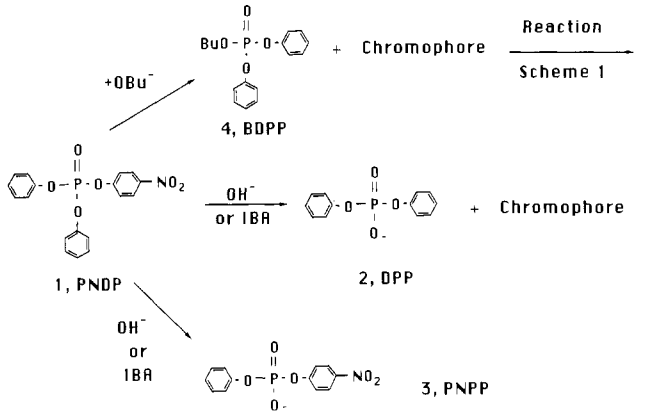
Table VI. Observed Percent Yields of BDPP Hydrolysis Products in Catalyzed CTAB Microemulsions

	DBP (+1.0 ppm)	TBP (−0.2)	BPP (−4.2)	DBPP (−5.5)	DPP (−10.0	BDPP (−11.0) substr
		CTAB pH 9				
13 days	0.0	0.0	4.0	0.0	2.3	93.6
		CTAB pH 12				
1 day	0.0	0.0	80.0	10.0	0.0	10.0
26 days[a]	6.1	0.5	88.5	3.8	0.7	0.0

[a] An uncharacterized product, 0.4%, appears at −3.2 ppm.

Scheme II



in catalyzed CTAB microemulsions are summarized in Table VI. In the presence of catalyst, BPP is the major product with a significant amount of BDPP remaining in CTAB pH 12. On the other hand, almost all of the BDPP remains in CTAB pH 9, even after 12 days. Thus, OBu^- is not an effective nucleophile at pH 9 in the CTAB microemulsion medium. In addition, IBA is probably not as effective as a catalyst for BDPP hydrolysis as it is for PNDP.

Discussion

The probable chemical transformations of PNDP are depicted in Scheme II. PNDP (1) is subject to nucleophilic attack by all three available nucleophiles, if present: OH^-, OBu^-, and IBA. The major product formed in all cases is DPP (2) which, along with the second major product, PNPP (3), are stable to any further attack. BDPP (4), formed only in the CTAB microemulsion, does undergo further hydrolysis which was already discussed.

In view of our product analysis it is clear that the rate of formation of the chromophore, *p*-nitophenoxide, is not equal to the rate of hydrolysis of PNDP. In a CTAB microemulsion the rate of chromophore formation is[6]

$$\text{rate} = [0.145[OH^-] + 1.22[IBA]][PNDP]$$

whereas, in a CTAC 1.1 microemulsion it is[10]

$$\text{rate} = [0.552[OH^-] + 9.0[IBA]][PNDP]$$

But, the rate law for hydrolysis contains two more terms:

$$k_{IBA}^{PNPP}[IBA][PNDP] + k_{OH}^{PNPP}[OH][PNDP]$$

where k_{IBA}^{PNPP} is the second-order rate constant for the IBA-catalyzed hydrolysis of PNDP to produce PNPP and k_{OH}^{PNPP} is the second-order rate constant for the OH^- hydrolysis of PNDP to produce PNPP. Assuming that yields of DPP and PNPP are proportional to the appropriate rate constants and neglecting the formation of BDPP we could make an estimate of the rate constants for the formation of PNPP. A more exact estimate of the rate of hydrolysis of phosphate esters could be gained by using a substrate such as *p*-nitrophenyl diethyl phosphate ester, for which a single product, diethyl phosphate anion, would most likely result. Nevertheless, we would find that the rate of hydrolysis of PNDP is approximately 10% to 15% higher than the rate of chromophore formation. Hence, the rate of chromophore formation remains as a good estimate of the rate of hydrolysis.

Registry No. 1, 10359-36-1; 2, 48168-03-2; 3, 113303-25-6; 4, 2752-95-6; 5, 113303-26-7; 6, 2528-36-1; 7, 126-73-8; 8, 32288-01-0; CTAB, 57-09-0; CTAC, 112-02-7; PP, 14057-64-8; *n*-butanol, 71-36-3; hexadecane, 544-76-3.

(10) Burnside, B. A., unpublished results.

A Skeletal Rearrangement of γ-(Acyloxy)-β-keto Phosphonates: Studies on the Formation of 2(3*H*)-Furanones

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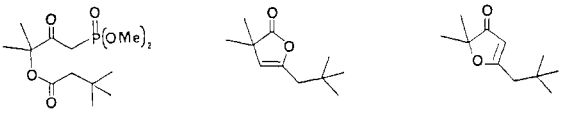
When treated with sodium hydride in dimethoxyethane, some γ-(acyloxy)-β-keto phosphonates react to give 2(3*H*)-furanones via an unexpected rearrangement which proceeds with carbon–carbon bond formation. Several possible mechanisms for this transformation have been tested through crossover experiments, rearrangement of an isotopically labeled substrate, and synthesis of a model intermediate. Results from these experiments allow elimination of several potential reaction pathways from further consideration and suggest a focus for future studies.

