Preparation of Spirocyclic Cyclopropyl Ketones through Condensation of Epoxides with β-Keto Phosphonates

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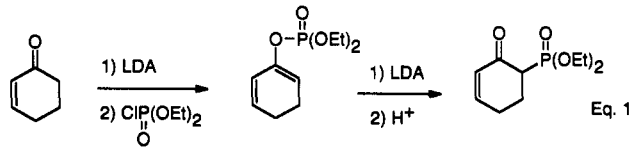
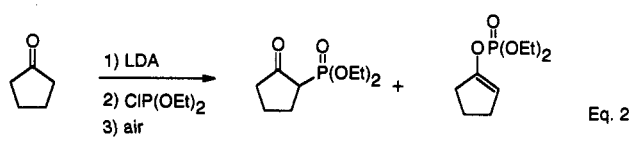
The β-keto phosphonate derivatives of several cyclic ketones have been shown to undergo condensation with epoxides upon treatment with base, affording spirocyclic cyclopropyl ketones. Moderate to reasonable yields were obtained under sealed tube conditions with ethylene oxide, propylene oxide, and styrene oxide, and the substituted epoxides gave a single diastereomer in each case. The process can be viewed as an example of regiospecific geminal dialkylation, and cleavage of the cyclopropyl ring allows access to additional α,α-dialkylated ketones.

Historically, synthesis of β-keto phosphonate derivatives of cyclic ketones has been difficult because traditional methods based on nucleophilic phosphorus reagents, such as the Arbuzov reaction, often fail.[1] Within the last few years, however, we have developed several methods for synthesis of β-keto phosphonates[2,3] and α-phosphono esters[3,4] and lactones[4] that are based on the use of electrophilic phosphorus reagents. For example, the dialkyl vinyl phosphate derivatives of 5- and 6-membered ring ketones rearrange to the corresponding β-keto phosphonates upon treatment with LDA (eq 1),[2] and the



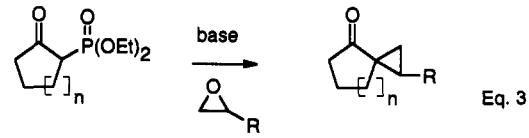
Eq. 1

reaction of ketone enolates with dialkyl phosphorochloridites, followed by air oxidation, also leads to β-keto phosphonates (eq 2).[3] Together, these methods make phosphonate derivatives of cyclic ketones readily available. During studies on the reactivity of these newly accessible compounds, we turned our attention to their reactions with epoxides.



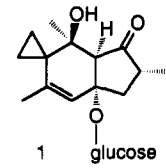
Eq. 2

Since the original report of phosphonate/epoxide condensations,[5] the literature contains occasional reference to reactions between phosphonates and epoxides yielding cyclopropyl compounds.[6] Most of these previous reports employed α-phosphono esters rather than phosphono ketones, and we have found no examples where this strategy has been employed to prepare spirocyclic ketones as shown in eq 3.



Eq. 3

In addition to the rather substantial interest in spirocyclic cyclopropyl compounds themselves,[6,7] this transformation can be viewed as a regiospecific geminal dialkylation of a ketone, an operation that is sometimes troublesome. Furthermore, spirocyclic cyclopropanes are features of some natural products, including such intriguing compounds as the braken fern carcinogen ptaquiloside (1).[8] For these reasons, an exploration of the reaction of



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epoxides with phosphonate derivatives of cyclic ketones appeared justified. In this paper we report preparation of a variety of spirocyclic cyclopropyl ketones based on condensation of β-keto phosphonates with epoxides.

As shown in Table I, these studies began with ethylene oxide as the epoxide component and the β-keto phosphonate derivatives of several different cyclic ketones. After a brief survey of base (NaH, LDA, and amines such as DBU), solvent (benzene, THF, DME, glyme), and temperature, we found that NaH in benzene gave generally reasonable yields of the desired spirocyclic cyclopropyl compounds. High reaction temperatures appeared to be required and, to minimize loss of this volatile epoxide, sealed tube conditions were routinely employed. Under these conditions the reaction is generally clean, with unreacted phosphonate the only compound accompanying

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(6) Tomoskozi, I. *Tetrahedron* **1966**, *22*, 179. Izydore, R. A.; Ghirardelli, R. G. *J. Org. Chem.* **1973**, *38*, 1790. Petter, R. C. *Tetrahedron Lett.* **1989**, *30*, 399. Petter, R. C.; Banerjee, S.; Englard, S. *J. Org. Chem.* **1990**, *55*, 3088. Fitzsimmons, B. J.; Fraser-Reid, B. *Tetrahedron* **1984**, *40*, 1279.
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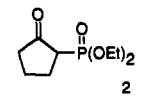
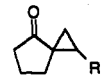
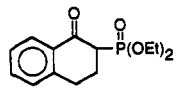
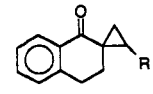
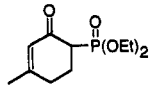
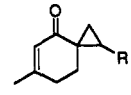
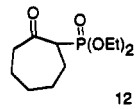
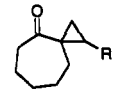
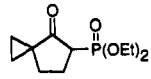
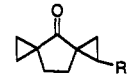
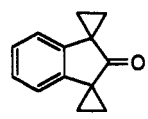
Table I. Synthesis of Spirocyclic Cyclopropyl Ketones

