Regiospecific Vinyl Phosphate/β-Keto Phosphonate Rearrangements Initiated by Halogen−Metal Exchange

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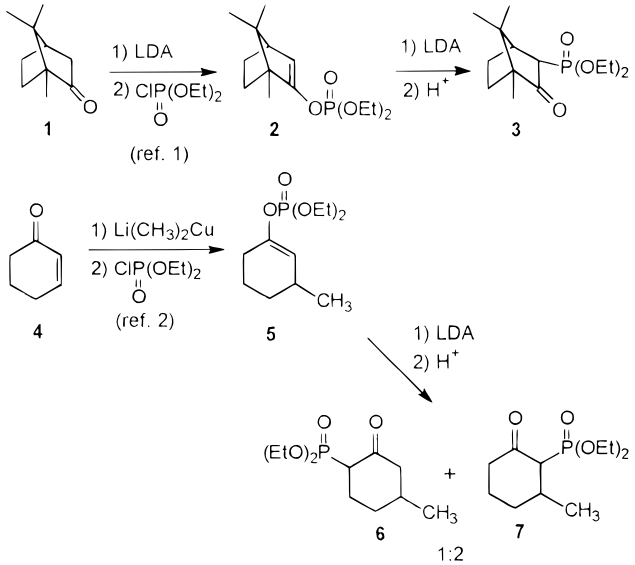
A new strategy has been developed for preparation of β-keto phosphonates via a halogen−metal exchange induced 1,3-phosphorus migration of 2-bromovinyl phosphates. These intermediates can be prepared through conversion of an α-bromo ketone to the appropriate enolate by reaction with strong base, or through conjugate addition to an α-bromo α,β-unsaturated ketone. In either case, trapping the resulting enolate by reaction with a dialkyl phosphorochloridate gives the 2-bromovinyl phosphate. Metalation can be accomplished upon treatment with *n*-BuLi, and rearrangement is facile once metalation has been achieved. Studies with isotopically labeled substrates have shown that this rearrangement is regiospecific, in contrast to vinyl phosphate/β-keto phosphonate rearrangements induced by strong base where regioisomeric products are sometimes obtained.

Some years ago we first reported the observation that vinyl phosphates derived from five- and six-membered ring ketones undergo rearrangement to β-keto phosphonates when treated with LDA.[1] Since our initial reports, the scope of this rearrangement has been expanded to include cyclic enones[2] and esters and lactones,[3] some mechanistic information has been generated,[1,2] and a diastereoselective variant has been unveiled.[4] This rearrangement has given access to phosphonates inaccessible or impossible to prepare by classical methods, including some derived from nonracemic ketones.[5] The product phosphonates have proven useful as intermediates for synthesis of natural products and some analogues,[6] as nonracemic ligands for transition metal catalysts[7] and as substrates for further studies of the reactivity of β-keto phosphonates.[8] At the same time, efforts to trap the intermediate anions have met with limited success[9] and with unsymmetrical ketones a mixture of regioisomers may result from the rearrangement. To obtain more insight on the utility of this rearrangement, and uncover strategies that allow regiocontrolled phosphonate formation, we embarked on this investigation of vinyl phosphate/β-keto phosphonate rearrangements initiated by halogen−metal exchange.[10]

From previous studies, it is clear that there are two categories of this rearrangement, those where formation of an intermediate vinyl anion is required and those which may proceed through formation of an allyl anion. Where formation of a vinyl anion is required, e.g. with the vinyl phosphate (**2**) derived from camphor (**1**), the rearrangements induced by base are regiospecific. However, in cases where formation of an allylic anion is involved, rearrangement can occur to either allylic terminus. For example, phosphonates **6** and **7** are formed in a 1:2 ratio upon rearrangement of vinyl phosphate **5**, even when the vinyl phosphate is prepared regiospecifically by conjugate addition to cyclohexenone (**4**).



To test the feasibility of conducting halogen−metal exchange in both such systems, those prone to formation of an allyl anion and those where formation of a vinyl anion is required, preparation of a representative 2-bromovinyl phosphate from each category was necessary. For the first example, bromocamphor (**8**) was treated

(1) (a) Calogeropoulou, T.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1987**, *52*, 4185−4190. (b) Hammond, G. B.; Calogeropoulou, T.; Wiemer, D. F. *Tetrahedron Lett.* **1986**, 4265−4268.

(2) Gloer, K. B.; Calogeropoulou, T.; Jackson, J. A.; Wiemer, D. F. *J. Org. Chem.* **1990**, *55*, 2842−46.

(3) Jackson, J. A.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1989**, *54*, 4750−4754.

(4) (a) An, Y. Z.; An, J. G.; Wiemer, D. F. *J. Org. Chem.* **1994** *59*, 8197−8202. (b) An, J.; Wilson, J. M.; An, Y. Z.; Wiemer, D. F. *J. Org. Chem.* **1996** *61*, 4040−4045.

(5) Wiemer, D. F. *Tetrahedron* **1997**, *53*, 16609−16644.

(6) (a) Lee, K.; Jackson, J. A.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 5967−5971. (b) An, J.; Wiemer, D. F. *J. Org. Chem.* **1996**, *61*, 8775−8779.

(7) Clarke, R. Gahagan, M.; Mackie, R. K.; Foster, D. F.; Cole-Hamilton, D. J.; Nicol, M.; Montford, A. W. *J. Chem. Soc., Dalton Trans. 1* **1995**, 1221−1226.

(8) a) Ruder, S. M.; Kulkarni, V. R. *J. Org. Chem.* **1995**, *60*, 3084−3091. (b) Vedejs, E.; Garcia-Rivas, J. A. *J. Org. Chem.* **1994**, *59*, 6517−6518. (c) Jacks, T. E.; Nibbe, H.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 4584−4588.

(9) Koerwitz, F. L.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1989**, *54*, 738−743.

(10) Presented in part at the 29th Great Lakes Regional ACS Meeting, May, 1996, Normal, IL.

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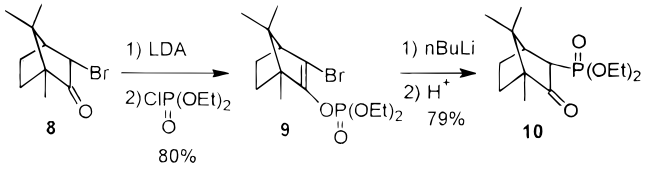
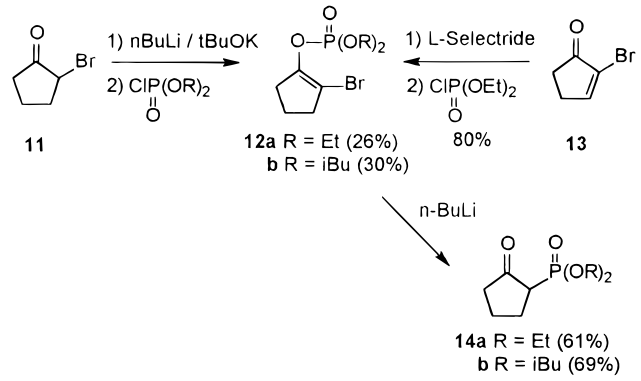
sequentially with LDA and diethyl phosphorochloridate, affording the bromovinyl phosphate **9** in good yield.