We recently reported the preparation of a series of γ-(acyloxy)-β-keto phosphonates for an evaluation of a potential intramolecular Horner–Wadsworth–Emmons route to the 3(2*H*)-furanone ring system.[1,2] During the course of this work, we discovered that treatment of phosphonate **1** with sodium hydride in dimethoxyethane (DME) gave the 2(3*H*)-furanone **2** as the major product, instead of the expected 3(2*H*)-furanone **3**. Because this rearrangement



1 2 3

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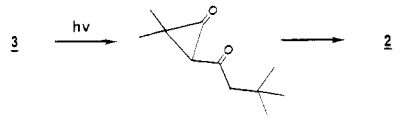
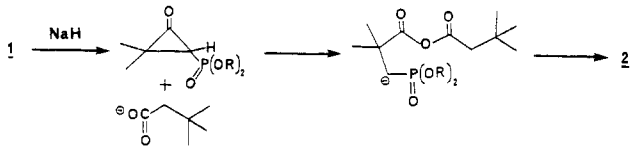
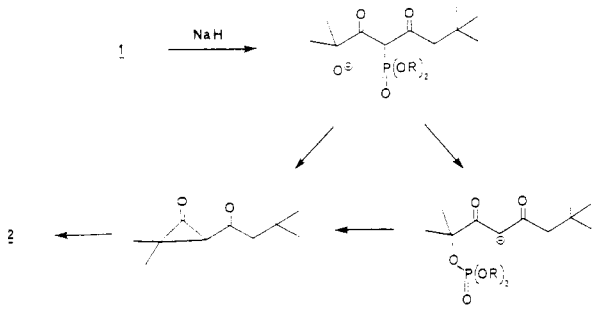
Scheme I



Scheme II



Scheme III

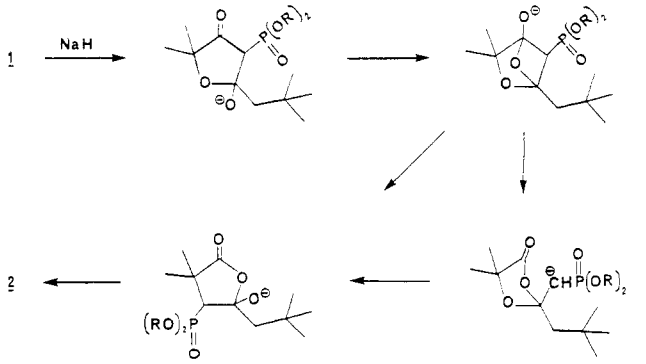


incorporates a carbon–carbon bond-forming step and results in the formation of a quaternary center, this transformation might have potential applications in natural product synthesis. For this reason, and because the mechanism of this rearrangement was not immediately obvious, this reaction was investigated further. We report here our efforts to define at least a formal reaction sequence to rationalize this transformation.

Four different reaction sequences were considered at the outset of the experimental work. Because there is a secure photochemical precedent,[3] it is conceivable that a "normal" Horner–Wadsworth–Emmons condensation to the 3-(2*H*)-furanone[1,2] is followed by an inadvertent photochemical rearrangement to the observed product (Scheme I). A second sequence, outlined in Scheme II, would include a Favorskii rearrangement,[4] with intramolecular displacement of carboxylate[5] by the stabilized γ-(acyloxy)-β-keto phosphonate anion. If the resulting cyclopropanone undergoes ring-opening via carboxylate attack, a final condensation with phosphate elimination would afford the observed product. An alternative sequence (Scheme III) would involve attack of the phosphonate-stabilized anion at the acyl carbonyl group rather than at the γ carbon to afford a transacylated intermediate. Elimination of phosphate[6] would afford an acylcyclopropanone, which could then undergo a 1,3-acyl shift[7] to yield the observed product. A variant of this sequence, where attack of the β-keto phosphonate anion on the ester carbonyl is followed by transannular addition to the ketone carbonyl and a semibenzylic type of rearrangement, is shown in Scheme IV.

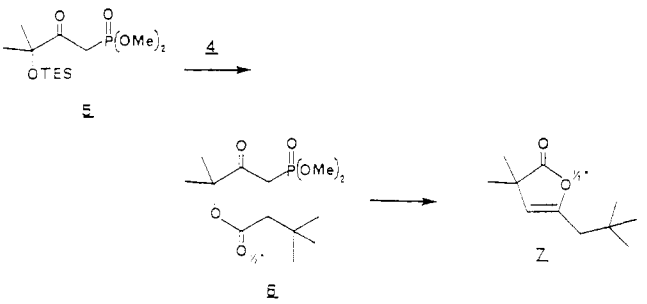
Several preliminary experiments were conducted to begin discriminating between possible reaction pathways. The viability of the sequence in Scheme I under the

