.8 Hz), 62.4 (d, J_{CP} = 6.6 Hz), 61.8 (d, J_{CP} = 6.3 Hz), 43.0 (d, J_{CP} = 145 Hz), 36.9 (d, J_{CP} = 3.8 Hz), 32.6 (d, J_{CP} = 13.0 Hz), 29.6, 25.2, 16.2 (d, J_{CP} = 5.2 Hz, 2); ^{31}P NMR +24.8; EIMS m/z (relative intensity) 217 (M^+ − 43, 2), 155 (36), 137 (6), 127 (47), 109 (14), 99 (100), 81 (38), 57 (20), 43 (37), 41 (59). Anal. Calcd for $C_{12}H_{21}O_4P{\cdot}0.5H_2O$: C, 53.53; H, 8.24. Found: C, 53.29; H, 8.22.

6-(Diethoxyphosphinyl)-5,5-dimethylcyclohex-2-en-1-one (30). A solution of 5,5-dimethylcyclohex-2-en-1-one[15] (**28**, 289 mg, 2.33 mmol) in 5 mL of THF was added dropwise to a THF solution of LDA (1.1 equiv in 20 mL) at −78 °C. After 20 min, 1.1 equiv of diethyl phosphorochloridate was added and the mixture was allowed to warm to room temperature. LDA (2.2 equiv) was added to dienyl phosphate **29** at −78 °C, and the resulting solution was allowed to warm to room temperature overnight. Standard workup and purification by flash chromatography (60:40 hexane/EtOAc) gave phosphonate **30** (247 mg, 41%): ^1H NMR δ 6.89 (ddd, J = 10.1, 5.6, 2.4 Hz, 1), 6.04 (dd, J = 10.1, 2.6 Hz, 1), 4.17–3.93 (m, 4), 3.04 (dt, J = 19.5, 2.7, 2.4 Hz, 1), 2.74 (d, J_{HP} = 24.4 Hz, 1), 2.02 (dd, J = 19.5, 5.6 Hz, 1), 1.33–1.21 (m, 6), 1.30 (br s, 3), 1.06 (d, J_{HP} = 2.7 Hz, 3); ^{13}C NMR δ 194.5 (d, J_{CP} = 2.9 Hz), 149.8, 127.9, 62.6 (d, J_{CP} = 7.2 Hz), 61.9 (J_{CP} = 7.1 Hz), 59.2 (d, J_{CP} = 123.5 Hz), 38.1, 35.8 (d, J_{CP} = 2.9 Hz), 29.5 (d, J_{CP} = 20.4 Hz), 28.6 (d, J_{CP} = 2.9 Hz), 16.3 (d, J_{CP} = 6.1 Hz, 2); ^{31}P NMR +20.7; EIMS m/z (relative intensity) 260 (M^+, 63), 245 (55), 217 (22), 215 (10), 193 (53), 189 (100), 165 (13), 162 (11); HRMS, calcd for $C_{12}H_{21}O_4P$ 260.1177, found 260.1191. Anal. Calcd for $C_{12}H_{21}O_4P{\cdot}0.5H_2O$: C, 53.53; H, 8.24. Found: C, 53.62; H, 8.43.