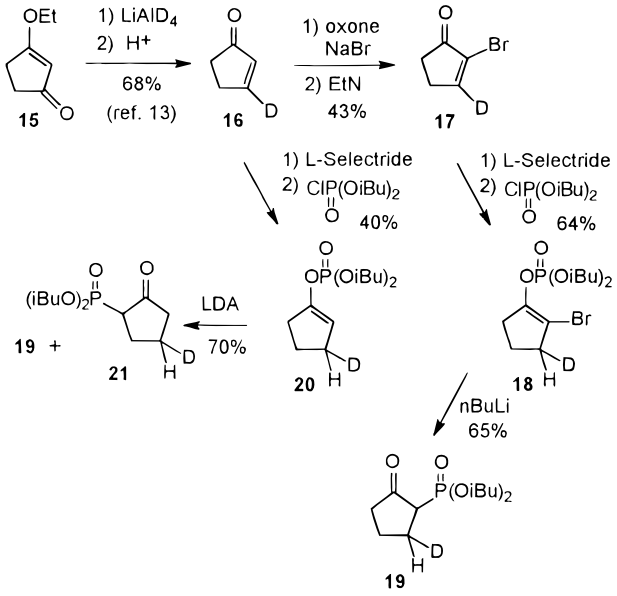


Reaction of α-bromo cyclopentanone (**11**) with these reagents under the same conditions gave only trace amounts of the desired product **12a**, and the yield was only slightly improved when a mixture of potassium *tert*-butoxide and n-BuLi was employed as the base.[11] Use of the corresponding diisobutyl phosphorochloridate[12] resulted in formation of the corresponding vinyl phosphate **12b**. This compound was more conveniently purified by chromatography but still was obtained in modest yield. However, compound **12a** could be prepared efficiently from α-bromo cyclopentenone (**13**) via reaction with L-Selectride (Aldrich) and trapping the resulting enolate with diethyl phosphorochloridate.



When the camphor derivative **9** was treated with n-BuLi, rearrangement to the *β*-keto phosphonate **10** proceeded smoothly. Because the product was obtained in a yield comparable to that obtained by treatment of the camphor-derived vinyl phosphate with base, it appears as though halogen−metal exchange competes very favorably with nucleophilic attack at phosphorus in this system. Although the isolated yields were somewhat diminished, both vinyl phosphates **12a** and **12b** also undergo rearrangement when treated with n-BuLi, providing the expected phosphonates **14a** and **14b**.

Loss of bromide in formation of phosphonates **14a** and **14b** establishes the involvement of halogen−metal exchange, but the symmetry of the product makes it more difficult to rule out formation of an allylic anion by proton transfer prior to rearrangement in this series. To establish that the vinyl phosphate/*β*-keto phosphonate rearrangement is regiospecific when induced by halogen−metal exchange we prepared two isotopically labeled cyclopentanone derivatives. Reduction of 2-ethoxycyclopentenone **15** with $LiAlD_4$ and workup of the reaction mixture with aqueous acid gave the labeled cyclopentenone **16**.[13] Treatment of compound **16** first with oxone and sodium bromide and then with Et_3N according to the procedure of Dieter[14] gave the brominated enone **17**. Treatment of enone **17** with L-Selectride and diisobutyl phosphorochloridate[11] resulted in regiospecific formation



of the 2-bromovinyl phosphate **18**. When compound **18** was treated with n-BuLi to induce rearrangement via halogen−metal exchange, compound **19** was obtained as a single regioisomer, and the expected substitution pattern was readily confirmed by the display of deuterium and phosphorus coupling in the ^{13}C NMR spectrum of the product. The nonbrominated enone **16** also was treated with L-Selectride and diisobutyl phosphorochloridate to effect a regiospecific synthesis of vinyl phosphate **20**, and rearrangement was induced in this system by subsequent reaction with LDA. In contrast to our results with phosphate **18**, a mixture of regioisomers **19** and **21** was obtained in this case. Taken together, this series of experiments establishes that rearrangement of phosphate **18** to phosphonate **19** is a regiospecific process centered on formation of a vinyl anion by halogen−metal exchange, while the base-induced rearrangement of phosphate **20** to phosphonates **19** and **21** involves formation of an allylic anion. The regiospecificity also suggests that rearrangement of the vinyl anion derived from compound **18** is fast compared to proton transfers that would afford an allylic anion.

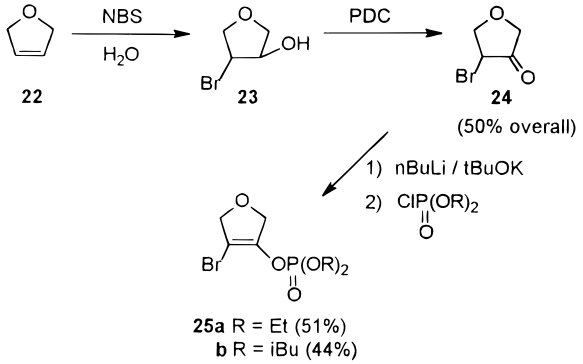
To determine if this new strategy for converting vinyl phosphates to *β*-keto phosphonates would significantly extend the range of the rearrangement, several other 2-bromovinyl phosphates were prepared parallel to cases where direct base induced rearrangements of the corresponding vinyl phosphates are known to be difficult. For one such case, reaction of dihydrofuran **22** with aqueous Br_2 was used to obtain the bromohydrin **23**, and oxidation with PDC gave the new α-bromo ketone **24**. Upon reaction with n-BuLi/KOtBu and diethyl or diisobutyl phosphorochloridate, the vinyl phosphates **25a** and **25b** were obtained in about 40−50% isolated yields. However, none of the desired phosphonates could be detected

(11) (a) Corey, E. J.; Rucker, C. *Tetrahedron Lett.* **1984**, *25*, 4345−4348. (b) Boche, G.; Etzrodt, H. *Tetrahedron Lett.* **1983**, *24*, 5477−5480. (c) Schlosser, M.; Strunk, S. *Tetrahedron Lett.* **1984**, *25*, 741−744.

(12) Sosnovsky, G.; Zaret, E. H. *J. Org. Chem.* **1969**, *34*, 968−970.