phosphonate	product	yield (%)
 2		3 R = H 40 4 R = CH_3 34 5 R = C_6H_5 50
 6		7 R = H 62 8 R = CH_3 76
 9		10 R = H 48 11 R = CH_3 44
 12		13 R = H 50 14 R = CH_3 56
 15		16 R = H 75 17 R = CH_3 51 18 R = C_6H_5 71

the product in any significant amount. In some cases the product itself is volatile, and low isolated yields can reflect significant handling losses.

Of special interest is the reaction sequence leading to compounds **16–18**. After preparation of the spirocyclic ketone **3**, the phosphonate **15** was prepared by a vinyl phosphate/β-keto phosphonate rearrangement (cf. eq 1)[2] and then treated with ethylene oxide and base under the conditions shown. The tricyclic compound **16** was obtained in good yield, with no apparent decomposition of the first cyclopropyl system during introduction of the second. This overall sequence appears to be a convenient route to compounds such as **19**, which have been prepared in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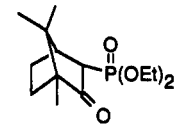
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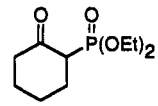
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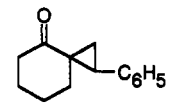
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connection with radical clock studies of reaction mechanisms.[9]

The condensation failed with the phosphonate derivative of camphor (**20**). Under standard conditions, only unreacted phosphonate was recovered. The reasons for this lack of reactivity are not yet clear, but may derive from hindered approach to the phosphonate anion and the rigidity of the bicyclic skeleton.

(9) Lemieux, R. P.; Beak, P. *J. Org. Chem.* **1990**, *55*, 5454. Gallagher, D. J.; Garrett, C. G.; Lemieux, R. P.; Beak, P. *J. Org. Chem.* **1991**, *56*, 853.

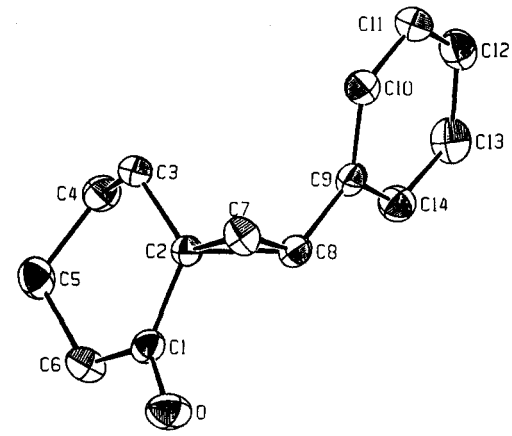
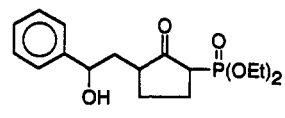


Figure 1. ORTEP drawing of compound **22**. Hydrogens are omitted for clarity.

We also have tested this reaction with substituted epoxides such as propylene oxide and styrene oxide. In some cases, the isolated yields were lower than those for the analogous ethylene oxide condensations while in others they were comparable. By definition, condensation with a monosubstituted epoxide results in a product containing two stereogenic centers, and such reactions might give mixtures of diastereomers. However, only one diastereomer was detected in each case based on ^1H NMR spectroscopy. If this condensation were under thermodynamic control, it would be reasonable to find a trans relationship between the carbonyl and alkyl substituents of the cyclopropyl system, but a spectroscopic confirmation of stereochemistry is complicated by the intervening quaternary center. Even though the ^1H resonances are generally resolved, we were unable to make a definitive assignment based on NOE experiments. Fortunately, the condensation of phosphonate **21** and styrene oxide gave a crystalline product **22**. A single-crystal diffraction analysis determined that the phenyl substituent is positioned in a trans orientation with respect to the carbonyl group, as shown in the ORTEP drawing of Figure 1. On this basis, assignment of a corresponding trans relationship to the other unsymmetrical cyclopropanes may be justified.

