Analogues of Phosphoenolpyruvate. 4.[1] Syntheses of Some New Vinyl- and Methylene-Substituted Phosphonate Derivatives

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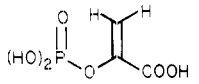
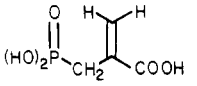
Some new vinyl- and methylene-substituted phosphonate analogues of phosphoenolpyruvic acid have been prepared. Tentative geometric assignments of these analogues have been made, and synthetic approaches to some related compounds are presented.

Phosphoenolpyruvic acid (PEP) is one of the most important biological substances with a high phosphate group transfer potential.[4] In 1972, Stubbe and Kenyon[5] reported the synthesis of the nonhydrolyzable phosphonate analogue of PEP, α-((dihydroxyphosphinyl)methyl)acrylic acid (**1**). This analogue has been found to replace PEP as a



PEP



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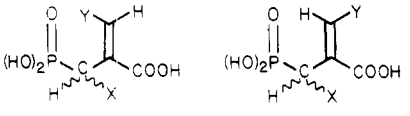
substrate in the enolase reaction[5,6] and to serve as a weak competitive inhibitor of rabbit muscle pyruvate kinase.[7] Later, in 1976, Davidson and Kenyon reported some new synthetic approaches to **1** and made unambiguous assignments of the vinyl protons in its NMR spectrum.[1]

In this paper, we report the preparation of a series of substituted analogues of PEP which, by virtue of being geometrically defined and conformationally restricted,[8] might mimic the preferred geometry, conformation, and distribution of charge of biologically important phosphates. Compounds of the types shown below have been prepared.

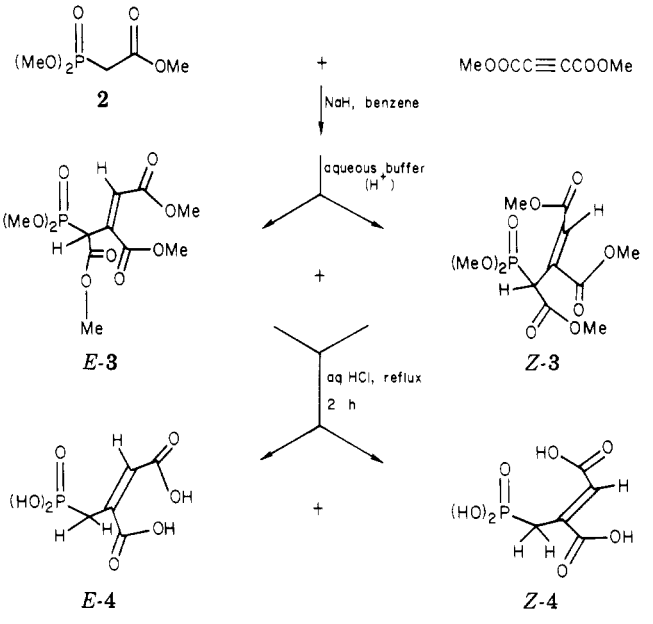


Here X is either a dihydroxyphosphinyl group, a carboxyl group, or a proton, and Y is either a phosphate group, a carboxyl group, or a hydroxyl group.