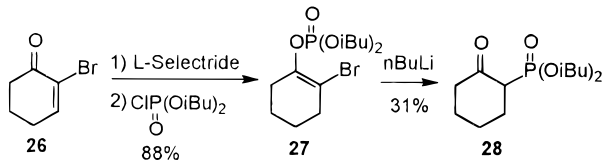
(13) Gannon, W. F.; House, H. O. *Org. Synth.* **1960**, *40*, 14−16.

(14) Dieter, R. K.; Nice, L. E.; Velu, S. E. *Tetrahedron Lett.* **1996**, *37*, 2377−2380.

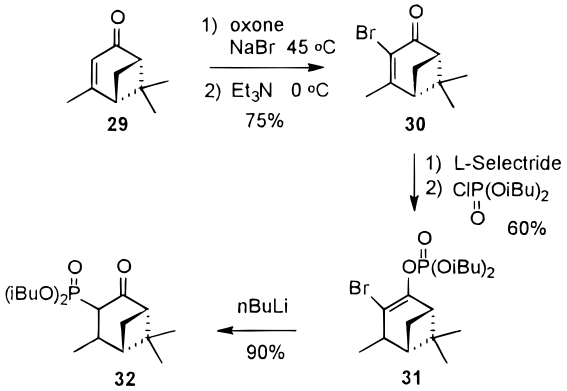


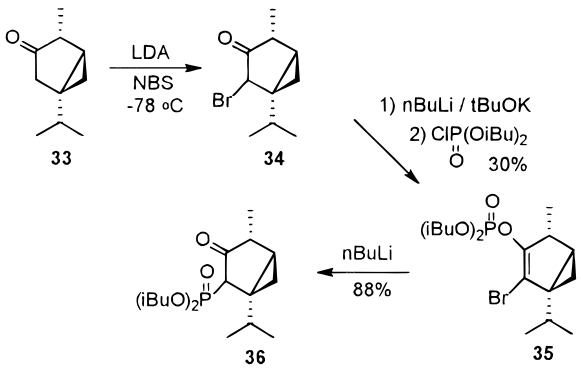
by ^{31}P NMR upon treatment of either vinyl phosphate **25a** or **25b** with n-BuLi under standard conditions. Instead, only decomposition was observed, as was the case when base-induced rearrangement of the parent vinyl phosphate was attempted.[15]

More encouraging results were obtained with some of the other cyclic ketones that were examined. The parent six-membered ring 2-bromovinyl phosphate (**27**) was prepared efficiently from α-bromocyclohexenone (**26**) by conjugate addition of hydride and trapping the resulting



enolate with diisobutyl phosphorochloridate. However, treatment with n-BuLi gave the desired β-keto phosphonate **28** in modest yield. Significantly better results were obtained with the more rigid system presented by (1*S*)−(−)-verbenone (**29**). This enone was converted to the α-bromo enone **30** through reaction with oxone, NaBr, and Et_3N, and subsequently converted to the 2-bromovinyl phosphate **31** in the usual manner. When compound **31** was treated with n-BuLi, clean rearrangement was observed, yielding the β-keto phosphonate **32** in 90% yield. Similar results were obtained with (−)-thujone (**33**). In this case, treatment of the parent ketone with LDA and NBS resulted in formation of the α-bromo ketone **34**, and treatment of compound **34** with base and diisobutyl phosphorochloridate gave the vinyl phosphate **35**. Even though technical grade thujone was employed in this sequence, and intermediates were not easily





purified until the vinyl phosphate stage, this compound was obtained in 30% overall yield based on the starting ketone. Treatment of compound **35** with n-BuLi also results in efficient halogen−metal exchange and rearrangement, as witnessed by an isolated yield of 88% of the β-keto phosphonate **36**.

In conclusion, these studies have demonstrated that it is possible to initiate a vinyl phosphate/β-keto phosphonate rearrangement via halogen−metal exchange in various systems without significant competition from nucleophilic attack at phosphorus. The isotopic labeling studies described above establish that the rearrangement is regiospecific when initiated by halogen−metal exchange, with the phosphoryl group of the product attached to the carbon formerly bearing the bromide. This strategy has been employed to prepare several cyclic β-keto phosphonates, including new nonracemic phosphonates derived from verbenone and thujone. These results suggest that it may be possible to employ this strategy to induce rearrangement in still other cyclic systems or to employ halogen−metal exchange to form vinyl phosphate anions that may be employed in other ways (e.g. by trapping with external electrophiles). Our further investigations along these lines will be the subject of future studies.

Experimental Section

Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. All nonaqueous reactions were conducted in oven-dried glassware, under an atmosphere of nitrogen or argon, and with magnetic stirring. Commercial $LiAlD_4$ (96 atom % D) was employed for preparation of compound **16**. Flash chromatography was carried out on Baker silica gel with 40 μm average particle diameter. Melting points are uncorrected. NMR spectra (^1H at 300 MHz and ^{13}C at 75 MHz) were recorded with $CDCl_3$ as solvent and $(CH_3)_4Si$ (^1H) 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). Both low and high resolution mass spectra were obtained at an ionization potential of 70 eV; only selected ions are reported here. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

3-Bromo-2-[(diethoxyphosphinyl)oxy]-1,7,7-trimethylbicyclo[2.2.1]-2-heptene (9). A solution of bromocamphor (1.89 g, 8.17 mmol) in THF (10 mL) was added dropwise to a solution of LDA [1.1 equiv, prepared in situ from diisopropylamine (1.08 g, 10.6 mmol) and *n*-BuLi (5.99 mL, 1.5 M in hexanes)] in THF (25 mL) at −78 °C. The resulting mixture was allowed to warm to 0 °C and was stirred for 30 min. After cooling to −78 °C, diethyl phosphorochloridate (1.55 g, 8.99 mmol) was added. The mixture was allowed to warm to room temperature over 2 h and then quenched by addition of saturated NH_4Cl. After the organic layer was separated, the

(15) Lee, K. Ph.D. Thesis, University of Iowa, 1993; page 59.

aqueous layer was extracted with ether, and the combined organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil. Purification by flash column chromatography (silica gel; 4:1 hexanes/EtOAc) produced an analytically pure sample (2.40 g, 80%): ^{1}H NMR δ 4.29−4.17 (m, 4H), 2.39 (d, J = 3.6 Hz, 1H), 1.91−1.81 (m, 1H), 1.65−1.49 (m, 2H), 1.38 (td, J = 7.2, J_{HP} = 1.2 Hz, 3H), 1.37 (td, J = 6.9, J_{HP} = 1.2 Hz, 3H), 1.32−1.24 (m, 1H), 1.09 (s, 3H), 0.99 (s, 3H), 0.77 (s, 3H); ^{13}C NMR δ 152.2 (d, J_{CP} = 7.6 Hz), 104.7 (d, J_{CP} = 7.6 Hz), 64.2 (d, J_{CP} = 1.5 Hz), 64.1 (d, J_{CP} = 2.3 Hz), 57.6 (d, J_{CP} = 1.5 Hz), 55.6, 55.4 (d, J_{CP} = 1.5 Hz), 31.6 (d, J_{CP} = 2.3 Hz), 24.7 (d, J_{CP} = 3.0 Hz), 19.1, 18.6, 15.8, 15.7, 9.8; ^{31}P NMR −6.5. Anal. Calcd for $C_{14}H_{24}BrO_4P$: C, 45.79; H, 6.59. Found: C, 45.53; H, 6.54.

