Stereocontrol in Horner-Wadsworth-Emmons Condensations of α-Phosphono Lactones with Aldehydes: A Synthesis of Integerrinecic Acid and Senecic Acid Lactones

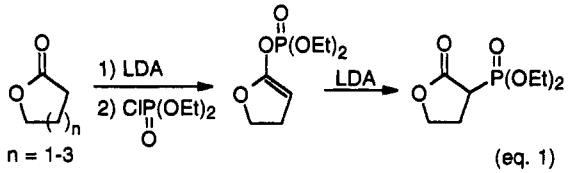
Koo Lee, John A. Jackson, and David F. Wiemer*

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

Received May 10, 1993•

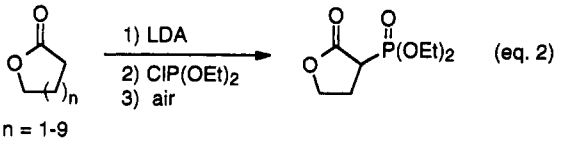
The Horner-Wadsworth-Emmons condensations of α-phosphono lactones were investigated under a variety of conditions. Upon treatment with KHMDS and 18-crown-6 in THF, condensations of the five-membered ring phosphono lactones **7a** and **8** with propionaldehyde afforded the *E* olefins cleanly. In contrast, these phosphonates gave predominantly the *Z* olefins upon treatment with propionaldehyde, K_2CO_3, and 18-crown-6 in THF. A similar, though somewhat less-pronounced trend was observed with the six-membered ring phosphono lactone **9a**. However, in its condensation with acetaldehyde the more functionalized phosphono lactone **4** gave the best *E* selectivity (ca. 9:1) when DBU/CH_3CN was used, providing the methyl ester of integerrinecic acid lactone (**5**) in 77% isolated yield. When K_2CO_3/18-crown-6/toluene was employed in a parallel reaction, only slight selectivity for the *Z* isomer was observed, but the methyl ester of senecic acid lactone (**6**) still was obtained in 43-46% yield from the product mixture.

Over the past few years, we have developed several new methods for synthesis of β-keto phosphonates,[1] a class of intermediates commonly used as precursors to α,β-unsaturated carbonyl compounds through the Horner-Wadsworth-Emmons (HWE) condensation. We have focused on methods that employ electrophilic phosphorus reagents, based on the premise that these approaches would be inherently complementary to traditional syntheses such as the Arbuzov reaction[2] and the acylation of alkyl phosphonate anions.[3] Two of our procedures have proven to be amenable to carboxylic acid derivatives, allowing facile preparation of α-phosphono esters and lactones via the corresponding enolates. One of these routes is based upon a 1,3-phosphorus migration in dialkyl vinyl phosphates (eq 1).[4] The other method employs the reaction



(eq. 1)

of an enolate with diethyl phosphorochloridite followed by air oxidation to obtain the desired α-phosphono compounds (eq 2).[1e,5] During the course of studies on applications of these readily accessible phosphonates,[6] we



(eq. 2)

turned our attention to HWE condensations of some α-phosphono lactones along with the potential application of this approach in the synthesis of natural products.

While stereoselective HWE condensations of α-phosphono esters have been studied extensively,[7] there are only a few reports on analogous condensations of α-phosphono lactones[8] despite the fact that α-alkylidene lactones are common features in natural products. Ethylidene lactones with six-membered rings have been key intermediates in syntheses of pyrrolizidine alkaloids such as usaramin (**1**)[9] and integerrimine (**2**).[9b,10] At this time a specific synthesis of the olefinic stereoisomer of compound **2**, the alkaloid senicionine (**3**), has not been reported. Accordingly, preparation of a functionalized phosphono lactone such as compound **4** would be attractive, particularly if it would allow stereoselective HWE condensations to both the *E*

• Abstract published in *Advance ACS Abstracts*, October 1, 1993.

(1) (a) Sampson, P.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1986**, *51*, 4342. (b) Calogeropoulou, T.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1987**, *52*, 4185. (c) Roussis, V.; Wiemer, D. F. *J. Org. Chem.* **1989**, *54*, 627. (d) Gloer, K. B.; Calogeropoulou, T.; Jackson, J. A.; Wiemer, D. F. *J. Org. Chem.* **1990**, *55*, 2842. (e) Lee, K.; Wiemer, D. F. *J. Org. Chem.* **1991**, *56*, 5556. (f) An, Y. Z.; Wiemer, D. F. *J. Org. Chem.*, **1992**, *57*, 317.

(2) (a) Arbuzov, B. A. *Pure Appl. Chem.* **1964**, *9*, 307. (b) Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415.

(3) (a) Corey, E. J.; Kwiatowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5654. (b) Coutrot, P.; Savignac, P.; Mathey, F. *Synthesis* **1978**, 36. (c) Mathey, F.; Savignac, P. *Tetrahedron* **1978**, 649. (d) Aboujaoude, E. E.; Collignon, N.; Savignac, P. *J. Organomet. Chem.* **1984**, *264*, 9.

(4) (a) Jackson, J. A.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1989**, *54*, 4750. (b) Jackson, J. A. Ph.D. Thesis, Univ. of Iowa, 1990.

(5) Phosphono lactones **7a** and **9a** were reported in a previous communication: Lee, K.; Wiemer, D. F. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1993**, *75*, 87.