Scheme IV



present conditions was called into question by an experiment that demonstrated the stability of the 3(2*H*)-furanone **3** to the reaction conditions. An attempted crossover experiment, in which sodium valerate was added to the reaction mixture, gave only the products of intramolecular reaction, but was of limited significance because the 3(2*H*)-furanone **3** became the major product under these conditions.[1,2]

For more information on the course of this rearrangement, the ^{18}O-labeled phosphonate **6** was prepared. *tert*-Butylacetyl chloride was hydrolyzed to the corresponding acid with $H_2{}^{18}O$ of approximately 98% isotopic enrichment. Upon treatment of this labeled acid with thionyl chloride, *tert*-butylacetyl chloride was obtained with 49% ^{18}O incorporation (**4**). Silyl ether **5**[1] was then esterified with the labeled acid chloride,[8] to obtain the expected phosphonate **6**. As determined by mass spectrometry, the product of this reaction sequence carried 47% ^{18}O, entirely in the acyl carbonyl oxygen.



When the isotopically labelled phosphonate **6** was treated with sodium hydride under the standard conditions, the expected rearrangement product was obtained. Mass spectral analysis of this product showed that it contained 47% ^{18}O, i.e. complete retention of label from phosphonate **6** to furanone **7**. If the 2(3*H*)-furanone product were formed by rearrangement of a 3(2*H*)-furanone intermediate, as in Scheme I, the condensation leading to the 3(2*H*) isomer would result in complete loss of label. Furthermore, if the formation of the furanone involved a Favorskii-type process with displacement of carboxylate, as shown in Scheme II, only 50% of the original label would be expected in the product. Accordingly, it would appear that processes such as these can be excluded from further consideration.

The reaction sequences described in Schemes III and IV are consistent with the observed retention of label in the rearrangement product. Either sequence also requires that the labeled oxygen reside within the ring of the product rather than in the carbonyl group. Mass spec-

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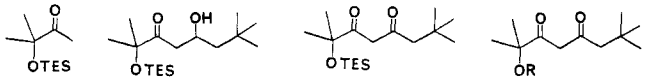
trometry was not particularly helpful for confirming the position of the isotope label. However, ^{18}O is known to exert a small isotope effect on the ^{13}C chemical shifts of attached carbons, a phenomenon that has been useful primarily in studies of biosynthesis.[9] This isotope effect was observed at *both* the carbonyl resonance and one olefinic carbon resonance (δ 152.6) in the ^{13}C NMR spectrum of compound **7**. These data provide unambiguous evidence that the labeled oxygen is within the ring, as predicted by sequences such as those shown in Schemes III and IV.

In an effort to distinguish between the latter two reaction sequences, preparation of the possible intermediate **12** was pursued. The β-diketone **11** was prepared by addition of the enolate of ketone **8** to 3,3-dimethylbutanal (**9**)[10] and Collins oxidation of the resulting aldol **10**.[11]



8 **10** **11**

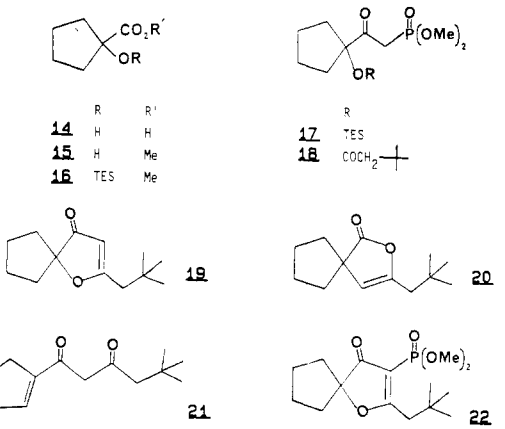
12 R = $-PO(OCH_3)_2$

13 R = $-COCF_3$

Efforts to prepare the phosphate **12** by reaction of a phosphorochloridate with this silyl ether, or the parent alcohol, have gone unrewarded, but it was possible to prepare the trifluoroacetate **13** by the reaction of trifluoroacetic anhydride with compound **11**. However, upon treatment with base, compound **13** gave only the 3(2*H*)-furanone **3**, identified by comparison with an authentic sample.[1] While these results cannot be used to rule out the specific reaction sequence summarized in Scheme III, they render it doubtful. Accordingly, a reaction sequence such as that outlined in Scheme IV appears most likely at this time.

The sequence proposed in Scheme IV may explain the delicate balance in the condensation/rearrangement ratio of γ-(acyloxy)-β-keto phosphonates (i.e. the product ratio between the 3(2*H*) and 2(3*H*) isomers), dependent upon the reaction conditions. Since phosphate elimination is presumably a syn process, if the initial attack results in a cis relationship between phosphonate and alkoxide groups, elimination to the 3(2*H*)-furanone may predominate. If the initial attack results in a trans relationship, rearrangement may occur. Our studies of this rearrangement in a related keto phosphonate address this question of balance.