2-Bromo-1-[(diethoxyphosphinyl)oxy]cyclopentene (12a). (General Procedures). 2-Methyl-2-propanol (0.941 g, 12.7 mmol) in 6 mL of THF was added to a suspension of KH (0.509 g, 12.7 mmol) in THF (20 mL) at room temperature. After 30 min, the mixture was cooled to −78 °C, *n*-BuLi (7.79 mL, 1.63 M in hexanes) was added, and the reaction mixture was stirred for 30 min. The α-bromo ketone **11** (1.87 g, 11.6 mmol) in 5 mL of THF was added dropwise, and the resulting mixture was stirred for 50 min. This mixture was then treated with diethyl phosphorochloridate (12.00 g, 17.32 mmol) and allowed to warm to room temperature. After 2 h, the reaction was quenched by addition of saturated NH_4Cl and extracted with ether. The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (33 to 50% EtOAc in hexanes) afforded compound **12a** (0.898 g, 26%): ^{1}H NMR δ 4.27−4.17 (m, 4H), 2.64−2.53 (m, 4H), 2.09−1.99 (m, 2H), 1.38 (td, J = 7.2, J_{HP} = 1.2 Hz, 6H),; ^{13}C NMR δ 146.2 (d, J_{CP} = 7.6 Hz), 101.5 (d, J_{CP} = 10.3 Hz), 64.3 (d, J_{CP} = 6.8 Hz, 2C), 34.2, 29.7, 19.5, 15.6 (d, J_{CP} = 6.8 Hz, 2C); ^{31}P NMR δ −6.4. Anal. Calcd for $C_9H_{16}BrO_4P\cdot 0.5H_2O$: C, 35.20; H, 5.58. Found: C, 35.36; H, 5.36.

For preparation of compound **12a** via conjugate addition, L-Selectride (1.64 mL, 1 M in THF) was added to a solution of bromo enone **13** (1.08 g, 6.73 mmol) in THF (25 mL) at −78 °C. After 1 h, diethyl phosphorochloridate (1.51 g, 8.75 mmol) was added, and the mixture was allowed to warm to room temperature. After an additional 1 h, the reaction was quenched by addition of a satuated solution of NH_4Cl. Standard workup as described above, and purification by flash column chromatography (33 to 50% EtOAc in hexanes) provided compound **12a** (1.61 g, 80%).

2-Bromo-1-[(diisobutoxyphosphinyl)oxy]cyclopentene (12b). According to the procedure described for compound **12a**, a suspension of KH (0.389 g, 9.70 mmol) in THF (26 mL) was treated sequentially with 2-methyl-2-propanol (0.719 g, 9.70 mmol) in 6 mL of THF, *n*-BuLi (5.74 mL, 1.69 M in hexanes), 2-bromocyclopentanone in 6 mL of THF, and then diisobutyl phosphorochloridate (2.62 g, 11.5 mmol) in 2 mL of THF. The reaction was allowed to warm to room temperature over 40 min and then treated as above. Flash column chromatography (100% $CHCl_3$) gave compound **12b** (0.936 g, 30%): ^{1}H NMR δ 3.92 (t, J = 6.4 Hz, 4H), 2.64−2.53 (m, 4H), 2.09−1.93 (m, 4H), 0.97 (d, J = 6.7 Hz, 12H); ^{13}C NMR δ 146.1 (d, J_{CP} = 7.6 Hz), 101.5 (d, J_{CP} = 7.6 Hz), 73.9 (d, J_{CP} = 6.8 Hz, 2C), 34.1, 29.8, 28.5 (d, J_{CP} = 7.6 Hz, 2C), 19.5, 18.1 (4C); ^{31}P NMR δ −6.3. Anal. Calcd for $C_{13}H_{24}BrO_4P$: C, 43.96; H, 6.81. Found: C, 44.05; H, 6.84.

3-(Diethoxyphosphinyl)camphor (10). (General Procedure). A solution of 2-bromovinyl phosphate **9** (197 mg, 0.535 mmol) in THF (9 mL) was treated dropwise with *n*-BuLi (0.71 mL, 1.66 M in hexanes) at −78 °C. The solution was allowed to warm to room temperature over 1 h. The reaction was quenched (NH_4Cl), extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the resulting oil by flash chromatography (33 to 50% EtOAc in hexanes) gave phosphonate **10**[1] (122 mg, 79%).

2-(Diethylphosphinyl)cyclopentanone (14a). According to the general procedure, 2-bromovinyl phosphate **12a** (51 mg, 0.17 mmol) was treated with *n*-BuLi (0.234 mL, 1.59 M in hexanes) at −78 °C. Standard workup and purification by flash column chromatography (20 to 25% EtOAc in hexanes) yielded phosphonate **14a** (23 mg, 61%).[1]

2-(Diisobutoxyphosphinyl)cyclopentanone (14b). According to the general procedure, 2-bromovinyl phosphate **12b** (245 mg, 0.692 mmol) in 8 mL of THF was treated with *n*-BuLi (0.901 mL, 1.69 M in hexanes) at −78 °C. Standard workup and purification by flash column chromatography (33 to 50% EtOAc in hexanes) yielded phosphonate **14b** (105 mg, 69%): ^{1}H NMR δ 3.94−3.78 (m, 4H), 2.76 (dt, J_{HP} = 26.0 Hz, J = 8.1 Hz, 1H), 2.49−2.25 (m, 4H), 2.25−2.09 (m, 1H), 2.05−1.83 (m, 3H), 0.96 (d, J = 2.6 Hz, 6H), 0.94 (d, J = 2.6 Hz, 6H); ^{13}C NMR δ 212.0, 72.2 (d, J_{CP} = 6.8 Hz), 72.0 (d, J_{CP} = 6.8 Hz), 46.7 (d, J_{CP} = 138.2 Hz), 38.9 (d, J_{CP} = 3.8 Hz), 29.2 (d, J_{CP} = 2.3 Hz), 29.1 (d, J_{CP} = 2.3 Hz), 25.5 (d, J_{CP} = 3.8 Hz), 21.6 (d, J_{CP} = 8.3 Hz), 18.5 (4C); ^{31}P NMR δ +23.3. Anal. Calcd for $C_{13}H_{25}O_4P$: C, 56.51; H, 9.12. Found: C, 56.42; H, 9.11.