Although the reaction was successful with all the combinations of epoxides and phosphonates shown in Table I, the modest yields obtained in some cases are frustrating. To better define competing reactions, special care was taken to study the minor byproducts from reaction of phosphonate **2** and styrene oxide. Direct analysis of the reaction mixture by ^{31}P NMR indicated trace amounts of several phosphonate-containing byproducts in addition to some unreacted β-keto phosphonate **2**. Purification of the reaction mixture by column chromatography gave two minor products, identified as the diastereomeric phosphonates **23** based on spectroscopic data. These byprod-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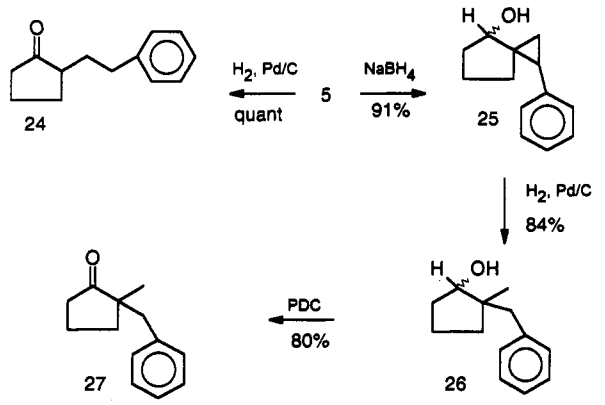
ucts may result from formation of trace amounts of a dianionic intermediate[10] followed by attack of the dianion on the epoxide. When this reaction was repeated with a

(10) Grieco, P. A.; Pogonowski, C. S. *J. Am. Chem. Soc.* **1973**, *95*, 3071.

slight deficiency of base, the magnitude of this side reaction was reduced.

Finally, to expand the potential for conducting regiospecific geminal dialkylation via this strategy, we attempted to cleave the cyclopropyl ring system of compound **5**. Upon treatment with H_2 in the presence of Pd/C, only cleavage to the phenylethyl compound **24** was observed, as might be expected based on the studies of Schultz.[11] If the carbonyl group of compound **5** were first



reduced to the corresponding alcohols **25** and this product then subjected to catalytic hydrogenation, cyclopropyl cleavage yielding the alcohols **26** was observed instead. Finally, oxidation of these alcohols (**26**) with PDC affords the α,α-disubstituted ketone **27**. While several steps are required to convert the original cyclopropyl ketone to the α,α-dialkylated ketone, all proceed cleanly and in high yield.

These studies have shown that cyclic β-keto phosphonates do undergo condensation with epoxides under basic conditions yielding spirocyclic cyclopropyl ketones. The reaction appears to be reasonably general and can be performed in the presence of olefins. This offers substantial advantages over alternate routes such as the metal-catalyzed decomposition of diazo compounds in the presence of an exocyclic olefin,[12] the Simmons–Smith reaction with an exocyclic olefin,[13] or the electrophilic sulfur reagent developed by Ronald.[14,15] A synthetic sequence including cyclopropanation, phosphonate formation, and cyclopropanation permits the facile formation of α,α'-dicyclopropyl ketones with strict control of the regiochemistry. With this sequence, unique dicyclopropyl ketones, of possible interest in both synthetic and mechanistic studies, are readily available. In some cases, isolated yields are modest and condensations leading to minor byproducts with unexpected regiochemistry have been demonstrated. However, especially with symmetrical epoxides this condensation can be a reasonable route to spirocyclic cyclopropyl ketones and regiospecific geminal dialkylation of ketones.

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(12) Fischer, E. O. *Pure Appl. Chem.* **1970**, *24*, 407. Rappoport, Z. *The Chemistry of the Cyclopropyl Group Part 1*; Wiley and Sons: New York, 1987; pp 320–344.
(13) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* **1973**, *20*, 1. Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974. Furukawa, J.; Kwawbata, N. *Adv. Organomet. Chem.* **1974**, *12*, 83. Ryu, I.; Murai, S.; Sonoda, N. *Tetrahedron Lett.* **1977**, 4611. Dinnocenzo, J. P.; Conlon, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 2324.
(14) Ruder, S. M.; Ronald, R. C. *Tetrahedron Lett.* **1984**, *25*, 5501.
(15) Kigoshi, H.; Tanaka, H.; Hirokawa, J.; Mizuta, K.; Yamada, K. *Tetrahedron Lett.* **1992**, *33*, 6647.

Experimental Section

THF was distilled from sodium/benzophenone and benzene was distilled from CaH_2, both immediately prior to use. DMF was distilled from P_2O_5 in vacuo and stored over 3-Å molecular sieves. All reactions in these solvents were conducted under a positive pressure of an inert gas or in sealed tubes. Oil-free NaH was prepared by washing mineral oil dispersions three times with pentane. The phrase "standard workup" refers to quenching with H_2O, extracting with ether (three times), washing with brine, and drying over $MgSO_4$. Column chromatography was done on Merck grade 62A silica gel (100–200 mesh), while radial chromatography was performed with a Chromatotron apparatus and Merck PF254 silica gel with $CaSO_4$·0.5H_2O. NMR spectra were recorded at 300 MHz for ^1H and 75 MHz for ^{13}C unless noted otherwise, with $CDCl_3$ as solvent; ^{31}P chemical shifts are reported in ppm relative to 85% H_3PO_4 (external standard). Low-resolution electron impact (EI) mass spectra were obtained at 70 eV; only selected ions are reported here. Microanalyses were conducted at Atlantic Microlabs, Norcross, GA.