(6) For example, spirocyclopropyl ketones recently were prepared through condensations of epoxides with phosphonate derivatives of cyclic ketones, cf.: Jacks, T. E.; Nibbe, H.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 4584.

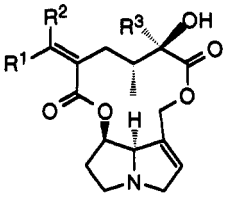
(7) Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3386. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(8) (a) Minami, T.; Niki, I.; Agawa, T. *J. Org. Chem.* **1974**, *39*, 3236. (b) Minami, T.; Kitajima, Y.; Chikugo, T. *Chem. Lett.* **1986**, 1229. (c) Falsone, G.; Wingen, U. *Tetrahedron Lett.* **1989**, *30*, 675. (d) Falsone, G.; Spur, B.; Peters, W. *Z. Naturforsch.* **1983**, *38b*, 493. (e) Herlem, D.; Kervagoret, J.; Khuong-Huu, F. *Tetrahedron Lett.* **1989**, *30*, 553. (f) Hoye, T. R.; Caruso, A. J. *J. Org. Chem.* **1981**, *46*, 1198.

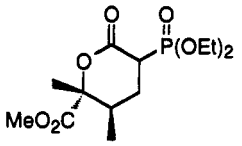
(9) (a) White, J. D.; Amedio, J. C., Jr.; Gut, S.; Jayasinghe, L. R. *J. Org. Chem.* **1989**, *54*, 4268. (b) White, J. D.; Amedio, J. C., Jr.; Gut, S.; Ohira, S.; Jayasinghe, L. R. *J. Org. Chem.* **1992**, *57*, 2270.

(10) (a) Narasaka, K.; Sakakura, T.; Uchimaru, T.; Guendin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954. (b) White, J. D.; Ohira, S. *J. Org. Chem.* **1986**, *51*, 5492. (c) White, J. D.; Jayasinghe, L. R. *Tetrahedron Lett.* **1988**, *29*, 2139. (d) Niwa, H.; Miyachi, Y.; Uosaki, Y.; Yamada, K. *Tetrahedron Lett.* **1986**, *27*, 4601. (e) Niwa, H.; Miyachi, Y.; Uosaki, Y.; Kuroda, A.; Ishiwata, H.; Yamada, K. *Tetrahedron Lett.* **1986**, *27*, 4609. (f) Narasaka, K.; Uchimaru, T. *Chem. Lett.* **1982**, 57. (g) Edwards, J. D., Jr.; Hase, T.; Hignite, C.; Matsumoto, T. *J. Org. Chem.* **1966**, *31*, 2282. (h) Kochetkov, N. K.; Vasil'ev, A. E.; Levchenko, S. N. *Zh. Obshch. Khim.* **1965**, *35*, 190. (i) Culvenor, C. C. C.; Geissman, T. A. *J. Am. Chem. Soc.* **1961**, *83*, 1647.

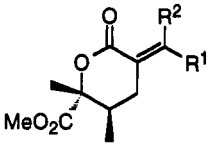
0022-3263/93/1958-5967$04.00/0



1, R^1 = H, R^2 = Me, R^3 = CH_2OH
2, R^1 = H, R^2 = R^3 = Me
3, R^1 = Me, R^2 = H, R^3 = Me



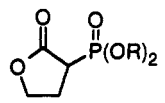
4



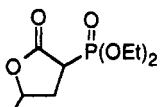
5, R^1 = Me, R^2 = H
6, R^1 = H, R^2 = Me

and *Z* olefins **5** and **6**. In this paper methods to obtain stereocontrol in the HWE condensations of some model phosphono lactones **7–9** are reported, along with synthesis of the methyl esters of integerrinecic acid lactone (**5**) and senecic acid lactone (**6**).

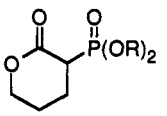
The phosphono lactones needed for this study should be available by either of the two general routes described above. Because diethyl phosphorochloridite is commercially available, preparation of phosphono lactones **7a**, **8**, and **9a** could be accomplished by straightforward preparation of the respective enolates, reaction with diethyl phosphorochloridite, and oxidation, providing these three phosphono lactones in good yield (69, 70, and 64%, respectively).[5] While the isopropyl phosphonates **7b** and **9b** presumably would be accessible via a parallel sequence, we chose to use diisopropyl phosphorochloridate instead. For this series, after treatment of the lactone enolate with diisopropyl phosphorochloridate, addition of more LDA and a standard acidic workup gave the isopropyl phosphonates **7b** and **9b** in good overall yields (67 and 72%).[4b]



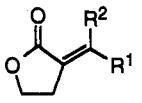
7a, R = Et
7b, R = *i*-Pr



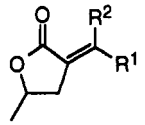
8



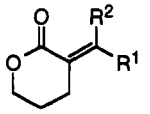
9a, R = Et
9b, R = *i*-Pr



10, R^1 = Et, R^2 = H
11, R^1 = H, R^2 = Et



12, R^1 = Et, R^2 = H
13, R^1 = H, R^2 = Et



14, R^1 = Et, R^2 = H
15, R^1 = H, R^2 = Et

As shown in Table I, the HWE experiments were begun with phosphono lactones **7a** and **7b**, propionaldehyde, and several standard base systems. The first choice of base reflected Still's conditions for *Z*-selective condensations of α-phosphono esters.[11] Treatment of phosphono lactone **7a** with potassium hexamethyldisilazide (KHMDS) in the presence of 18-crown-6 to form the phosphonate anion, followed by condensation with propionaldehyde, resulted in exclusive formation of *E*-propylidene lactone **10** (entry 1). In contrast, when phosphonate **7a** was treated with 1 equiv of potassium carbonate and 18-crown-6 in THF, followed by condensation with propionaldehyde, the *Z* propylidene lactone **11** was the major product (*E*/*Z* ratio of 1:5.6, entry 2). The *E* and *Z* products are readily distinguished by the olefinic resonances, δ 6.71 and 6.21, respectively, and integration of the ^{1}H NMR spectra was used to approximate the *E*/*Z* ratio.