2-Bromo-3-deuterio-2-cyclopenten-1-one (17). According to the procedure of Dieter, sodium bromide (0.382 g, 3.71 mmol) was added as a solid to a vigorously stirring solution of oxone (2.28 g, 3.71 mmol) in carbon tetrachloride and H_2O (10 mL/3 mL) at 0 °C. After 15 min, 3-deuterio-2-cyclopenten-1-one (**16**, 0.154 g, 1.86 mmol) in CH_2Cl_2 (1 mL) was added, and the resulting mixture was allowed to warm to room temperature. After 1 h, the reaction was cooled to 0 °C, and triethylamine (0.376 g, 3.71 mmol) was added to eliminate hydrogen bromide. After 30 min, the solution was allowed to warm to room temperature and then quenched by addition of NH_4Cl. The resulting solution was extracted with CH_2Cl_2, and the combined organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. Compound **17** was obtained as an oil (0.269 g, 45%) following purification by flash column chromatography (20 to 25% EtOAc in hexanes): ^{1}H NMR δ 2.72−2.69 (m, 2H), 2.55−2.52 (m, 2H); ^{13}C NMR δ 201.7, 161.6 (t, J_{CD} = 26.4 Hz), 125.7, 32.2, 27.7; GCMS, *m*/*z* (rel intensity) 163 (M^+ + 2, 40), 161 (M^+, 45), 135 (16), 133 (18), 107 (4), 105 (3), 82 (15), 54 (100).

2-Bromo-3-deuterio-1-[(diisobutoxyphosphinyl)oxy]-cyclopentene (18). L-Selectride (0.377 mL, 1 M in THF) was added to a solution of bromo enone **17** (55 mg, 0.34 mmol) in THF (4 mL) at −78 °C. The resulting solution was stirred for 1 h, and then diisobutyl phosphorochloridate (102 mg, 0.446 mmol) in 0.5 mL of THF was added and the reaction mixture was allowed to warm to room temperature. After 50 min, the reaction was quenched (NH_4Cl) and then extracted with ether. The combined organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (7:1 hexanes/EtOAc) afforded vinyl phosphate **18** (78 mg, 64%): ^{1}H NMR δ 3.92 (t, J = 6.6 Hz, 4H), 2.63−2.51 (m, 3H), 2.07−1.93 (m, 4H), 0.97 (d, J = 6.8 Hz, 12H); ^{13}C NMR δ 146.5 (d, J_{CP} = 7.6 Hz), 101.8 (d, J_{CP} = 7.6 Hz), 74.3, 74.2, 34.1 (t, J_{CD} = 20.7 Hz), 30.1, 28.9, 28.8, 19.7, 18.4 (4C); ^{31}P NMR δ −6.27; GCMS, *m*/*z* (rel intensity) 357 (M^+ + 2, 2), 355 (M^+, 2), 301 (1), 299 (1), 245 (14), 243 (15), 164 (100), 99 (7), 84 (23), 66 (19), 57 (34), 41 (38).

3-Deuterio-2-(diisobutoxyphosphinyl)cyclopentanone (19). A solution of 2-bromovinyl phosphate **18** (78 mg, 0.22 mmol) in THF (3 mL) was treated with *n*-BuLi (0.291 mL, 1.66 M in hexanes) at −78 °C. The reaction was allowed to warm to room temperature over 50 min and then quenched by addition of NH_4Cl. The aqueous phase was extracted with ether, and the combined organic layer was washed with brine and dried over $MgSO_4$. After the solution was concentrated in vacuo, purification by flash column chromatography (25 to 50% EtOAc in hexanes) gave phosphonate **19** (40 mg, 65%): ^{1}H NMR δ 3.94−3.78 (m, 4H), 2.78 (dd, J_{HP} = 26.1 Hz, J = 8.5 Hz, 1H), 2.42−2.09 (m, 4H), 2.05−1.83 (m, 3H), 0.95 (d, J = 6.7 Hz, 6H), 0.94 (d, J = 6.7 Hz, 6H); ^{13}C NMR δ 212.0, 72.3 (d, J_{CP} = 7.6 Hz), 72.1 (d, J_{CP} = 7.6 Hz), 46.7 (dd, J_{CP} = 137.2 Hz, J_{CD} = 1.1 Hz), 38.9 (d, J_{CP} = 3.0 Hz), 29.2 (d, J_{CP} = 2.3 Hz), 29.1 (d, J_{CP} = 2.3 Hz), 25.2 (td, J_{CD} = 20.0 Hz, J_{CP} = 3.0 Hz), 21.5 (d, J_{CP} = 9.1 Hz), 18.6 (d, J_{CP} = 1.5 Hz, 4C); ^{31}P NMR δ +23.28; GCMS, *m*/*z* (rel intensity) 278 (M^+ + 1, 0.2), 222 (13), 166 (100), 110 (59), 83 (91), 68 (5), 57 (27), 41 (27).

3-Deuterio-1-[(diisobutoxyphosphinyl)oxy]cyclopentene (20). L-Selectride (0.99 mL, 1 M in THF) added to

a solution of enone **16**[13] (75 mg, 0.90 mmol) in THF (10 mL) at −78 °C. After 1 h, diisobutyl phosphorochloridate (267 mg, 1.17 mmol) in 1 mL of THF was added, and the mixture was allowed to warm to room temperature. After 35 min, the reaction was quenched (NH_4Cl) and extracted with ether. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. The resulting oil was purified by flash column chromatography (14 to 20% EtOAc in hexanes) to obtain phosphate **20** (99 mg, 40%): ^{1}H NMR δ 5.26−5.24 (m, 1H), 3.86 (td, J = 6.6, 0.9 Hz, 4H), 2.49−2.42 (m, 2H), 2.35−2.27 (m, 1H), 2.04−1.88 (m, 4H), 0.96 (d, J = 6.7 Hz, 12H); ^{13}C NMR δ 150.1 (d, J_{CP} = 7.6 Hz), 109.1 (d, J_{CP} = 6.0 Hz), 74.1, 74.0, 31.4 (d, J_{CP} = 5.3 Hz), 29.0, 28.9, 28.0 (t, J_{CD} = 20.0 Hz), 20.7, 18.5 (4C); ^{31}P NMR δ −5.44; GCMS, *m*/*z* (rel intensity) 277 (M^+, 3), 221 (2), 165 (100), 99 (31), 84 (59), 67 (37), 57 (25), 41 (30).