Spiro[2.4]heptan-4-one (3). 2-(Diethoxyphosphinyl)cyclopentanone (**2**, 2.09 g, 9.5 mmol) was added dropwise to oil-free NaH (80%, 330 mg, 11 mmol) in a 25-mL screw-top flask at 0 °C, the flask was allowed to warm to rt, and stirring was continued for 1 h. The flask was then cooled to 0 °C, and ethylene oxide (1.5 mL, 30 mmol) was added via cannula. After the flask was sealed, it was heated at 125 °C for 6 h. Standard workup, concentration at atmospheric pressure, and bulb to bulb distillation (oven temp of 40 °C, 4.6 mmHg) gave 416 mg (40%) of compound **3**[16] as a colorless oil: ^1H NMR δ 2.34 (m, 2H), 2.03 (m, 4H), 1.14 (dd, J = 6.9, 3.5 Hz, 2H), 0.85 (dd, J = 6.9, 3.5 Hz, 2H); ^{13}C NMR δ 219.6, 38.9, 31.9, 29.4, 20.9, 17.7.

α-Tetralone 8. General Procedure for Epoxide Condensations. A 50-mL screw-top round-bottom flask was charged with oil-free NaH (0.36 g, 12.0 mmol) and anhydrous benzene (25 mL). Phosphonate **6** (3.05 g, 10.3 mmol) in benzene (5 mL) was added dropwise over 20 min at rt. The reaction mixture was stirred at ambient temperature for 60 min, and then propylene oxide (1.40 mL, 20.0 mmol) was added. The flask was fitted with a Teflon screw cap, and the reaction mixture was heated at 130 °C for 72 h. The solvent was removed in vacuo and the residue distilled (bulb to bulb) to yield 1.47 g (76%) of a light yellow oil >95% pure based on ^1H NMR analysis. An analytically pure sample was obtained by flash silica gel chromatography (5% EtOAc in hexanes): ^1H NMR δ 7.97 (d, J = 7.7 Hz, 1H), 7.44 (dd, J = 7.4, 7.3 Hz, 1H), 7.32 (dd, J = 7.4, 7.3 Hz, 1H), 7.26 (d, J = 7.7 Hz, 1H), 2.97 (t, J = 6.2 Hz, 2H), 2.04 (t, J = 6.2 Hz, 2H), 1.80–1.67 (m, 1H), 1.58 (dd, J = 8.9, 3.2 Hz, 1H), 1.22 (d, J = 6.6 Hz, 3H), 0.53 (dd, J = 6.6, 3.3 Hz, 1H); ^{13}C NMR δ 199.2, 143.9, 133.0, 132.9, 128.4, 127.0, 126.6, 31.6, 28.7, 26.4, 25.0, 24.1, 13.4; EIMS m/z (rel intensity) 186 (M^+, 100), 185 (75), 171 (15), 157 (19), 143 (52), 129 (20), 115 (36), 91 (14), 77 (12), 63 (6). Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.66; H, 7.63.

1-Methylspiro[2.4]heptan-4-one (4). According to the general procedure, a solution of phosphonate **2** (926 mg, 4.2 mmol) in benzene was treated with NaH (80% 135 mg, 4.5 mmol) and propylene oxide (0.6 mL, 500 mg, 8.6 mmol) for 36 h at 110 °C. After standard workup, final purification by bulb to bulb distillation gave 161 mg (34%) of compound **4**[17] as a colorless liquid: ^1H NMR δ 2.33 (t, J = 7.7 Hz, 2H), 2.05 (m, 2H), 1.98–1.84 (m, 2H), 1.36 (m, 2H), 1.10 (d, J = 5.8 Hz, 3H), 0.53 (dd, J = 6.0, 3.0 Hz, 1H); ^{13}C NMR δ 219.7, 38.8, 34.3, 27.2, 25.3, 23.2, 21.1, 14.4; EIMS m/z (rel intensity) 124 (M^+, 67), 109 (12), 95 (58), 81 (34), 67 (100), 55 (47).

1-Phenylspiro[2.4]heptan-4-one (5). According to the general procedure, phosphonate **2** (231 mg, 1.05 mmol) was treated with NaH (80%, 36 mg, 1.2 mmol) and styrene oxide (0.14 mL, 144 mg, 1.2 mmol) in benzene (5 mL). After 72 h at 130 °C, standard workup and purification by flash chromatography (silica gel; 3% EtOAc in hexanes) gave 97 mg (50%) of compound **5**[18] as a yellow oil: ^1H NMR δ 7.32–7.19 (m, 3H), 7.08 (d, J = 7.0 Hz,

(16) Crandall, J. K.; Seidewand, R. J. *J. Org. Chem.* **1970**, *35*, 697.
(17) Marr, D. H.; Stothers, J. B. *Can. J. Chem.* **1967**, *45*, 225.
(18) Takaki, K.; Takahashi, H.; Ohshiro, Y.; Agawa, T. *J. Chem. Soc., Chem. Commun.* **1977**, 675.