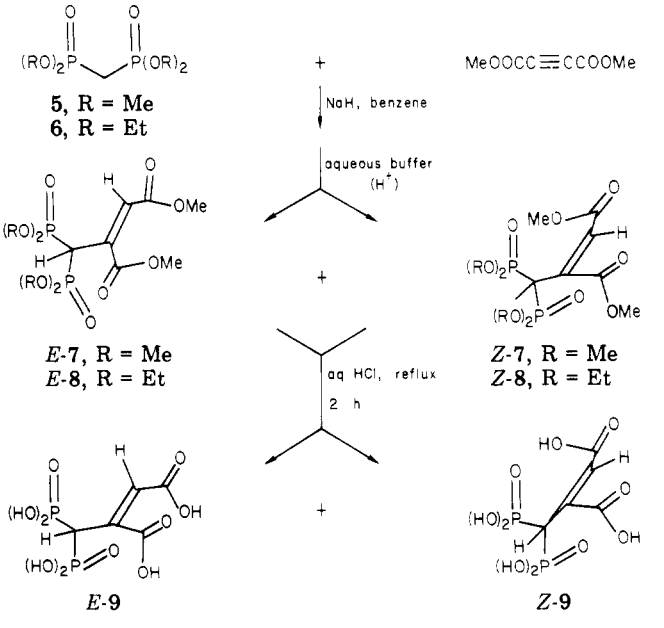
Results and Discussion

One synthetic approach to phosphonate analogues of phosphoenolpyruvic acid that was explored used the conjugate ("Michael") addition of stabilized phosphonate carbanions to acetylenedicarboxylate esters. When the preformed α anion of methyl (dimethoxyphosphinyl)-acetate (**2**) was treated with dimethyl acetylenedicarboxylate, an *E*–*Z* mixture of two isomeric β,γ-unsaturated phosphonates (*E*- and *Z*-**3**) was isolated in 37% yield (Scheme I). In an analogous fashion, the preformed α anion of bis(dimethoxyphosphinyl)methane (**5**) and bis(diethoxyphosphinyl)methane (**6**) were treated successively with dimethyl acetylenedicarboxylate to generate *E*–*Z*

Scheme I



Scheme II



(1) Part 3: Davidson, R. M.; Kenyon, G. L. *J. Org. Chem.* **1977**, *42*, 1030–1035. A preliminary report of these results was presented at the International Conference on Phosphorus Chemistry Directed Towards Biology, Burzenin, Poland, Sept 25–28, 1979.

(2) National Institutes of Health Predoctoral Trainee, 1973–1976.

(3) Recipient of a Research Career Development Award, AM 00014, from the National Institute of Arthritis, Metabolism and Digestive Diseases, 1975–1980.

(4) Lehninger, A. L. "Bioenergetics", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1971; pp 67–68.

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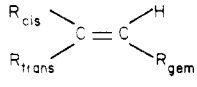
mixtures of isomeric β,γ-unsaturated phosphonates (*E*- and *Z*-**7** and *E*- and *Z*-**8**) in 45% and 44% yield, respectively (Scheme II). No evidence for base-catalyzed rearrangement to α,β-unsaturated phosphonates[9,10] was observed in either reaction. By treatment with aqueous HCl, esters of the type **3** and **8** may be hydrolyzed to the free acids **4** and **9** without apparent double-bond rearrangement in 55% and 61% yield, respectively. Upon hydrolysis, **3** underwent decarboxylation to give **4**.

Compound *E*-**4** was successfully purified by fractional recrystallization of a mixture of *E*- and *Z*-**4** from water and then further characterized by its ^{31}P and ^{13}C NMR spectra. Similarly, several fractional recrystallizations of a mixture of *E*- and *Z*-**9** from water gave a sample highly enriched in *E*-**9**. Tentative assignments of the *E* and *Z* designations to pairs of geometrical isomers in this paper have been made with the additive shielding increments for chemical shifts of olefinic protons derived by Matter et al.[11] by a least-squares treatment of a large body of NMR data. By this method, the chemical shifts of an olefinic proton (δ C=CH) in parts per million from tetramethylsilane are given by eq 1, where 5.25 is the chemical shift of ethylene



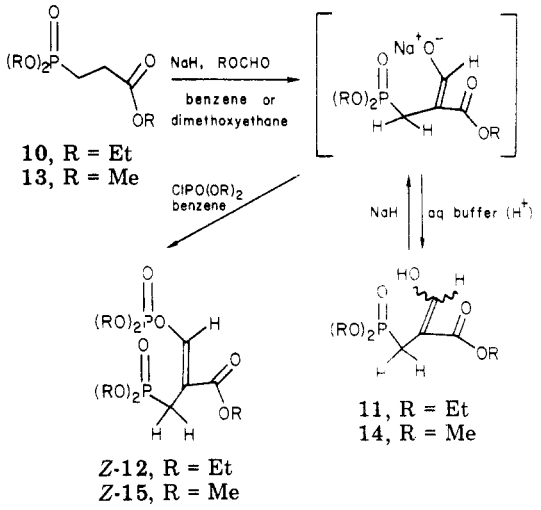
$$\delta(C{=}C_H) = 5.25 + Z_{gem} + Z_{cis} + Z_{trans} \quad (1)$$

and added increment *Z* values for 43 common functional groups are given in Matter et al.[11] The assignments for the *E* and *Z* pairs of **3**, **4**, and **14** are reasonably secure since both the calculated and observed differences in chemical shift for the olefinic protons are fairly large. The corresponding assignments for the *E* and *Z* pairs of the diphosphonates **7**, **8**, and **9** are less certain since these chemical-shift differences are minimal. In the case of **7**, **8**, and **9**, the *E* and *Z* assignments were first made for **9** (using the additive increment method). Since **9** was derived from **8**, it was assumed that hydrolysis did not alter the 60:40 *E* to *Z* ratio of isomers. Hence, *E* and *Z* assignments were made to **8** on that basis, and the corresponding assignments for **7** were made by comparing NMR parameters of **7** with those of the very closely related **8**.