Rearrangement of Vinyl Phosphate 20. Compound **20** (89 mg, 0.32 mmol) in THF (0.5 mL) was added to a solution of LDA (3.5 equiv) in THF (2 mL) at −78 °C, and the resulting mixture was allowed to warm to room temperature. After 1.5 h, the reaction was quenched by addition of saturated NH_4Cl. The aqueous phase was extracted with ether, and the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash column chromatography (25 to 50% EtOAc in hexanes) afforded a mixture of keto phosphonates **19** and **21** (62 mg, 70%). The ^{1}H NMR spectrum was generally indistinguishable from that reported for compound **19**, except for the CHP(O) resonance. This signal appeared as a six-line pattern interpreted as a doublet of triplets (the resonance from the minor isomer **21** where the α-hydrogen is coupled to phosphorus and two adjacent H's) overlapping a doublet of doublets (the resonance from the major isomer **19** where the α-hydrogen is coupled to phosphorus and one adjacent H). Overlap of these key resonances prevented determination of the isomer ratio from the ^{1}H spectrum. In an inverse gated broadband decoupled ^{13}C NMR spectrum, the integrated intensity of signals at δ 46.7 and 46.8, and those at δ 38.9 and 38.8, was 5:1, with the major resonances corresponding to those observed for compound **19**. For the mixture of phosphonates **19** and **21**: ^{13}C NMR (125 MHz) δ 212.0 (d, J_{CP} = 12.5 Hz), 72.3 (d, J_{CP} = 6.3 Hz), 72.1 (d, J_{CP} = 7.5 Hz), 46.8 (d, J_{CP} = 136.3 Hz), 46.7 (d, J_{CP} = 137.5 Hz), 38.9 (d, J_{CP} = 3.8 Hz), 38.8 (d, J_{CP} = 3.8 Hz), 29.2 (d, J_{CP} = 3.8 Hz), 29.1 (d, J_{CP} = 3.8 Hz), 25.4 (d, J_{CP} = 3.8 Hz), 25.2 (td, J_{CD} = 20 Hz, J_{CP} = 3.8 Hz), 21.6 (d, J_{CP} = 8.8 Hz), 21.4 (td, J_{CD} = 21.3 Hz, J_{CP} = 7.5 Hz), 18.6 (4C). ^{31}P NMR δ +23.23; GCMS, *m*/*z* (rel intensity) 278 (M^+ + 1, 0.2), 222 (11), 166 (100), 110 (59), 83 (91), 68 (14), 57 (25), 41 (34).

4-Bromo-3-hydroxytetrahydrofuran (23). Recrystallized *N*-bromosuccinimide (11.44 g, 64.27 mmol) was added as a solid to a solution of 2,5-dihydrofuran (4.29 g, 61.2 mmol) in distilled H_2O (275 mL). After 6 h, the solution was extracted with ether. The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give compound **23** (6.03 g, 66%) as a yellow oil: ^{1}H NMR δ 4.58−4.57 (m, 1H), 4.42 (dd, J = 10.5, 4.5 Hz, 1H), 4.26 (dd, J = 9.9, 4.2 Hz, 1H), 4.21−4.19 (m, 1H), 4.08 (dd, J = 10.5, 2.4 Hz, 1H), 3.81 (dd, J = 10.2, 0.6 Hz, 1H); ^{13}C NMR δ 78.6, 74.2, 73.3, 51.5.

Ketone 24. Pyridinium dichromate (20.74 g, 55.12 mmol) and molecular sieves (21 g) were added in portions to a solution of bromohydrin **23** (3.68 g, 22.1 mmol) in CH_2Cl_2 (200 mL) and allowed to stir overnight. The resulting mixture was filtered through a 2 cm pad of Celite, and the pad was rinsed thoroughly with CH_2Cl_2. After the filtrate was concentrated in vacuo, the resulting oil was purified by flash column chromatography (3:1 hexanes/EtOAc) to give bromo ketone **24** (1.82 g, 75%): ^{1}H NMR δ 4.53 (ddd, J = 10.8, 6.0, 0.9 Hz, 1H), 4.36 (td, J = 5.7, 0.6 Hz, 1H), 4.23 (ddd, J = 10.8, 5.1, 0.6 Hz, 1H), 4.13 (dd, J = 17.4, 0.9 Hz), 3.99 (dd, J = 17.4, 0.6 Hz, 1H); ^{13}C NMR δ 207.2, 73.8, 68.9, 42.3. Anal. Calcd for $C_4H_5BrO_2$: C, 29.12; H, 3.05. Found: C, 28.90; H, 3.10.

4-Bromo-3-[(diethoxyphosphinyl)oxy]-2,5-dihydrofuran (25a). According to the general procedure bromo ketone **24** (437 mg, 2.65 mmol) was treated with KH (64 mg, 1.6 mmol), 2-methyl-2-propanol (118 mg, 1.59 mmol), *n*-BuLi (1.00 mL, 1.59 M in hexanes), and diethyl phosphorochloridate (686 mg, 3.98 mmol). Standard workup and purification by flash column chromatography (20 to 25% EtOAc in hexanes) gave compound **25a** (407 mg, 51%): ^{1}H NMR δ 4.69−4.59 (m, 4H), 4.29−4.19 (m, 4H),), 1.37 (td, J = 6.9, J_{HP} = 1.2 Hz, 6H); ^{13}C NMR δ 142.3 (d, J_{CP} = 7.6 Hz), 95.0 (d, J_{CP} = 10.6 Hz), 74.6, 70.1, 64.9, 64.8, 15.5 (d, J_{CP} = 6.0 Hz, 2C); ^{31}P NMR δ −6.1. Anal. Calcd for $C_8H_{14}BrO_5P\cdot 0.5H_2O$: C, 31.09; H, 4.89. Found: C, 31.10; H, 4.58.

4-Bromo-3-[(diisobutoxyphosphinyl)oxy]-2,5-dihydrofuran (25b). According to the general procedure bromo ketone **24** (533 mg, 3.23 mmol) was treated with KH (78 mg, 1.9 mmol), 2-methyl-2-propanol (411 mg, 1.94 mmol), *n*-BuLi (1.22 mL, 1.59 M in hexanes), and diisobutyl phosphorochloridate (884 mg, 3.88 mmol). Standard workup and purification by flash column chromatography (20 to 25% EtOAc in hexanes) gave compound **25b** (508 mg, 44%): ^{1}H NMR δ 4.69−4.59 (m, 4H), 3.93 (td, J = 6.6, 1.2 Hz, 4H), 2.09−1.94 (m, 2H), 0.97 (d, J = 6.7 Hz, 12H); ^{13}C NMR δ 140.3, 95.6 (d, J_{CP} = 10.6 Hz), 75.1 (d, J_{CP} = 3.8 Hz), 75.0 (d, J_{CP} = 2.3 Hz), 73.4 (d, J_{CP} = 6.0 Hz), 70.5, 28.8 (d, J_{CP} = 6.8 Hz, 2C), 18.3 (d, J_{CP} = 7.6 Hz, 4C); ^{31}P NMR δ −6.0; HR FAB-MS: calcd for $C_{12}H_{21}O_5BrP$ $(M + H - H_2)^+$, 355.0310; found, 355.0302.