Table I. Horner–Wadsworth–Emmons Condensations of α-Phosphono Lactones 7–9 with Propionaldehyde

entry	phosphonate	conditions[a]	product ratio[b] (*E*/*Z*)	% yield
1	**7a**	A	>25:1	75 (*E*, **10**)
2	**7a**	B	1:5.6	
3	**7b**	B	1:6.5	87 (*Z*, **11**)
4	**7a**	C	4:1	
5	**7b**	C	4:1	
6	**7a**	D	1:2.7	
7	**7b**	D	1:1.7	
8	**7a**	E	1:2.4	
9	**7b**	E	1:3.8	
10	**7a**	F	2.6:1	
11	**7b**	F	2.6:1	
12	**8**	A	*E* only	64 (*E*, **12**)
13	**8**	B	1:4.5	63 (*Z*, **13**)
14	**9a**	A	*E* only	58 (*E*, **14**)
15	**9a**	B	1:3.4	56 (*Z*, **15**)
16	**9b**	B	1:1.5	
17	**9a**	C	1.6:1	
18	**9b**	C	2.8:1	

[a] A = KHMDS, 18-crown-6, THF, −78 °C; B = K_2CO_3, 18-crown-6, THF, rt; C = DBU, CH_3CN, rt; D = KO-*t*Bu, THF, −78 °C; E = LDA, THF, −78 °C; F = NaH, toluene, rt. [b] Analysis by integration of ^{1}H NMR spectrum.

We also have examined condensations of the isopropyl-substituted phosphono lactone **7b** under conditions that might favor either *E*- or *Z*-olefin formation. Despite Kishi's report that use of isopropyl groups enhanced the formation of *E*-olefins from phosphono esters,[12] condensation of phosphono lactone **7b** with propionaldehyde in the presence of K_2CO_3 and 18-crown-6 produced an enhanced yield of the *Z*-olefin **11**, an improvement to 1:6.5 (entry 3). These results suggest that predictions made by comparison of phosphono lactones to phosphono esters in the HWE condensation may be questionable. Nevertheless, both the *E* and *Z* propylidene lactones could be obtained from γ-butyrolactone phosphonates, with good stereocontrol and in good isolated yields.

Masamune has reported that DBU/LiCl is a useful system in some HWE condensations of phosphono esters.[13] The present study suggests that addition of LiCl is not required with phosphono lactones. Only a moderate degree of stereoselectivity was obtained when DBU alone was used in condensations with either ethyl phosphonate **7a** or isopropyl phosphonate **7b** (entries 4, 5).

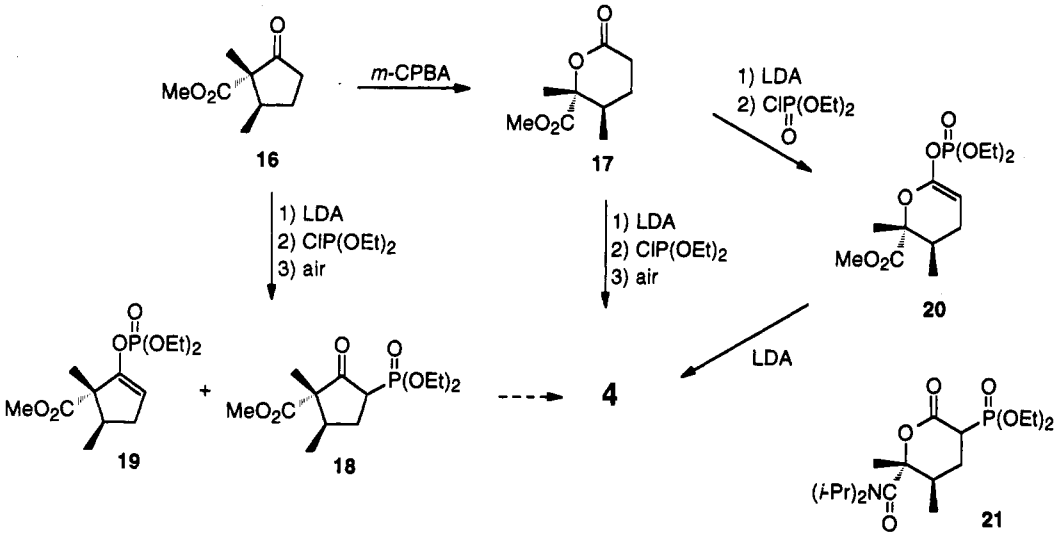
We also have explored several other standard base systems that might favor *Z* olefination of phosphono

(11) Cis selectivities were reported in HWE condensations of various aldehydes with some phosphono esters when KHMDS/18-crown-6 was employed, cf.: (a) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405. (b) Marshall, J. A.; Dehoff, B. S.; Cleary, D. C. *J. Org. Chem.* **1986**, *51*, 1735.