The siloxy phosphonate **17** was prepared from cyclopentanone via cyanohydrin formation,[12] hydrolysis to the hydroxy acid **14**,[13] esterification (**15**),[14] silylation (**16**), and displacement with dimethyl methylphosphonate anion.[1,15] A final esterification by treatment of compound **17** with *tert*-butylacetyl chloride and $FeCl_3$ gave the phosphonate **18**. Upon treatment with NaH in DME, this phosphonate gave significant amounts of the two furanones **19** and **20** by GC analysis, but two other products were detected as well. One of these byproducts was identified as the diketone **21**, which may result from decomposition of the product furanone **19**. The other was characterized as the phosphonate **22**, presumably the result of a dehydration that may be favored by a trans relationship between the phosphorus and alkoxide oxygen of an initial adduct. With



	R	R'
14	H	H
15	H	Me
16	TES	Me

	R
17	TES
18	$COCH_2$

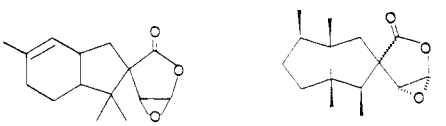
19 **20**

21 **22**

the structures of these two products established, trace amounts of analogous products from the previous rearrangement could be detected by GCMS.

With both the ^{18}O-labeled phosphonate **6** and phosphonate **18** in hand, it was possible to conduct a second, more significant crossover experiment. When a mixture of compounds **6** and **18** was treated with NaH in DME according to our standard protocol, only those products of intramolecular reaction could be detected, even when comparisons with authentic material were made by GCMS.

In conclusion, while our studies of this unusual transformation do not provide complete mechanistic detail, they provide support for one rationalization of the observed transformation, at the expense of others. Our results indicate that this reaction is an intramolecular process and that sequences involving displacement of carboxylate or the "traditional" Horner–Wadsworth–Emmons condensation can be ruled out. Furthermore, while the functionality obtained in this rearrangement might appear esoteric, a growing number of natural products contain epoxy lactone rings that might be derived from an enol lactone, including dysetherin (**23**)[16] and ptychanolide (**24**).[17] While this



23 **24**

suggests applications in the synthesis of more complex natural products, effects of other substituents on the rearrangement/condensation ratio still must be established. However, the present work should provide the basis for further mechanistic investigations, while at the same time allowing some exploitation of the synthetic potential of this reaction based on the information at hand.

Experimental Section

Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Tetrahydrofuran (THF) and DME were distilled from sodium/benzophenone immediately prior to use. In general, nonaqueous reactions were conducted under a positive pressure of an inert gas. Flash column chromatography was done on Merck grade 60 silica gel (230–400 mesh),

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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 Brucker WM-360 spectrometer, with deuteriochloroform as the 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 Kratos MS-50 instrument at the Midwest Center for Mass Spectrometry, on an AEI MS-30 instrument at the University of Minnesota Mass Spectrometry Service Laboratory, or on a VG Instruments ZAB-HF spectrometer at the University of Iowa Mass Spectrometry Facility. Microanalyses were conducted by Desert Analytics, Tucson, AZ.

***tert*-Butylacetyl Chloride-^{18}O (4).** $H_2{}^{18}O$ (0.31 mL, 17.2 mmol, 98% ^{18}O enrichment) was added to a cold (0 °C) solution of *tert*-butylacetyl chloride (2.32 g, 17.2 mmol) in anhydrous ether (5 mL) and, after being warmed to room temperature, the mixture was stirred overnight. The solvent was removed in vacuo and the residue (99% pure *tert*-butylacetic acid by GC) was carried to the next step without further purification: EIMS, m/z (rel intensity) 105 ($M^+ + 4 - 15$, 4.0), 103 ($M^+ + 2 - 15$, 11.2), 101 ($M^+ - 15$, 6.4), 57 (100).

Thionyl chloride (3.26 g, 27.4 mmol) was added over 30 min to a refluxing solution of *tert*-butylacetic acid (1.96 g, 16.6 mmol, 98% ^{18}O incorporation) in ether (10 mL). The reaction mixture was maintained at reflux for 1.6 h, when complete reaction was indicated by GC analysis. The mixture was concentrated in vacuo and the residue was distilled (bp 55 °C/80 Torr) to afford 2.20 g (98%) of pure *tert*-butylacetyl chloride-^{18}O (4, 49% ^{18}O enrichment): EIMS, m/z (rel intensity) 121 ($M^+ + 2 - 15$, 11.7), 119 ($M^+ - 15$, 8.4), 101 (98), 99 (100).