2-Bromo-1-[(diisobutoxyphosphinyl)oxy]cyclohexene (27). According to the general procedure for conjugate addition, 2-bromo-2-cyclohexen-1-one[14] (240 mg, 1.37 mmol) was treated with L-Selectride (1.51 mL, 1 M in THF) and diisobutyl phosphorochloridate (406 mg, 1.78 mmol). Standard workup and purification by flash column chromatography (20 to 25% EtOAc in hexanes) gave compound **27** (455 mg, 88%): ^{1}H NMR δ 3.92 (t, J = 6.3 Hz, 4H), 2.54−2.43 (m, 4H), 2.06−1.93 (m, 2H), 1.81−1.65 (m, 4H), 0.97 (d, J = 6.7 Hz, 12H); ^{13}C NMR δ 143.9 (d, J_{CP} = 3.0 Hz), 107.0 (d, J_{CP} = 7.6 Hz), 73.7 (d, J_{CP} = 6.8 Hz, 2C), 33.9, 28.7 (d, J_{CP} = 6.0 Hz, 2C), 28.5, 23.4, 22.1, 18.1 (4C); ^{31}P NMR δ −6.4. Anal. Calcd for $C_{14}H_{26}BrO_4P$: C, 45.54; H, 7.10. Found: C, 45.68; H, 7.16.

2-(Diisobutylphosphinyl)cyclohexanone (28). To a cooled solution (−90 °C)[1a] of 2-bromovinyl phosphate **27** (229 mg, 0.620 mmol) in THF (12 mL) was added *n*-BuLi (0.834 mL, 1.63 M in hexanes) dropwise. After 3.5 h at −90 °C, the reaction was quenched by addition of NH_4Cl. The aqueous phase was extracted with ether, and the combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash column chromatography (33 to 50% EtOAc in hexanes) gave phosphonate **28** (55 mg, 31%): ^{1}H NMR δ 3.89−3.81 (m, 4H), 3.01 (dt, J_{HP} = 23.4 Hz, J = 5.8 Hz, 1H), 2.71−2.60 (m, 1H), 2.43−2.34 (m, 1H), 2.33−1.57 (m, 8H), 0.95 (d, J = 3.1 Hz, 6H), 0.93 (d, J = 3.1 Hz, 6H); ^{13}C NMR δ 206.1 (d, J_{CP} = 7.6 Hz), 72.2, 72.1, 50.1 (d, J_{CP} = 132.1 Hz), 41.5 (d, J_{CP} = 2.3 Hz), 29.2, 29.1, 27.9 (d, J_{CP} = 5.3 Hz), 26.5, 22.5 (d, J_{CP} = 6.8 Hz), 18.6 (4C); ^{31}P NMR δ +27.64, +23.68 (keto−enol tautomerism); HRFAB calcd for $C_{14}H_{27}O_4P$ $(M + Na)^+$ 313.1545, found 313.1544.

3-Bromo-4,6,6-trimethylbicyclo[3.1.1]-3-hepten-2-one (30). Sodium bromide (0.895 g, 8.70 mmol) was added to a vigorously stirring solution of oxone (5.35 g, 8.70 mmol) in carbon tetrachloride (25 mL) and H_2O (5 mL) at 0 °C. The resulting mixture was heated to 45 °C and (−)-verbenone (0.653 g, 4.35 mmol) in CH_2Cl_2 (1.5 mL) was added. After 1 h, the reaction was cooled to 0 °C, and triethylamine (0.880 g, 8.70 mmol) was added dropwise. The reaction was allowed to warm to room temperature, quenched (NH_4Cl), and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by radial chromatography (4:1 hexanes/EtOAc) gave compound **30** (0.498 g, 50%) along with some of the intermediate dibromide. Treatment of the dibromide with triethylamine gave an additional batch of the desired product (0.245 g), raising the total yield to 75%: ^{1}H NMR δ 2.90−2.78 (m, 2H), 2.64 (dd, J = 6.6, 5.4 Hz, 1H), 2.19 (s, 3H), 2.17 (d, J = 9.0 Hz, 1H), 1.50 (s, 3H), 1.00 (s, 3H); ^{13}C NMR δ 195.5, 166.6, 116.7, 57.2, 54.7, 51.5, 40.0, 26.0, 23.7, 21.8; HR FAB MS calcd for $C_{10}H_{14}BrO$ $(M + H)^+$ 229.0228, found 229.0223.

3-Bromo-2-[(diisobutoxyphosphinyl)oxy]-4,6,6-trimethylbicyclo[3.1.1]-2-heptene (31). According to the general procedure, bromo enone **30** (341 mg, 1.49 mmol) was treated with L-Selectride (1.64 mL, 1 M in THF) and diisobutyl phosphorochloridate (442 mg, 1.94 mmol). Standard workup and purification by flash column chromatography (4:1 hexanes/EtOAc) provided compound **31** (378 mg, 60%): ^{1}H NMR δ 3.95−3.88 (m, 4H), 2.86−2.76 (m, 1H), 2.66 (t, J = 5.9 Hz, 1H), 2.57 (dt, J = 9.3, 5.7 Hz, 1H), 2.16 (td, J = 6.3, 2.4 Hz, 1H), 2.06−1.92 (m, 2H), 1.53 (d, J = 9.3 Hz, 1H) 1.34 (s, 3H), 1.25 (d, J = 7.5 Hz, 3H) 1.08 (s, 3H), 0.96 (d, J = 6.7 Hz, 12H); ^{13}C NMR δ 151.1 (d, J_{CP} = 7.6 Hz), 106.7 (d, J_{CP} = 7.6 Hz), 74.0 (d, J_{CP} = 7.6 Hz, 2C), 48.5, 47.0 (d, J_{CP} = 1.5 Hz), 42.5, 40.5 (d, J_{CP} = 1.5 Hz), 28.8 (d, J_{CP} = 1.8 Hz), 28.7 (J_{CP} = 1.8 Hz), 26.2, 23.3, 18.3 (4C), 17.2 (d, J_{CP} = 1.5 Hz); ^{31}P NMR δ −6.7. Anal. Calcd for $C_{18}H_{32}BrO_4P$: C, 51.07; H, 7.62. Found: C, 51.18; H, 7.64.