(12) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109.

(13) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

Scheme I



lactones **7a** and **7b**, including bases such as KO-*t*Bu, LDA, and NaH, but no improvement in stereoselectivity was observed (entries 6–11). Therefore the best conditions for both *E* and *Z* olefin formation were examined with the phosphonate derivatives of γ-valerolactone (**8**). As expected, in both cases the desired stereoselectivities were obtained with good isolated yields (entries 12, 13).

When these studies were extended to the six-membered ring phosphono lactones **9** under the conditions established for both *E*- and *Z*-selective olefinations, the trends appeared to remain constant. The use of KHMDS/18-crown-6 with phosphonate **9a** afforded exclusive formation of the *E*-olefin **14** (entry 14). Condensation of phosphono lactone **9a** with propionaldehyde under K_2CO_3/crown ether conditions produced 1:3.4 mixtures of *E* and *Z* olefins, respectively (entry 15). However, with isopropyl phosphonate **9b** a considerable drop in stereocontrol under the same conditions was noted (entry 16). It may be reasonable to assume that as the ring size of the phosphono lactone is increased, a more ester-like reactivity is developed. Finally, when DBU was used the phosphonates **9** showed markedly diminished stereoselectivities (entries 17, 18).

The necic acid lactones **5** and **6** were chosen as initial targets for this methodology, in part because both olefin isomers are well known. The requisite starting compounds, ketone **16** and lactone **17**, were prepared from 2-methyl cyclopentenone according to literature procedures.[10a] Phosphorylation of the ketone enolate with diethyl phosphorochloridite, followed by air oxidation, afforded only a small amount of β-keto phosphonate **18** (<5%), and vinyl phosphate **19** was observed as the major product. Under the same reaction conditions, lactone **17** provided the desired phosphonate **4** in somewhat better yields (up to 39%) accompanied by the vinyl phosphate **20** (Scheme I).

When the vinyl phosphate/β-keto phosphonate rearrangement was applied to lactone **17**, a much improved yield of phosphonate **4** was obtained.[4] Vinyl phosphate **20**, prepared from the lactone enolate and diethyl phosphorochloridate in 86% yield, undergoes the 1,3-phosphorus rearrangement to give the desired phosphonate product **4** in 91% yield (or 78% overall). However, the carboxylate ester in vinyl phosphate **20** was found to be somewhat unstable to LDA, giving amide **21** as a byproduct. Use of the more hindered base, LTMP, did not give a better conversion to the desired phosphonate **4**. To minimize these byproducts, short reaction times with LDA were employed before quenching the phosphonate anion by addition of acid.

Table II. Horner–Wadsworth–Emmons Condensations of α-Phosphono Lactone 4 with Acetaldehyde

entry	base	solvent	temp, °C	product ratio[a] (5/6)	% yield
1	KHMDS/18-c-6	THF	−78	2.2:1	
2	DBU	CH_3CN	rt	9:1	77 (**5**)
3	K_2CO_3/18-c-6	THF	rt	2.2:1	
4	K_2CO_3/18-c-6	THF	0	1.8:1	
5	K_2CO_3/18-c-6	benzene	rt	2.4:1	
6	K_2CO_3/18-c-6	toluene	0	1:1	45 (**5**), 43 (**6**)
7	K_2CO_3/18-c-6	toluene	−78	1:1.2	40 (**5**), 46 (**6**)

[a] Analysis by integration of ^1H NMR spectrum.

Because phosphono lactone **4** is similar to phosphonate **9a**, the same trends of stereoselectivities might be expected in HWE condensations. However, condensations of functionalized phosphono lactone **4** with acetaldehyde showed somewhat different results from preliminary HWE experiments. As shown in Table II, when the HWE reaction of phosphonate **4** and acetaldehyde was attempted using KHMDS, the product ratio was a disappointing 2.2:1 ratio of *E* and *Z* olefins **5** and **6** (entry 1). On the other hand, the highest *E* selectivity was observed when DBU was used as the base (entry 2). From this reaction, which gave a 9:1 ratio of *E* and *Z* products, the *E*-isomer **5** was easily isolated in 77% yield.

Treatment of phosphonate **4** with acetaldehyde and potassium carbonate in THF at room temperature (entry 3) favored the *E* olefin **5** in a 2.2:1 ratio of *E* and *Z* olefins unlike earlier results with the model phosphono lactones. To optimize *Z* olefination, modified reaction conditions were required. As expected, at low temperature (0 °C) in THF, the phosphonate **4** gave a slightly greater amount of the *Z* isomer, but the *E* product still predominated (entry 4). In some recent HWE condensations of phosphono esters, an excess of potassium carbonate in toluene was employed.[11a,14] Under these conditions, phosphonate **4** provided a markedly enhanced ratio for the *Z* olefin **6** (ca. 1:1), with complete reaction in 3 h at 0 °C (entry 6). Although still lower temperature (−78 °C) slightly increased the ratio for the *Z* olefin (to 1:1.2), these conditions

(14) Villieras, J.; Rambaud, M.; Kirschleeger, B. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1983**, *14*, 385.

appear to require substantially longer reaction times (24 h, entry 7). Other solvents such as benzene (entry 5) and *n*-hexane were found to be ineffective at *Z*-olefin promotion.