2H), 2.63 (dd, J = 9.0, 7.1 Hz, 1H), 2.62 (m, 1H), 2.04–1.60 (m, 6H), 1.38 (dd, J = 7.1, 4.4 Hz, 1H); ^{13}C NMR δ 218.5, 137.1, 128.3, 128.2, 128.1, 127.9, 126.7, 38.7, 37.5, 34.1, 27.2, 20.8, 20.5; EIMS m/z (rel intensity) 186 (M^+, 100), 158 (10), 141 (11), 129 (69), 115 (47), 91 (43), 77 (17), 51 (15).

α-Tetralone (7). The β-keto phosphonate **6** (770 mg, 2.73 mmol) was treated with NaH (80%, 94 mg, 3.13 mmol) and ethylene oxide in benzene for 4 h at 130 °C according to the general procedure. Standard workup and purification by flash chromatography (silica gel; 5% EtOAc in hexanes) gave 292 mg (62%) of compound **7**[19] as a white crystalline solid: mp 52–53 °C (lit.[19a] 53–54 °C); ^{1}H NMR δ 8.01 (dd, J = 7.7, 1.1 Hz, 1H), 7.46 (m, 1H), 7.34–7.25 (m, 2H), 3.00 (t, J = 6.2 Hz, 2H), 1.99 (t, J = 6.2 Hz, 2H), 1.40 (dd, J = 6.7, 3.6 Hz, 2H), 0.83 (dd, J = 6.7, 3.6 Hz, 2H); ^{13}C NMR δ 198.9, 144.3, 133.0, 128.5, 127.0, 126.5, 31.8, 28.6, 27.6, 17.6; EIMS m/z (rel intensity) 172 (M^+, 100), 171 (83), 144 (29), 128 (37), 118 (42), 90 (23), 77 (8). Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.30; H, 7.13.

6-Methylspiro[2.5]oct-5-en-4-one (10). According to the general procedure, phosphonate **9** (501 mg, 2.04 mmol) was treated with NaH (80%, 75 mg, 2.5 mmol) and ethylene oxide (1 mL, 19.8 mmol) in anhydrous benzene and then heated at 115 °C for 3 h. Standard workup and purification by flash chromatography (silica gel; 5:1 petroleum ether/ether) gave 132 mg (48%) of compound **10**[20] as a colorless oil: ^{1}H NMR δ 5.94 (br s, 1H), 2.35 (t, J = 6.2 Hz, 2H), 1.99 (br s, 3H), 1.84 (t, J = 6.2 Hz, 2H), 1.18 (dd, J = 6.7, 3.7 Hz, 2H), 0.64 (dd, J = 6.7, 3.7 Hz, 2H); ^{13}C NMR δ 199.2, 161.7, 126.7, 30.9, 29.9, 25.0, 24.3, 15.4; EIMS m/z (rel intensity) 136 (M^+, 62), 135 (63), 121 (24), 108 (22), 93 (33), 91 (49), 82 (100), 77 (36).

1,6-Dimethylspiro[2.5]oct-5-en-4-one (11). A solution of β-keto phosphonate **9** (263 mg, 1.07 mmol) in benzene (1.5 mL) was treated with oil-free NaH (80%, 39 mg, 1.3 mmol) in anhydrous benzene (6 mL). After addition of propylene oxide (0.37 mL, 5.35 mmol), the flask was heated at 130 °C for 48 h. Standard workup and purification by flash chromatography (silica gel; 5% ether in pentane) gave 71 mg (44%) of a colorless oil: ^{1}H NMR δ 5.85 (br s, 1H), 2.32 (t, J = 6.2 Hz, 2H), 1.98 (s, 3H), 1.91 (t, J = 6.2 Hz, 2H), 1.56–1.49 (m, 1H), 1.35 (dd, J = 8.9, 3.5 Hz, 1H), 1.14 (d, J = 6.3 Hz, 3H), 0.34 (dd, J = 6.3, 3.5 Hz, 1H); ^{13}C NMR δ 199.7, 160.9, 126.6, 30.1, 29.1, 25.6, 24.3, 22.9, 21.7, 13.2; EIMS m/z (rel intensity) 150 (M^+, 91), 149 (57), 135 (27), 121 (57), 107 (52), 91 (66), 82 (100), 77 (34). Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.83; H, 9.42.

Spiro[2.6]nonan-4-one (13). As described in the general procedure, β-keto phosphonate **12** (506 mg, 1.95 mmol) was treated with NaH (80%, 68 mg, 2.25 mmol) and ethylene oxide (1 mL, 19 mmol) in benzene for 72 h at 110 °C. Standard workup and purification by bulb to bulb distillation gave 148 mg (55%) of compound **13**[20] as a colorless oil: ^{1}H NMR δ 2.64 (m, 2H), 1.81–1.62 (m, 8H), 1.24 (dd, J = 6.3, 3.4 Hz, 2H), 0.66 (dd, J = 6.3, 3.4 Hz, 2H); ^{13}C NMR δ 214.7, 44.4, 34.5, 31.3, 31.0, 28.4, 24.9, 20.2; EIMS m/z (rel intensity) 138 (M^+, 66), 137 (19), 110 (58), 109 (100), 95 (33), 81 (45), 67 (68), 55 (45).