This experiment also gave 10 mg (1.6%) of the isomeric vinyl phosphonate 2-(diethoxyphosphinyl)-5,5-dimethylcyclohex-2-en-1-one: ^1H NMR δ 7.79 (dt, J_{HP} = 20.5, J = 4.0 Hz, 1), 4.19–4.08 (m, 4), 2.39 (t, J = 3.7 Hz, 2), 2.33 (br s, 2), 1.30 (t, J = 7.1 Hz, 6), 1.03 (s, 6); ^{13}C NMR δ 196.2 (d, J_{CP} = 5.9 Hz), 161.6 (d, J_{CP} = 5.6 Hz), 130.5 (d, J_{CP} = 181.6 Hz), 62.4 (d, J_{CP} = 5.8 Hz, 2), 52.1 (d, J_{CP} = 7.4 Hz), 40.9 (d, J_{CP} = 14.8 Hz), 33.7, 28.1 (2), 16.4 (d, J_{CP} = 6.2 Hz, 2); ^{31}P NMR +13.6; EIMS m/z (relative intensity) 260 (M^+, 65), 245 (82), 232 (31), 217 (85), 215 (42), 204 (69), 189 (62), 187 (57), 176 (100), 169 (50); HRMS, calcd for $C_{12}H_{21}O_4P$ 260.1177, found 260.1162. Anal. Calcd for $C_{12}H_{21}O_4P{\cdot}0.5H_2O$: C, 53.53; H, 8.24. Found: C, 53.48; H, 8.15.

Hydrogenation of Phosphonate 17. Compound **17**[3] (114.3 mg, 0.46 mmol) in 10 mL of methanol was added to Pd/C (5%, ca. 20 mg), and the resulting mixture was hydrogenated at 23 psi for 6 h on a Parr apparatus.[10] After the catalyst was removed by filtration, the solution was concentrated. The residual oil was passed through a short plug of silica gel, eluting with ether. Upon concentration of the filtrate, compound **11** was obtained as a pale yellow oil (100.1 mg, 87%).

Synthesis of Phosphonate 10 by Hydrogenation. Pd/C (5%, ca. 20 mg) was added to a solution of keto phosphonate **24** (98 mg, 0.40 mmol) in methanol (10 mL), and the resulting mixture was hydrogenated at 23 psi in a Parr apparatus. After 4.5 h, the suspension was filtered and the filtrate was concentrated in vacuo. Complete conversion to compound **10** was noted by comparison with an authentic sample (^{31}P NMR and GC).

1-(Diethoxyphosphinyl)-1-hydroxycyclohepta-2,6-diene (34). Cyclohept-2-en-1-one (**31**, 1.03 mL, 9.1 mmol) in THF (10 mL) was added to a solution of LDA (1.1 equiv) in 50 mL of THF at −70 °C. The resulting mixture was stirred for 0.5 h, and diethyl phosphorochloridate (1.45 mL, 10.0 mmol) was added. After 18 h at temperatures up to 0 °C, the dienyl phosphate **32** was added to an LDA solution (2.3 equiv in 40 mL of THF) at −70 °C, and the resulting red-brown solution was allowed to stir for 0.5 h. The standard workup gave an oil, which was partially purified by flash chromatography (1:1 $CHCl_3$/EtOAc). Fractions containing the major product were rechromatographed to give 400 mg (18%) of compound **34**: ^1H NMR δ 5.87–5.80 (m, 2), 5.46 (dd, J = 11.7, J_{HP} = 3.5 Hz, 2), 4.10–4.00 (m, 4), 2.42–2.30 (m, 2), 2.05–1.88 (m, 2), 1.20–1.16 (m, 6); ^{13}C NMR δ 132.9 (d, J_{CP} = 11.4 Hz, 2), 129.5 (2), 76.2 (d, J_{CP} = 158.4 Hz), 63.3 (d, J_{CP} = 7.4 Hz, 2), 26.0 (2), 16.2 (d, J_{CP} = 5.3 Hz, 2); ^{31}P NMR +22.1; EIMS m/z (relative intensity 246 (M^+, 6), 245 (6), 217 (3), 155 (10), 138 (16), 111 (100), 109 (58), 108 (38); HRMS, calcd for $C_{11}H_{19}O_4P$ 246.1021, found 246.1023. Anal. Calcd for $C_{11}H_{19}O_4P$: C, 53.65; H, 7.78. Found: C, 53.65; H, 7.60.

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Supplementary Material Available: A general procedure for the isolation of dienyl phosphates is provided, along with the spectral data used to characterize these intermediates (3 pages). Ordering information is given on any current masthead page.

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