Dimethyl [3-(*tert*-Butylacetoxy)-3-methyl-2-oxobutyl]-phosphonate-^{18}O (6). *tert*-Butylacetyl chloride (4, 0.50 g, 3.7 mmol, 49% ^{18}O) was added dropwise to a stirred solution of the siloxy phosphonate 5[1] (1.25 g, 3.9 mmol) and $FeCl_3$ (0.81 g, 5.0 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C and then allowed to warm slowly to room temperature. After being stirred overnight, the resulting mixture was diluted with $CHCl_3$ (50 mL), washed with 1 M HCl (3 × 30 mL), saturated $NaHCO_3$ (3 × 30 mL), and brine (30 mL), and finally dried over $MgSO_4$. After concentration in vacuo, purification by flash chromatography (50% EtOAc, 50% hexane) afforded 1.05 g (92%) of pure *tert*-butylacetoxy phosphonate 6: ^1H NMR δ 3.79 (d, J_{HP} = 11 Hz, 6), 3.17 (d, J_{HP} = 21.2 Hz, 2), 2.21 (s, 2), 1.51 (s, 6), 1.04 (s, 9); ^{13}C NMR 200.0 (d, J_{CP} = 6.6 Hz), 171.52 (^{18}O=C), 171.48 (^{16}O=C), 83.2 (d, J_{CP} = 3.4 Hz), 52.7, 47.4, 35.4 (d, J_{CP} = 136 Hz), 30.7, 29.3, 22.9; EIMS, m/z (rel intensity) 252 ($M^+ - 58$, 0.1), 124 (100); HRMS, calcd for $C_{13}H_{24}O_5{}^{18}OP$ 309.1376 ($M^+ - 1$), found 309.1347. Anal. Calcd for $C_{13}H_{25}O_5{}^{18}OP$: C, 50.49; H, 8.15. Found: C, 50.17; H, 8.35.

3,3-Dimethyl-5-(2,2-dimethylpropyl)-2(3*H*)-furanone-^{18}O (7). The *tert*-butylacetoxy phosphonate 6 (200 mg, 0.7 mmol) in anhydrous DME (1 mL) was added dropwise to a stirred suspension of sodium hydride (32 mg, 0.8 mmol, 60% dispersion in oil, washed with 3 × 2 mL portions of DME) in the same solvent (5 mL). The mixture, which soon became a thick slush, was stirred at room temperature for 45 min and then heated at reflux overnight. The reaction was quenched by addition of 1 N HCl (10 mL) and extracted with pentane (4 × 20 mL). The organic layer was dried over $MgSO_4$. Removal of the solvents, followed by flash column chromatography (80% pentane, 20% Et_2O), gave 18 mg (15%) of the 2(3*H*)-furanone 7 and 30 mg (25%) of the 3(2*H*)-furanone 3. GCMS analysis of the products indicated complete retention of ^{18}O in the butenolide 7. For compound 7: ^1H NMR δ 5.15 (s, 1), 2.12 (s, 2), 1.30 (s, 6), 0.98 (s, 9); ^{13}C NMR 182.88 (^{18}O—C(=O)—), 182.84 (^{16}O—C(=O)—), 152.63 (^{18}O—C(=O)—), 152.60 (^{16}O—C(=C)—), 113.4, 44.4, 42.0, 30.9, 29.6, 24.6; EIMS, m/z (rel intensity) 184 ($M^+ + 2$, 4.9), 182 (M^+, 6.6), 128 (35), 126 (38), 113 (44), 111 (48), 57 (100). The ^{18}O enrichment was established from the ratios of the 128/126 and 113/111 fragments.

3-Methyl-3-(triethylsiloxy)-2-butanone (8). The triethylsilyl ether of 3-hydroxy-3-methyl-2-butanone was prepared in a manner analogous to that used for preparation of the trimethylsilyl ether:[11] ^1H NMR δ 2.21 (s, 3), 1.32 (s, 6), 0.97 (t, J = 8.0 Hz, 9), 0.66 (q, J = 8.0 Hz, 6); EIMS, m/z (rel intensity) 216 (M^+, 0.2), 115 (100). Anal. Calcd for $C_{11}H_{24}O_2Si$: C, 61.06; H, 11.18. Found: C, 60.76; H, 11.18.

2,7,7-Trimethyl-5-hydroxy-2-(triethylsiloxy)-3-octanone (10). The triethylsilyl ether 8 (180 mg, 0.8 mmol) was added to a solution of LDA (0.9 mmol) at −78 °C, and the resulting solution was stirred for 30 min while warming from −80 °C to −65 °C. The reaction mixture was cooled to −80 °C again, and the aldehyde 9[10] (100 mg, 1.0 mmol) was added via syringe. The mixture was stirred at −80 °C for 15 min and then quenched with aqueous NH_4Cl (20 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 25 mL) and the combined organic extracts were dried over $MgSO_4$. After concentration in vacuo, purification of the residue by column chromatography (90% $CHCl_3$, 10% EtOAc) afforded 195 mg (74%) of the hydroxy ketone 10: ^1H NMR δ 4.18–4.13 (m, 1), 3.02 (br s, 1), 2.81 (dd, J = 18.5, 3.6 Hz, 1), 2.79 (dd, J = 18.5, 8.4 Hz, 1), 1.50 (dd, J = 14.4, 8.5 Hz, 1), 1.33 (s, 3), 1.32 (s, 3), 1.23 (dd, J = 14.4, 2.8 Hz, 1), 0.97 (s, 9), 0.97 (t, J = 7.9 Hz, 9), 0.63 (q, J = 7.8 Hz, 6); ^{13}C NMR 217.1, 79.8, 65.5, 50.1, 44.8, 30.3, 30.1, 27.1, 26.9, 7.0, 6.6; EIMS, m/z (rel intensity) 283 ($M^+ - 33$, 0.1), 187 (43), 115 (100); HRMS, calcd for $C_9H_{19}O_2Si$ 187.1154 ($M^+ - C_8H_{17}O$), found 187.1150.