3-(Diisobutoxyphosphinyl)verbenone (32). A solution of 2-bromovinyl phosphate **31** (98 mg, 0.23 mmol) in THF (3 mL) was treated with *n*-BuLi (0.333 mL, 1.53 M in hexanes) at −78 °C. The reaction was allowed to warm to room temperature over 1 h, quenched by addition of NH_4Cl, and extracted with ether. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash column chromatography (20 to 33% EtOAc in hexanes) gave analytically pure material as an oil (72 mg, 90%): ^{1}H NMR δ 3.96−3.80 (m, 4H), 2.76 (dd, J_{HP} = 32.1 Hz, J = 5.7 Hz, 1H), 2.82−2.66 (m, 1H), 2.61−2.50 (m, 2H), 2.18−2.13 (m, 1H), 2.04−1.91 (m, 3H), 1.35 (s, 3H), 1.26 (d, J = 7.2 Hz, 3H), 0.96 (m 15H); ^{13}C NMR δ 206.7 (d, J_{CP} = 7.6 Hz), 72.9 (d, J_{CP} = 7.6 Hz), 71.6 (d, J_{CP} = 7.6 Hz), 57.9 (d, J_{CP} = 1.5 Hz), 51.7 (d, J_{CP} = 129.9 Hz), 46.6 (d, J_{CP} = 6.0 Hz), 40.9 (d, J_{CP} = 2.3 Hz), 33.4 (d, J_{CP} = 3.8 Hz), 29.2 (d, J_{CP} = 6.0 Hz), 29.1 (d, J_{CP} = 6.8 Hz), 26.8, 26.1 (d, J_{CP} = 1.5 Hz), 23.9, 20.7 (d, J_{CP} = 3.8 Hz), 18.64 (d, J_{CP} = 2.3 Hz, 2C), 18.61 (d, J_{CP} = 2.3 Hz, 2C); ^{31}P NMR +25.5. Anal. Calcd for $C_{18}H_{33}O_4P$: C, 62.77; H, 9.66. Found: C, 62.69; H, 9.53.

2-Bromo-1-isopropyl-4-methylbicyclo[3.1.0]hexane-3-one (34). Thujone (0.306 g, 2.01 mmol, tech grade) in 2 mL of THF was added dropwise to a solution of LDA (1.1 equiv) in THF (15 mL) at −78 °C. After 1.5 h, NBS (1.07 g, 6.03 mmol) was added as a solid to the resulting enolate, and the reaction was allowed to stir at −78 °C for 40 min. The reaction mixture was allowed to warm to room temperature over 1 h and then quenched by addition of a saturated solution of NH_4Cl followed by standard workup. Because separation of the product from other terpenoids present in the technical grade thujone proved difficult, the product mixture was utilized directly in the next experiment without further purification.

2-Bromo-3-[(diisobutoxyphosphinyl)oxy]-1-isopropyl-4-methylbicyclo[3.1.0]-2-hexene (35). According to the general procedure, bromo ketone **33** (236 mg, 1.02 mmol) was treated with 2-methyl-2-propanol (45 mg, 0.61 mmol), KH (25 mg, 0.61 mmol), *n*-BuLi (0.369 mL, 1.66 M in hexanes), and diisobutyl phosphorochloridate (303 mg, 1.33 mmol). Standard workup and purification by flash column chromatography (6:1 hexanes/EtOAc) provided compound **34** (264 mg, 30%): ^{1}H NMR δ 3.95−3.83 (m, 4H), 2.83 (qd, J = 6.9, 2.1 Hz, 1H), 2.10−1.91 (m, 3H), 1.19 (d, J = 6.9 Hz, 3H), 1.12 (dd, J = 7.8, 4.5 Hz, 1H), 0.99 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.7 Hz, 6H), 0.95 (d, J = 6.8 Hz, 7H), 0.77 (d, J = 7.0 Hz, 3H), 0.37 (t, J = 4.6 Hz, 1H); ^{13}C NMR δ 148.0 (d, J_{CP} = 7.6 Hz), 111.1 (d, J_{CP} = 7.6 Hz), 74.2 (d, J_{CP} = 2.3 Hz), 74.1 (d, J_{CP} = 2.3 Hz), 40.0 (d, J_{CP} = 0.8 Hz), 36.1 (d, J_{CP} = 0.8 Hz), 28.9, 28.8, 26.8, 21.8, 20.6, 19.7 (d, J_{CP} = 3.0 Hz), 19.3 (d, J_{CP} = 1.5 Hz), 18.4 (4C), 18.1; ^{31}P NMR δ −7.0. HR FAB MS calcd for $C_{18}H_{32}BrO_4P$ (M + Na)$^+$ 445.1119, found 445.1112.

4-(Diisobutoxyphosphinyl)thujone (36). *n*-BuLi (0.305 mL, 1.53 M in hexanes) was added dropwise to 2-bromovinyl phosphate **35** (90 mg, 0.21 mmol) in THF (2.5 mL) at −78 °C. The mixture was allowed to warm to room temperature over 30 min. Standard workup and purification of the resulting oil by flash column chromatography (20 to 25% EtOAc in hexanes) gave phosphonate **36** (64 mg, 88%): ^{1}H NMR δ 3.97−3.78 (m, 4H), 3.23 (dt, J_{HP} = 27.0 Hz, J = 1.5 Hz, 1H), 2.35 (q, J = 7.5 Hz, 1H), 2.16−2.07 (m, 1H), 2.01−1.80 (m, 2H), 1.17 (d, J = 7.5 Hz, 3H), 1.06 (br s, 2H), 1.03 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.8 Hz, 6H), 0.95 (d, J = 6.6 Hz, 6H), 0.76 (d, J = 7.2 Hz, 3H); ^{13}C NMR δ 214.6, 72.2 (d, J_{CP} = 6.8 Hz), 71.9 (d, J_{CP} = 6.8 Hz), 50.7 (d, J_{CP} = 119.9 Hz), 47.0 (d, J_{CP} = 1.5 Hz), 31.0 (d, J_{CP} = 1.5 Hz), 29.2 (d, J_{CP} = 1.5 Hz), 29.1 (d J_{CP} = 1.5 Hz), 28.5, 21.2 (d, J_{CP} = 10.6 Hz), 20.2, 18.7 (4C), 18.3, 17.5 (d, J_{CP} = 0.8 Hz), 16.3 (d, J_{CP} = 5.3 Hz); ^{31}P NMR δ +23.3. Anal. Calcd for $C_{18}H_{33}O_4P$: C, 62.77; H, 9.66. Found: C, 62.59; H, 9.58.

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Supporting Information Available: Copies of NMR spectra (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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