1-Methylspiro[2.6]nonan-4-one (14). β-Keto phosphonate **12** (1.54 g, 6.21 mmol) in benzene was treated with NaH (80%, 195 mg, 6.5 mmol) and propylene oxide (1.75 mL, 25 mmol). After 48 h at 115 °C, the solvent was removed by distillation at atmospheric pressure and the residue distilled (52 °C oven temperature, 0.9 Torr) by bulb to bulb distillation to give 526 mg (56%) of a colorless liquid >95% pure by ^{1}H NMR. An analytically pure sample was obtained by flash chromatography (silica gel; 10% ether in pentane): ^{1}H NMR δ 2.63 (dd, J = 7.5, 4.1 Hz, 2H), 1.74 (m, 8H), 1.53 (m, 1H), 1.39 (dd, J = 9.0, 3.0 Hz, 1H), 1.12 (d, J = 6.3 Hz, 3H), 0.35 (dd, J = 6.8, 3.0 Hz, 1H); ^{13}C NMR δ 215.0, 44.2, 35.6, 31.0, 28.8, 28.4, 27.1, 25.8, 24.9, 13.5; EIMS m/z (rel intensity) 152 (M^+, 42), 137 (6), 123 (62), 111 (19), 109 (23), 98 (39), 95 (43), 81 (40), 67 (100), 55 (59). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.79; H, 10.55.

5-(Diethoxyphosphinyl)spiro[2.4]heptan-4-one (15). A solution of 0.464 g (4.2 mmol) of cyclopentanone **3** in anhydrous THF (2 mL) was added dropwise to 4.5 mmol of LDA in THF (10 mL) at −70 °C over 15 min via syringe pump. After the solution was stirred at this temperature for 60 min, diethyl phosphorochloridate (0.65 mL, 4.5 mmol) was added, and the mixture was allowed to warm to 0 °C over 2 h. The solution was then cooled to −70 °C and transferred, via cannula, to 2.2 equiv of LDA in THF (20 mL) at −70 °C. The resulting solution was allowed to warm to ambient temperature over several hours and quenched by addition of acetic acid in ether (1 M, 4.4 equiv), and the resulting mixture was then filtered through a 1-cm pad of Florisil. Purification by flash chromatography (silica gel; 3:1 EtOAc/hexanes) gave 735 mg (71%) of a yellow oil: ^{1}H NMR δ 4.24–4.11 (m, 4H), 2.95 (ddt, J_{HP} = 25.1 Hz, J = 9.0, 6.7 Hz, 1H), 2.48–2.34 (m, 2H), 2.23 (m, 1H), 2.01 (m, 1H), 1.33 (m, 6H), 1.23 (m, 2H), 0.96 (m, 2H); ^{13}C NMR δ 211.8 (d, J_{CP} = 5.0 Hz), 62.4 (d, J_{CP} = 17.0 Hz), 47.9 (d, J_{CP} = 138 Hz), 30.4 (d, J_{CP} = 6.4 Hz), 23.3 (d, J_{CP} = 3.7 Hz), 18.8, 18.4, 16.4, 16.3; ^{31}P NMR +27.4; EIMS m/z (rel intensity) 246 (M^+, 39), 218 (38), 175 (16), 162 (16), 137 (16), 109 (70), 108 (100), 91 (35), 80 (57), 65 (19), 54 (30). Anal. Calcd for $C_{11}H_{19}O_4P$: C, 53.65; H, 7.78. Found: C, 53.64; H, 7.81.

Dispiro[2.1.2.2]octan-4-one (16). According to the general procedure, phosphonate **15** (0.267 g, 1.09 mmol) was treated with NaH (80%, 0.033 g, 1.10 mmol) and ethylene oxide (1 mL, 19.5 mmol) in anhydrous benzene. After the solution was heated at 110 °C for 12 h, standard workup and purification by flash chromatography (silica gel; 5% ether in pentane) gave 111 mg (75%) of compound **16**[20] as a colorless oil: ^{1}H NMR δ 2.10 (s, 4H), 1.17 (dd, J = 6.9, 3.7 Hz, 4H), 0.88 (dd, J = 6.9, 3.7 Hz, 4H); ^{13}C NMR δ 219.0, 30.0, 29.8, 17.4; EIMS m/z (rel intensity) 136 (M^+, 67), 135 (53), 121 (37), 91 (56), 79 (100), 54 (53), 51 (20).