2,7,7-Trimethyl-2-(triethylsiloxy)-3,5-octanedione (11). The hydroxy ketone 10 (600 mg, 1.9 mmol) was added to a slurry of Collins reagent (10 equiv) in anhydrous CH_2Cl_2 (35 mL) and stirring was continued until the reaction was complete as indicated by GC analysis (2 h). The reaction mixture was quenched by addition of 1 N NaOH, the aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL), and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvents in vacuo, purification of the residue by flash column chromatography (98% hexane, 2% EtOAc) afforded 423 mg (73%) of the 1,3-diketone 11: ^1H NMR δ 5.98 (s, 1), 2.15 (s, 2), 1.39 (s, 6), 1.05 (s, 9), 0.97 (t, J = 8.0 Hz, 9), 0.63 (q, J = 8.0 Hz, 6); ^{13}C NMR 202.9, 189.6, 96.7, 51.4, 31.7, 29.9, 29.6, 28.1, 7.0, 6.7; EIMS, m/z (rel intensity) 285 ($M^+ - 29$, 3.2), 99 (100), 57 (93); HRMS, calcd for $C_{15}H_{29}O_3Si$ 285.1885, found 285.1884. Anal. Calcd for $C_{17}H_{34}O_3Si$: C, 64.92; H, 10.90. Found: C, 65.10; H, 10.97.

2,7,7-Trimethyl-2-(trifluoroacetoxy)-3,5-octanedione (13). Ferric chloride (20 mg) was added to a cold (0 °C) solution of the 1,3-diketone 11 (130 mg, 0.4 mmol) and trifluoroacetic anhydride (250 mg, 1.2 mmol) in anhydrous hexane (10 mL), and the resulting mixture was allowed to warm slowly to room temperature overnight. After the reaction mixture was quenched by addition of aqueous NH_4Cl (5 mL), the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$. The solvents were removed in vacuo to give the trifluoroacetate 13 as an unstable oil: EIMS, m/z (rel intensity) 278 ($M^+ - 18$, 1), 263 (2), 222 (26), 207 (40), 153 (23), 121 (43), 69 (100), 57 (54), 41 (89).

Reaction of 2,7,7-Trimethyl-2-(trifluoroacetoxy)-3,5-octanedione with Sodium Hydroxide. The trifluoroacetoxy diketone 13 (40 mg) in THF (1 mL) was added to 5 N NaOH (5 mL), and the resulting solution was stirred for 1 h at room temperature. The mixture was extracted with pentane and analyzed by GCMS. The single reaction product had a retention time and mass spectrum identical with those of the 3(2*H*)-furanone 3.

1-Hydroxycyclopentane-1-carboxylic Acid (14). Cyclopentanone (42 mL, 480 mmol) was converted to 1-hydroxycyclopentane-1-sulfonic acid[12] by reaction with sodium metabisulfite (90 g, 480 mmol). The resulting product (73.6 g, 92%) was suspended in water (50 mL), and aqueous potassium cyanide (28.8 g, 440 mmol in 20 mL of H_2O) was added slowly. After 1 h at room temperature, the cyanohydrin[12] was obtained as a yellow oil (36.9 g, 75%) which darkened upon standing. The freshly prepared cyanohydrin (36.9 g, 332 mmol) was carefully combined with concentrated hydrochloric acid (65 mL) in an efficient fume hood. The mixture was heated at reflux for 2.5 h and then allowed to cool, first to room temperature and then with an ice bath, causing the hydroxy acid to crystallize. After filtration, the hydroxy acid was dissolved in ether and this solution was combined with ether extracts of the mother liquor. After the ether solution was dried over $MgSO_4$, evaporation of the solvent gave the crude hydroxy acid as a yellow solid. After trituration with cold pentane, pure 1-hydroxycyclopentane-1-carboxylic acid (14)

was obtained (21.3 g, 49% from the cyanohydrin; 34% overall yield from cyclopentanone): mp 103–103.5 °C (lit.[13] mp 103.5–104.5 °C); ^{1}H NMR δ 7.66 (br s, 2), 1.81 (br s, 8).

Methyl 1-Hydroxycyclopentane-1-carboxylate (15). Hydroxy acid **14** (5.00 g, 38 mmol) was dissolved in methanol (35 mL) containing 5 drops of sulfuric acid. The mixture was stirred at room temperature until complete conversion to the ester was indicated by GC analysis. Following concentration in vacuo, the residual oil was dissolved in 100 mL of ether and the ethereal solution was washed with cold $NaHCO_3$ solution (15 mL) and water (10 mL). After the organic layer was dried over $MgSO_4$, concentration in vacuo gave 5.02 g (92%) of the methyl ester **15**[14] as a pale yellow oil: ^{1}H NMR δ 3.40 (s, 3), 2.00–1.50 (m, 8); ^{13}C NMR 177.3, 81.7, 52.0, 39.3, 24.5; EIMS, *m/z* (rel intensity) 129 (M^+ – 15, 0.1), 85 (100), 67 (48).