In summary, with the simple phosphono lactones studied, good selectivity could be obtained for either the *E*- or *Z*-propylidene lactones. Good *E*-selectivity also was obtained in preparation of the *E*-ethylidene lactone **5**, integerrinecic acid lactone. This compound was prepared from lactone **17** via the phosphono lactone **4** in 59% overall yield, a yield comparable to reported yields obtained through two-step aldol condensation/dehydration procedures (60%[10a], 50%[9b]). The *Z*-isomer **6**, senecic acid lactone, was prepared in 35% overall yield even though high *Z*-selectivity was not obtained in the Horner–Wadsworth–Emmons condensation. Thus, while ideal conditions may vary with the precise structure of the phosphono lactone, it appears to be possible to obtain either *E*- or *Z*-alkylidene products from intermediate phosphono lactones.

Experimental Section

Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. Acetonitrile and toluene were distilled from calcium hydride and stored over 3-Å molecular sieves. All reactions in these solvents were conducted under a positive pressure of an inert gas. Column chromatography was done on Merck grade 62 silica gel (60–200 mesh), while radial chromatography was performed with a Chromatotron apparatus and Merck PF254 silica gel with $CaSO_4 \cdot 0.5H_2O$. NMR spectra (^1H and ^{13}C) were recorded with $CDCl_3$ as solvent and internal standard; ^{31}P chemical shifts are reported in ppm relative to H_3PO_4 (external standard). Low-resolution electron impact (EI) mass spectra were recorded with a Hewlett-Packard 5985B instrument or a VG Instruments Trio 1 spectrometer, both operating at 70 eV; only selected ions are reported here. High-resolution mass spectra were recorded on a VG Instruments ZAB-HF spectrometer at the University of Iowa Mass Spectrometry Facility.

α-(Diethoxyphosphinyl)-γ-butyrolactone (7a). General Procedure for Preparation of α-(Diethoxyphosphinyl) Lactones. A solution of γ-butyrolactone (0.192 mL, 2.5 mmol) was added dropwise via syringe to a stirred solution of LDA [2.75 mmol, prepared in situ from diisopropylamine (0.38 mL) and *n*-BuLi (1.90 mL, 1.6 M in hexane] in diethyl ether (6 mL) at −78 °C. After 30 min, $(EtO)_2PCl$ (0.39 mL, 2.75 mmol) was added dropwise to the resulting lactone enolate, and the reaction mixture was allowed to warm to rt over 2 h. The reaction was quenched by slow addition of acetic acid in ether (1 N, 3 mL), and the mixture was filtered through a Florisil pad (60–120 mesh). After concentration in vacuo, the resulting oil was magnetically stirred in a reaction vessel open to air overnight and then purified by column chromatography (silica gel, EtOAc) to give phosphono lactone **7a** (383 mg, 69%). This compound was identical (by ^1H NMR, ^{31}P NMR) to an authentic sample prepared by rearrangement of the vinyl phosphate.[4]

α-(Diethoxyphosphinyl)-γ-valerolactone (8). According to the general procedure, γ-valerolactone (250 mg, 2.5 mmol) was treated with LDA (1.1 equiv) in ether. After addition of $(EtO)_2PCl$ (2.75 mmol) to the resulting enolate, standard workup, followed by air oxidation and purification by flash chromatography (20% hexane in EtOAc), afforded the desired phosphonate **8** (412 mg, 70%).[4,8c]

α-(Diethoxyphosphinyl)-δ-valerolactone (9a). According to the general procedure, δ-valerolactone (250 mg, 2.5 mmol) was treated with LDA (1.1 equiv) in ether. After addition of HMPA (0.48 mL, 2.75 mmol) to the resulting enolate, $(EtO)_2PCl$ (2.75 mmol) was added. Standard workup, followed by air oxidation and purification by flash chromatography (EtOAc), afforded the desired phosphonate **9a** (377 mg, 64%).[4]

α-(Diisopropoxyphosphinyl)-γ-butyrolactone (7b). General Procedure for Preparation of α-(Diisopropoxyphosphinyl) Lactones. To a solution of LDA (5.5 mmol) in THF (15 mL) at −78 °C was added dropwise via syringe γ-butyrolactone (0.38 mL, 5 mmol). After 30 min, a solution of $(iPrO)_2POCl$[15] (1.00 mL, 5.5 mmol) in HMPA (0.99 mL, 5.7 mmol) was added to the lactone enolate, and the resulting mixture was allowed to warm to rt over the course of 30 min. After the reaction mixture was cooled to −78 °C, a solution of LDA (2.2 equiv in 15 mL of THF) was added *via* syringe, and the reaction mixture was allowed to warm to rt over 2 h. The reaction was quenched by slow addition of acetic acid in ether (1 M, 4.4 equiv), and the resulting mixture was filtered through a Florisil pad. Final purification by column chromatography (silica gel, 50% hexane in EtOAc, followed by 50% CH_3CN in EtOAc), afforded compound **7b** (832 mg, 67%): ^1H NMR δ 4.77–4.64 (m, 2H), 4.28–4.21 (m, 2H), 2.92 (ddd, 1H, J_{HP} = 23.3 Hz, J = 6.7, 6.7 Hz), 2.53–2.44 (m, 2H), 1.28 (d, 12H, J = 6.2 Hz); ^{31}P NMR +18.74; EIMS, *m/z* (rel inten) 250 (M^+, 2), 193 (46), 167 (100), 166 (40), 149 (29), 123 (11), 109 (9), 86 (27). Anal. Calcd for $C_{10}H_{19}O_5P$: C, 48.00; H, 7.65. Found: C, 47.95; H, 7.91.