1-Methyldispiro[2.1.2.2]octan-4-one (17). β-Keto phosphonate **15** (224 mg, 0.91 mmol) was treated with NaH (60%, 44 mg, 1.11 mmol) and propylene oxide (0.35 mL, 5 mmol) in benzene for 60 h at 125 °C. Standard workup and purification by flash chromatography (silica gel; 8% ether in pentane) gave 69 mg (51%) of compound **17** as a colorless oil: ^{1}H NMR δ 2.19–1.90 (m, 4H), 1.46–1.33 (m, 2H), 1.39–1.14 (m, 2H), 1.12 (d, J = 5.9 Hz, 3H), 0.90–0.82 (m, 2H), 0.54 (dd, J = 6.8, 3.2 Hz, 1H); ^{13}C NMR δ 219.1, 34.8, 29.9, 29.8, 25.1, 25.0, 22.7, 17.6, 17.1, 14.4; EIMS m/z (rel intensity) 150 (M^+, 100), 135 (52), 121 (28), 107 (37), 91 (54), 79 (92), 67 (86), 53 (45). Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.84; H, 9.38.

1-Phenyldispiro[2.1.2.2]octan-4-one (18). Phosphonate **15** (192 mg, 0.78 mmol) was treated with NaH (80%, 1.0 mmol) and styrene oxide (247 mg, 2.0 mmol) in benzene for 72 h at 110 °C. Standard workup and purification by flash chromatography (silica gel; 2%–6% EtOAc in hexanes gradient) gave 118 mg (71%) of compound **18** as a colorless oil: ^{1}H NMR δ 7.34–7.13 (m, 5H), 2.65 (dd, J = 9.0, 6.9 Hz, 1H), 1.95 (m, 3H), 1.73 (m, 2H), 1.40 (dd, J = 7.0, 4.5 Hz, 1H), 1.22 (m, 2H), 0.89 (m, 2H); ^{13}C NMR δ 217.7, 137.3, 128.8, 128.3, 126.6, 38.0, 33.7, 29.8, 29.5, 20.3, 18.2, 17.0; EIMS m/z (rel intensity) 212 (M^+, 98), 197 (111), 155 (22), 141 (27), 115 (69), 91 (100), 77 (45). Anal. Calcd for $C_{15}H_{16}O$: C, 84.86; H, 7.60. Found: C, 84.91; H, 7.63.

1-Phenylspiro[2.5]octan-4-one (22). Phosphonate **21**[2] (234 mg, 1.0 mmol) was treated with oil-free KH (35%, 137 mg, 1.2 mmol) in anhydrous benzene (7 mL). After the solution was stirred at rt for 1 h, 18-Cr-6 (316 mg, 1.2 mmol) and styrene oxide (0.11 mL, 1.0 mmol) were added. The flask was sealed with a Teflon screw top, and the solution was heated at 115 °C for 72 h. Standard workup and flash chromatography (silica gel; 10% EtOAc in hexanes) gave 110 mg (55%) of compound **22** as a colorless oil that solidified on standing. Crystallization from petroleum ether/ether gave colorless needles: mp 56–57 °C; ^{1}H NMR δ 7.34–7.23 (m, 4H), 7.19 (d, J = 6.6 Hz, 1H), 2.69 (dd, J = 8.8, 7.2 Hz, 1H), 2.47 (m, 2H), 1.88 (m, 2H), 1.81 (dd, J = 8.8, 4.4 Hz, 1H), 1.57–1.31 (m, 4H), 1.12 (dd, J = 7.2, 4.4 Hz, 1H); ^{13}C NMR δ 210.8, 136.7, 129.2, 128.1, 126.7, 39.9, 35.3, 34.3, 28.1, 24.1, 23.1, 19.5; EIMS m/z (rel intensity) 200 (M^+, 90), 199 (38), 185 (4), 171 (10), 157 (16), 129 (64), 115 (62), 104 (100), 91 (92), 77 (34). Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.90; H, 8.12.

X-ray Analysis of Compound 22. X-ray diffraction intensity data were obtained from a triangularly shaped colorless crystal fragment (0.6 × 0.6 × 0.6 mm and 0.4 mm thick) using an Enraf-Nonius CAD4 diffractometer. Graphite-monochromatized Mo

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radiation (λ(av) = 0.709 26 Å) was used at 295 K. Data collection parameters: ω–2θ scan 0.8 + 0.35 tan(θ), background 25% below and above range; peak/background counting time 2/1; scan speed 0.9–5.5°/min depending on intensity; hemisphere of data collected from 2 to 40° 2θ. Measured reflections = 4535; net average = 1035, used in refinement $>3\sigma$ = 804; agreement among equivalent reflections (on F; 1.8%). Intensities were corrected for absorption (by empirical method) max/min = 1.00/0.98 and for decay (1.0–1.08, on F). The cell dimensions [a = 8.173(4) Å, b = 12.648(6) Å, c = 21.532(9) Å, V = 2225.8(1.8) Å^3] were obtained from 25 reflections between 20 and 35° 2θ. With an empirical formula of $C_{14}H_{16}O$ and a formula weight of 200.28, Z = 8, the space group is *Pbca* and the density D = 1.195 g/cm^3.