Dimethyl [2-Oxo-2-[1-[(triethylsilyl)oxy]cyclopentyl]-ethyl]phosphonate (17). The hydroxy ester **15** (3.2 g, 22 mmol) in anhydrous THF (20 mL) was added slowly to a solution of LDA (22 mmol) in anhydrous THF (50 mL) at –60 °C, and the mixture was stirred for 10 min. A mixture of triethylsilyl chloride (4.3 g, 28.6 mmol, 1.3 equiv) and anhydrous triethylamine (3 mL) was added all at once to the stirred solution. The resulting mixture was allowed to warm to room temperature overnight and then poured into ice water. The aqueous layer was acidified with 1 N HCl, ether was added, the phases were separated, and the aqueous layer was extracted with several additional portions of ether. The combined organic extracts were dried over $MgSO_4$, and the solvents were evaporated to give a pale yellow oil (**16**) which was utilized without further purification: EIMS, *m/z* (rel intensity) 229 (M^+ – 29, 65), 201 (67), 117 (100), 115 (13), 89 (38), 59 (22).

Dimethyl methylphosphonate (11.5 g, 93 mmol, ca 4.2 equiv) was added, neat and dropwise, to a solution of LDA (93 mmol) in THF (100 mL) at –80 °C. The mixture was stirred for 1 h at –80° to –90 °C and then was allowed to warm to –60 °C. The resulting phosphonate anion was transferred (Teflon and stainless steel cannula) to a solution of triethylsilyl ether **16** in anhydrous THF (100 mL), as prepared above. After the mixture was stirred for 1 h at –60 °C to –80 °C, the reaction was quenched by addition of 1 M acetic acid in ether (100 mL). The resulting thick slurry was stirred for 30 min and then filtered through a pad of Florisil. The filtrate, combined with repeated washings of the pad with ether and ethyl acetate, was concentrated in vacuo to give a yellow oil. Final purification by column chromatography (EtOAc/hexane gradient) provided 4.38 g (57% overall) of phosphonate **17** as a pale yellow oil: ^{1}H NMR δ 3.80 (d, J_{HP} = 11.2 Hz, 6), 3.34 (d, J_{HP} = 20.5 Hz, 2), 1.90–1.60 (m, 8), 0.95 (t, *J* = 7.9 Hz, 9), 0.62 (q, *J* = 7.9 Hz, 6); ^{31}P NMR +24.7; EIMS, *m/z* (rel intensity) 321 (M^+ – 29, 47), 199 (100), 115 (60), 109 (32), 87 (41); HRMS, calcd for $C_{13}H_{26}O_5PSi$ 321.1287 ($M^+ - C_2H_5$), found 321.1276. Anal. Calcd for $C_{15}H_{31}O_5PSi$: C, 51.41; H, 8.92. Found: C, 51.21; H, 9.08.

1-[(Dimethoxyphosphinyl)acetyl]cyclopentyl 3,3-Dimethylbutanoate (18). A solution of keto phosphonate **17** (750 mg, 2.1 mmol) in 8 mL of hexanes (stored over 4A sieves) was cooled to 0 °C, $FeCl_3$ (448 mg, 2.8 mmol) was added, and the mixture was stirred for 10 min. A solution of *tert*-butylacetyl chloride (0.39 mL, 2.8 mmol) in hexanes (7 mL) was added dropwise to the cooled suspension, and the mixture was allowed to warm to room temperature overnight. After addition of dichloromethane (20 mL), the organic solution was washed with successive portions of 1 N HCl, H_2O, saturated $NaHCO_3$, and H_2O. The organic solution was dried over $MgSO_4$ and then concentrated in vacuo to give a yellow-brown oil. This residual oil was purified by column chromatography (EtOAc/hexane gradient) to afford 536 mg (76%) of pure γ-(acyloxy)-β-keto phosphonate **18**: ^{1}H NMR δ 3.77 (d, J_{HP} = 11.2 Hz, 6), 3.09 (d, J_{HP} = 21.1 Hz, 2), 2.21 (s, 2), 1.90–1.82 (m, 4), 1.80–1.65 (m, 4), 1.02 (s, 9); ^{13}C NMR 199.2, 172.3, 93.9, 53.0 (d, J_{CP} = 6.5 Hz), 47.6, 35.3, 35.0 (d, J_{CP} = 137 Hz), 31.0, 29.6, 24.7; ^{31}P NMR +23.3; EIMS, *m/z* (rel intensity) 222 (M^+ – 112, 6), 151 (47), 124 (100), 109 (46), 57 (56); HRMS, calcd for $C_9H_{16}O_4P$ ($M^+ - C_6H_{11}O_2$) 219.0786, found 219.0787. Anal. Calcd for $C_{15}H_{27}O_6P$: C, 53.89; H, 8.14. Found: C, 53.79; H, 8.37.