α-(Diisopropoxyphosphinyl)-γ-valerolactone (9b). According to the general procedure, γ-valerolactone (**5**, 500 mg, 5.0 mmol) was treated with LDA (1.1 equiv), HMPA (0.99 mL, 5.7 mmol), and $(iPrO)_2POCl$[15] (1.00 mL, 5.5 mmol). The resulting vinyl phosphate was treated with LDA (2.2 equiv) and quenched by acidic workup. After purification by flash chromatography phosphono lactone **9b** (951 mg, 72%) was obtained: ^1H NMR δ 5.05–4.61 (m, 2H), 4.49–4.25 (m, 2H), 3.11 (ddd, 1H, J_{HP} = 27.2 Hz, J = 7.1, 7.0 Hz), 2.34–1.67 (m, 4H), 1.36 (d, 12H, J = 6.2 Hz); ^{31}P NMR +20.5; EIMS, *m/z* (rel inten) 249 (M^+ − 15, 2), 205 (19), 181 (97), 180 (61), 163 (100), 135, (31), 100 (33), 99 (24), 82 (29). Anal. Calcd for $C_{11}H_{21}O_5P \cdot {}^1/_2H_2O$: C, 48.35; H, 8.11. Found: C, 48.31; H, 8.09.

α(*E*)-Propylidene-γ-butyrolactone (10). To a solution of phosphono lactone **7a** (222 mg, 1.0 mmol) and 18-crown-6 (1.32 g, 5.0 mmol) in 25 mL of THF at −78 °C was added KHMDS (1.27 mL, 1.4 M in THF, 1.1 mmol). After the reaction mixture was stirred for 30 min at − 78 °C, propionaldehyde (0.087 mL, 1.2 mmol) was added dropwise to the phosphonate anion. The mixture was allowed to warm to rt over the course of 1 h and then stirred for an additional 2 h before it was quenched by addition of saturated NH_4Cl. After extracting the aqueous layer with ether (3 × 50 mL), the combined ether extract was washed with water (50 mL) and brine (50 mL) and then dried ($MgSO_4$). Removal of solvent in vacuo gave a mixture of compounds **10** and **11** in a ratio >25:1. Purification by flash chromatography (silica gel, 10% EtOAc in hexane) produced pure **10** (95 mg, 75%). The ^1H NMR data for compound **10** was identical with that previously reported.[8a] EIMS, *m/z* (rel inten) 126 (M^+, 42), 111 (16), 97 (9), 81 (25), 68 (31), 67 (100), 65 (18) 53 (34), 44 (25), 41 (34).

α(*Z*)-Propylidene-γ-butyrolactone (11). To a mixture of phosphono lactone **7b** (250 mg, 1.0 mmol) and 18-crown-6 (264 mg, 1.0 mmol) in 15 mL of THF was added K_2CO_3 (152 mg, 1.1 mmol) at rt. After the mixture was stirred for 1 h, propionaldehyde (0.086 mL, 1.2 mmol) was added dropwise and the reaction was stirred overnight. The mixture was quenched by addition of saturated NH_4Cl, and the aqueous layer was extracted with ether (3 × 50 mL). The combined ether extracts were washed with water (50 mL) and brine (50 mL) and then dried over $MgSO_4$. Concentration in vacuo produced an oil (179 mg), which was shown by ^1H NMR to consist of a mixture of compounds **10** and **11** in a 1:6.5 ratio. Purification of the oil by column chromatography (silica gel, 20% EtOAc in hexane) produced compound **11** (109 mg, 86%). Compound **11** had ^1H NMR data identical to that previously reported.[8a] EIMS, *m/z* (rel inten) 126 (M^+, 72), 111 (27), 97 (10), 83 (33), 81 (60), 79 (68), 69 (20), 68 (22), 67 (100), 53 (59), 41 (68).

α(*E*)-Propylidene-γ-valerolactone (12). To a solution of phosphono lactone **8** (150 mg, 0.64 mmol) and 18-crown-6 (5.5 equiv) in 25 mL of THF at −78 °C was added dropwise KHMDS (1.1 equiv, 1.4 M in THF). The resulting solution was stirred at reduced temperature for 30 min, at which time dropwise addition of propionaldehyde (1.2 equiv) was begun. When addition was complete, the reaction mixture was allowed to come to rt over

(15) Sosnovsky, G. Zaret, E. H. *J. Org. Chem.* **1969**, *34*, 968.

the course of 1 h and then was allowed to stir overnight. Standard aqueous workup produced a product which was determined by ^{1}H NMR to consist solely of the *E*-isomer **12**. Final purification by flash chromatography (silica gel, 10% EtOAc in hexane) produced the desired product **12** (57 mg, 64%): ^{1}H NMR δ 6.71 (tt, 1H, J = 7.7, 2.9 Hz), 4.86–4.49 (m, 1H), 3.17–2.87 (m, 1H), 2.56–2.42 (m, 1H), 2.35–2.03 (m, 2H), 1.42 (d, 3H, J = 6.2 Hz), 1.01 (t, 3H, J = 7.7 Hz); ^{13}C NMR δ 169.7, 145.3, 124.3, 73.7, 36.8, 21.7, 21.0, 13.5; EIMS, *m/z* (rel inten) 140 (M^+, 27), 125 (10), 96 (57), 81 (49), 79 (37), 68 (68), 67 (100), 53 (37), 41 (47). Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.21; H, 8.66.