The structure was solved using MULTAN and electron density difference maps. Full-matrix refinement was carried out anisotropically on all non-hydrogen atoms and isotropically for all hydrogen atoms. Total parameters were 200. [Refinement on hydrogen parameters was justified by finding all the atoms on a difference map, and their isotropic temperature factors ranged from 0.2 to 3.6 on refinement. The lower than normal data/parameter ratio (4:1 rather than 10:1) may be justified by the fact that the observed data were an average of four independent observations of symmetry equivalent reflections.] Least-squares refinement continued until the largest parameter shift/esd = 0.4. The SDOUW was 1.186, and final R values of R_1 = 0.047 and R_2 = 0.060 were obtained. The residual electron density on a difference map <0.3 e/Å^3.

1-Phenylspiro[2.4]heptan-4-ol (25). To a solution of cyclopentanone **5** (207 mg, 1.11 mmol) in methanol (10 mL) was added, in several portions, $NaBH_4$ (195 mg, 5.13 mmol) at 0 °C. After being stirred at ambient temperature overnight, the mixture was cooled to 0 °C and water (4 mL) was carefully added, followed by addition of 1 M HCl (1 mL). The solution was concentrated in vacuo, and 20 mL of ether was added. After the resulting layers were separated, the aqueous phase was extracted with ether (4 × 10 mL) and the combined organic extracts were washed with brine and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography (silica gel; 20% EtOAc in hexanes) gave 190 mg (91%) of **25** as a colorless oil (1:1 mixture of diastereomers): ^{1}H NMR δ 7.29–7.12 (m, 5H), 3.71 (m, 1H), 2.34 (dd, J = 9.0, 6.1 Hz, 1H), 2.03 (m, 1H), 1.79–1.51 (m, 5H), 1.36–1.24 (m, 1H), 1.10 (dd, J = 9.0, 4.7 Hz, 1H), 0.98 (m, 1H); ^{13}C NMR δ 139.9, 128.1, 128.0, 125.6, 79.8, 36.7, 35.4, 28.4, 23.8, 22.3, 18.7; EIMS m/z (rel intensity) 188 (M$^+$, 3), 170 (8), 155 (4), 141 (12), 129 (14), 107 (28), 84 (100), 77 (25), 67 (15). Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.80; H, 8.61.

2-Methyl-2-benzylcyclopentanol (26). A 50-mL round-bottom flask was charged with alcohols **25** (180 mg, 0.96 mmol), 50 mg of 5% Pd/C, and EtOAc (20 mL). A bladder filled with H_2 gas at atmospheric pressure was affixed to the reaction flask, and the contents were allowed to stir overnight at rt. The mixture was filtered through a pad of Celite and the residue purified by chromatography on silica gel (15% EtOAc in hexanes) to give 0.153 g (84%) of a 1:1 mixture of diastereomeric alcohols **26**: ^{1}H NMR δ 7.29–7.19 (m, 5H), 3.75 (m, 1H), 2.80 (d, J = 13.0 Hz, 1H), 2.64 (d, J = 13.0 Hz, 1H), 2.08 (m, 1H), 1.82–1.59 (m, 4H), 1.27 (m, 1H), 0.77 (s, 3H); ^{13}C NMR δ 140.0, 130.3, 127.8, 125.7, 80.5, 47.1, 40.7, 34.9, 33.0, 23.1, 20.0; EIMS m/z (rel intensity) 190 (M$^+$, 7), 172 (42), 157 (16), 129 (20), 115 (17), 91 (100), 65 (22).

2-Methyl-2-benzylcyclopentanone (27). PDC (1.03 g, 2.75 mmol) was added in one portion to a stirred solution of the alcohols (148 mg, 0.78 mmol) **26** in anhydrous DMF (4.5 mL). The mixture, which turned brown immediately, was allowed to stir for 4 h at which time it was poured into 35 mL of water. After 20 mL of ether was added, the phases were separated, and the aqueous phase was extracted with ether (4 × 20 mL). The combined organic extracts were washed with water (10 mL) and brine and then dried over Na_2SO_4. Removal of solvent in vacuo and purification by chromatography (silica; 5% EtOAc in hexanes) gave 0.118 g (80%) of compound **27** as a colorless oil: ^{1}H NMR δ 7.31–7.12 (m, 5H), 2.88 (d, J = 13.3 Hz, 1H), 2.61 (d, J = 13.3 Hz, 1H), 2.30 (m, 1H), 2.10–2.00 (m, 2H), 1.82–1.62 (m, 3H), 1.04 (s, 3H); ^{13}C NMR δ 223.3, 138.0, 130.2, 128.1, 126.4, 49.8, 42.6, 38.0, 34.6, 22.7, 18.6; EIMS m/z (rel intensity) 188 (M$^+$, 20), 173 (15), 117 (26), 115 (9), 91 (100), 77 (3). Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.70; H, 8.59.

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