Reaction of Phosphonate 18 with Sodium Hydride. Sodium hydride (33 mg of a 60% oil dispersion, 0.8 mmol) was washed with anhydrous DME (3 × 2 mL) and then suspended in 5 mL of the same solvent. The γ-(acyloxy)-β-keto phosphonate **18** (250 mg, 0.75 mmol) was dissolved in 5 mL of anhydrous DME and added over a 5-min period to the stirred suspension. After 5 min at room temperature, the mixture was heated slowly and maintained at reflux overnight. After dilution with dichloromethane, the reaction mixture was washed with 1 N NaOH, water, and brine and then dried over $MgSO_4$. Concentration in vacuo gave 161 mg of a yellow oil containing four major products, along with a small amount of starting material (by GC analysis). The product mixture was subjected to column chromatography (90% pentane, 10% ether), and compounds **19** and **22** were isolated. The two other major components, compounds **20** and **21**, coeluted during column chromatography, but were separated by reversed-phase HPLC (C_{18}, 90% methanol, 10% water).

2-(2,2-Dimethylpropyl)-1-oxaspiro[4.4]non-2-en-4-one (19): ^{1}H NMR δ 5.35 (s, 1), 2.34 (s, 2), 2.00–1.70 (m, 8), 0.99 (s, 9); ^{13}C NMR 206.4, 190.3, 104.5, 98.5, 44.7, 37.0, 31.8, 29.8, 25.5; EIMS, *m/z* (rel intensity) 208 (M^+, 22), 167 (100), 111 (51), 57 (44); HRMS, calcd for $C_{13}H_{20}O_2$ 208.1463 (M^+), found 208.1464.

3-(2,2-Dimethylpropyl)-2-oxaspiro[4.4]non-3-en-1-one (20): ^{1}H NMR δ 5.16 (s, 1), 2.14 (s, 2), 2.05–1.90 (m, 4), 1.80–1.71 (m, 4), 0.95 (s, 9); ^{13}C NMR 183.7, 152.6, 112.2, 53.7, 42.1, 37.5, 30.9, 29.6, 25.9; EIMS, *m/z* (rel intensity) 208 (M^+, 15), 152 (100), 151 (57), 124 (23), 109 (72), 57 (69); HRMS, calcd for $C_{13}H_{20}O_2$ 208.1463 (M^+), found 208.1464.

1-(1-Cyclopenten-1-yl)-5,5-dimethyl-1,3-hexanedione (21): (enol form) ^{1}H NMR δ 15.21 (br s, 1), 6.72 (br s, 1), 5.55 (s, 1), 2.52 (t, *J* = 7.7 Hz, 4), 2.19 (s, 2), 1.96 (m, *J* = 7.4 Hz, 2), 1.01 (s, 9); ^{13}C NMR 196.7, 179.0, 141.0, 140.3, 99.6, 53.4, 33.7, 31.8, 30.8, 30.0, 23.1; EIMS, *m/z* (rel intensity) 208 (M^+, 29), 180 (28), 152 (28), 137 (100), 124 (72), 109 (20), 95 (68), 69 (42), 57 (46); HRMS, calcd for $C_{13}H_{20}O_2$ 208.1463 (M^+), found 208.1464.

Dimethyl [2-(2,2-dimethylpropyl)-4-oxo-1-oxaspiro[4.4]-non-2-en-3-yl]phosphonate (22): ^{1}H NMR δ 3.72 (d, J_{HP} = 11.5 Hz, 6), 2.88 (d, J_{HP} = 0.83 Hz, 2), 2.10–1.80 (m, 8), 1.04 (s, 9); ^{13}C NMR 202.6 (d, J_{CP} = 5.8 Hz), 198.0 (d, J_{CP} = 27.5 Hz), 103.5 (d, J_{CP} = 211.9 Hz), 99.0 (d, J_{CP} = 11.7 Hz), 52.6 (d, J_{CP} = 5.8 Hz), 42.8, 37.1, 32.7, 30.1, 25.4; ^{31}P NMR +14.3; EIMS, *m/z* (rel intensity) 316 (M^+, 7), 301 (57), 275 (36), 219 (100); HRMS, calcd for $C_{15}H_{25}O_5P$ 316.1439 (M^+), found 316.1447. Anal. Calcd for $C_{15}H_{25}O_5P$: C, 56.95; H, 7.97. Found: C, 56.85; H, 8.00.

Attempted Crossover Experiment with 6 and 18. A solution of compound **6** (130 mg, 0.4 mmol) and compound **18** (140 mg, 0.4 mmol) in DME (5 mL) was added to a stirred suspension of NaH in DME (2 mL), and the resulting mixture was heated at reflux for 2 h. Analysis of the reaction mixture by GCMS indicated that the only products were those of intramolecular reaction, compounds **3** and **7** and compounds **19** and **20**.

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