α(*Z*)-Propylidene-γ-valerolactone (13). To a solution of phosphono lactone **8** (150 mg, 0.64 mmol), K_2CO_3 (1.1 equiv), and 18-crown-6 (1.1 equiv) in 25 mL of THF at rt was added propionaldehyde (1.1 equiv). After stirring for 8 h, standard aqueous workup produced a 1:4.5 mixture of olefinic isomers **12** and **13**. Purification by flash chromatography (silica gel, 5% EtOAc in hexane) produced compound **13** (56 mg, 63%): ^{1}H NMR δ 6.17 (tt, 1H, J = 7.7, 2.3 Hz), 4.63–4.57 (m, 1H), 3.04–2.95 (m, 1H), 2.76–2.66 (m, 2H), 2.54–2.44 (m, 1H), 1.39 (d, 3H, J = 6.2 Hz), 1.04 (t, 3H, J = 7.6 Hz); ^{13}C NMR δ 171.0, 142.0, 126.0, 73.9, 32.7, 23.5, 22.3, 12.6; EIMS, *m/z* (rel inten) 140 (M^+, 58), 125 (23), 111 (20), 95 (69), 81 (43), 79 (80), 67 (100), 53 (52), 43 (47); HRMS, calcd for $C_8H_{12}O_2$ 140.0837, found 140.0853.

α(*E*)-Propylidene-δ-valerolactone (14). To a solution of phosphono lactone **9a** (260 mg, 1.1 mmol) and 18-crown-6 (1.62 g, 6.2 mmol) in 25 mL of THF at −78 °C was added KHMDS (0.86 mL, 1.4 M in THF, 1.2 mmol). After stirring for 30 min at −78 °C, propionaldehyde (0.087 mL, 1.2 mmol) was added dropwise. The mixture was allowed to warm to rt over the course of 1 h and stirred for an additional 2 h. After standard aqueous workup, a mixture consisting primarily of *E*-olefin **14** was observed by ^{1}H NMR. Purification by flash chromatography (silica gel, 10% EtOAc in hexane) produced pure compound **14** (89.3 mg, 58%). The ^{1}H NMR spectrum was identical with previously published data.[16] EIMS, *m/z* (rel inten) 140 (M^+, 37), 125 (3), 112 (27), 109 (22), 97 (25), 95 (29), 81 (33), 79 (24), 67 (100).

α(*Z*)-Propylidene-δ-valerolactone (15). To a mixture of compound **9a** (236 mg, 1.0 mmol) and 18-crown-6 (264 mg, 1.0 mmol) in 15 mL of THF at rt was added K_2CO_3 (152 mg, 1.1 mmol). After the solution was stirred for 1 h, propionaldehyde (0.087 mL, 1.2 mmol) was added dropwise and the reaction was stirred overnight. Standard aqueous workup resulted in an oil (147 mg), which was shown by ^{1}H NMR to consist of a mixture of the propylidene lactones **14** and **15** in a 1:3.4 ratio. Purification by column chromatography produced pure lactone **15** (78 mg, 56%). The ^{1}H NMR spectrum was consistent with published data:[16] EIMS *m/z* (rel inten) 140 (M^+, 41), 125 (3), 112 (27), 109 (22), 97 (25), 95 (21), 94 (23), 79 (22), 67 (100).

2-(Diethoxyphosphinyl)-5-(methoxycarbonyl)-4,5-dimethyl-5-pentanolide (4). Method A. To a solution of LDA (2.2 mmol) in anhydrous THF (6 mL) at −78 °C was added dropwise via syringe a solution of lactone **17** (372 mg, 2 mmol) in THF (1.5 mL). After the solution was stirred for 1 h, $(EtO)_2POCl$ (0.32 mL, 2.2 mmol) was added to the lactone enolate, and the mixture was allowed to warm to rt over the course of 30 min. A solution of acetic acid in diethyl ether (1 N, 2.5 mL) was added slowly, and the resulting suspension was filtered through Celite. The filtrate was concentrated in vacuo to give a yellow oil. Purification by column chromatography (silica gel, 50% EtOAc in hexane) gave pure compound **20** (552 mg, 86%): ^{1}H NMR δ 4.19–4.09 (m, 4H), 3.58 (s, 3H), 3.43 (d, 1H, J = 4.3 Hz), 2.40–2.27 (m, 2H), 1.43 (s, 3H), 1.35 (2 dt, 6H, J = 7.1 Hz, J_{HP} = 3.3 Hz), 1.25–1.20 (m, 1H), 1.05 (d, 3H, J = 6.8 Hz); ^{13}C NMR δ 173.1, 111.8 (J_{CP} = 8.7 Hz), 91.4 (J_{CP} = 7.13 Hz), 64.1 (J_{CP} = 6.7 Hz), 53.6, 48.2, 35.5, 29.8, 15.7 (J_{CP} = 6.3 Hz), 13.3, 11.3; ^{31}P NMR ($CDCl_3$) −5.6 ppm. Anal. Calcd for $C_{13}H_{23}O_7P$: C, 48.49; H, 7.20. Found: C, 48.55; H, 7.21.

To a cooled solution of vinyl phosphate **20** (161 mg, 0.5 mmol) in anhydrous THF (2 mL) at −78 °C was added at once a cooled solution of freshly prepared LDA (4.4 mL, THF, 1.0 mmol) via syringe. The reaction vessel was immediately removed from the cold bath, the mixture stirred for 5 min at ambient temperature, and the resulting yellow solution was quenched by rapid addition of acetic acid in ether (1 N, 1.4 mL). After the resulting suspension was filtered through Celite, the filtrate was concentrated to afford an oil. The oil was purified by radial chromatography (66% EtOAc in hexane) to give pure phosphonate **4** (147 mg, 91%) as a ca. 4:3 mixture of diastereomers: ^{1}H NMR major diastereomer, δ 4.20–4.10 (m, 4H), 3.71 (s, 3H), 3.06 (ddd, 1H, J_{HP} = 28.3 Hz, J = 10.9, 7.6 Hz), 1.43 (s, 3H), 1.26 (t, 6H, J = 7.1 Hz), 1.00 (d, 3H, J = 7.1 Hz); minor diastereomer, 3.69 (s, 3H), 3.07 (ddd, 1H, J_{HP} = 28.1 Hz, J = 9.1, 9.1 Hz), 1.46 (s, 3H), 0.96 (d, 3H, J = 6.9 Hz); ^{31}P NMR ($CDCl_3$) +21.8. Anal. Calcd for $C_{13}H_{23}O_7P$: C, 48.49; H, 7.20. Found: C, 48.70; H, 7.22.

Method B. A solution of lactone **17** (372 mg, 2.0 mmol) in ether (1.5 mL) was added dropwise via syringe to a stirred solution of freshly prepared LDA (2.2 mmol) in diethyl ether (6 mL) at −78 °C. After 40 min, $(EtO)_2PCl$ (0.39 mL, 2.75 mmol) was added dropwise to the resulting enolate, and the reaction mixture was allowed to warm to rt over 2 h. The reaction was quenched by addition of acetic acid in ether (1 N, 3 mL) and the mixture was filtered through Celite. After concentration in vacuo, the resulting oil was magnetically stirred in a reaction vessel open to air for 7 days and then purified by flash chromatography (silica gel, 33% to 50% EtOAc in hexane) to afford phosphonate **4** (249 mg, 39%). This material was identical with that prepared by rearrangement of vinyl phosphate **20**.

2(*E*)-Ethylidene-5-(methoxycarbonyl)-4,5-dimethyl-5-pentanolide (5). To a solution of phosphono lactone **4** (128 mg, 0.4 mmol) and DBU (61 mg, 0.4 mmol) in 5 mL of CH_3CN at rt was added dropwise a solution of CH_3CHO (1 M in THF, 0.48 mL). After the solution was stirred overnight, it was concentrated in vacuo. The resulting residue was dissolved in ether, and this solution was washed with saturated NH_4Cl and brine. Concentration in vacuo gave a mixture of ethylidene lactones **5** and **6** (85 mg), in a ratio of 9:1 as measured by ^{1}H NMR. Following final purification by flash chromatography (silica gel, 10% EtOAc in hexane), pure olefin **5**[9b,10a] was obtained (65 mg, 77%): ^{1}H NMR δ 7.18 (qt, 1H, J = 7.3, 1.9 Hz), 3.72 (s, 3H), 2.43–2.28 (m, 3H), 1.72 (dt, 3H, J = 7.3, 1.5 Hz), 1.49 (s, 3H), 0.99 (d, 3H, J = 6.9 Hz); ^{13}C NMR δ 173.0, 165.1, 142.8, 123.3, 84.1, 52.8, 32.2, 28.6, 21.6, 14.1, 13.8.

2(*Z*)-Ethylidene-5-(methoxycarbonyl)-4,5-dimethyl-5-pentanolide (6). A suspension of finely ground K_2CO_3 (232 mg, 2.4 mmol) and 18-crown-6 (1.268 g, 4.8 mmol) in anhydrous toluene (3 mL) was stirred for 1 h at rt and then cooled to −20 °C. To this was added a toluene solution of phosphono lactone **4** (129 mg, 0.4 mmol, in 1 mL) at the same temperature. The resulting solution was stirred 30 min, a solution of acetaldehyde in toluene (1 N, 0.6 mL) was added, and the mixture was stirred for 3 h at 0 °C. After warming to rt and standard aqueous workup of the resulting suspension, a mixture of ethylidene lactones **5** and **6** (ca. 1:1) was obtained. Purification by radial chromatography (10 to 20% EtOAc in hexane) afforded compounds **5** (38.3 mg, 45%) and **6**[10a] (36.5 mg, 43%). For compound **6**: ^{1}H NMR δ 6.15 (qm, 1H, J = 7.3 Hz), 3.71 (s, 3H), 2.54–2.46 (m, 1H), 2.37–2.27 (m, 1H), 2.28–2.15 (m, 1H), 2.11 (dm, 3H, J = 7.3 Hz), 1.46 (s, 3H), 0.97 (d, 3H, J = 7.0 Hz); ^{13}C NMR δ 173.3, 163.9, 145.0, 122.1, 84.6, 52.8, 35.0, 32.9, 21.5, 16.2, 13.5.

Acknowledgment. The financial support of the National Institutes of Health is gratefully acknowledged.

(16) Murray, W.; Reed, R. G. *Synthesis* **1985**, 35.