It should be pointed out that many examples are known where the anisotropic deshielding effect of a carbonyl group substituted on a carbon–carbon double bond results in the vinyl proton substituted cis to be downfield from the geometrical isomer with the corresponding vinyl proton substituted trans.[11] By independently assigning the vinyl protons of α-((dihydroxyphosphinyl)methyl)acrylic acid (**1**), Davidson and Kenyon[1], for example, showed that the anisotropic deshielding of a vinyl proton by a carboxyl group attached to a carbon–carbon double bond is greater than that of a phosphinylmethyl group similarly attached to such a double bond.[7] Hence, by analogy, one might reason that *E*- and *Z*-**4** and *E*- and *Z*-**9** may be assigned their geometries based on anisotropic deshielding effects similar to those observed in compound **1**.

Another approach to the synthesis of phosphonate analogues of PEP that was explored employed a crossed-Claisen condensation of ethyl formate and diethyl β-(carboethoxy)ethylphosphonate (**10**) in a manner similar

Scheme III



to that of Kreutzkamp and Mengel.[12] The sodium enolate anion of the known compound, ethyl ((diethoxyphosphinyl)methyl)(hydroxymethylene)acetate (**11**), was then treated without isolation with diethyl phosphorochloridate to give a single enol phosphate, presumably *Z*-**12**, in 83% yield (Scheme III). Similarly, a crossed-Claisen condensation of methyl formate and dimethyl β-(carbomethoxy)ethylphosphonate (**13**) gave methyl ((dimethoxyphosphinyl)methyl)(hydroxymethylene)-acetate (**14**) in 77% yield. The preformed sodium enolate anion of **14** was then phosphorylated with dimethyl phosphorochloridate to give a single enol phosphate, presumably *Z*-**15**, in 94% yield.

Tentative geometric assignments of the enol phosphates **12** and **15** may be made on the basis of the following two assumptions: (1) the thermodynamically favored enolate tautomers have an *Z* configuration, and (2) it is the thermodynamically favored enolate tautomers that are phosphorylated to give enol phosphates with an *Z* configuration. Support for these assumptions is found in the work of Aksnes and Gramstad[13] and Stiles et al.[14] In the former work,[13] infrared spectral studies of model compounds suggested that phosphoryl groups are stronger hydrogen-bond acceptors than are carboxyl groups as evidenced by their larger association constants (K_{assoc}) to hydrogen-bond donors. In the latter work,[14] it was shown that the thermodynamically favored enolate anion of a similar compound was phosphorylated preferentially.

On the basis of its ^1H NMR spectrum, compound **14** appears to be involved in a slow equilibrium among tautomeric forms in both aprotic and protic solvents, with an enol tautomer, presumably *Z*-**14**, predominating. The presence of at least one enol tautomer in the equilibrium mixture of **14** is supported by the observation of both vinyl and allylic protons in the NMR spectrum. Also, the observed $^4J_{^{31}P-^1H}$ and $^2J_{^{31}P-^1H}$ values of 5.2 and 20.4 Hz, respectively, are indicative of a β,γ-unsaturated phosphonate.[15] These *J* values are similar to those observed for the enol phosphate *Z*-**15**, where $^4J_{^{31}P-^1H}$ = 6.2 Hz and $^2J_{^{31}P-^1H}$ = 21.8 Hz. The IR spectrum of compound **14** lends

(9) Ionin, B. I.; Petrov, A. A. *J. Gen. Chem. USSR (Engl. Transl.)* **1963**, *33*, 426–430.
(10) Martin, D. J.; Gordon, M.; Griffin, C. E. *J. Org. Chem.* **1967**, *23*, 181–1840.
(11) Matter, U. E.; Pascual, C.; Pretsch, E.; Pross, A.; Simon, W.; Sternhell, S. *Tetrahedron* **1969**, *25*, 691–697. See also: Jackman, L. M.; Sternhell, S. "Application of Nuclear Magnetic Resonance Spectroscopy to Organic Chemistry"; Pergammon Press: Oxford, 1969.
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(14) Stiles, A. R.; Reilly, C. A.; Pollard, G. R.; Tieman, C. H.; Ward, L. F.; Phillips, D. D.; Soloway, S. B.; Whetstone, R. R. *J. Org. Chem.* **1961**, *26*, 3960. See also: Schrader, G. *Angew. Chem. Monograph* **1952**, *62*, 48.
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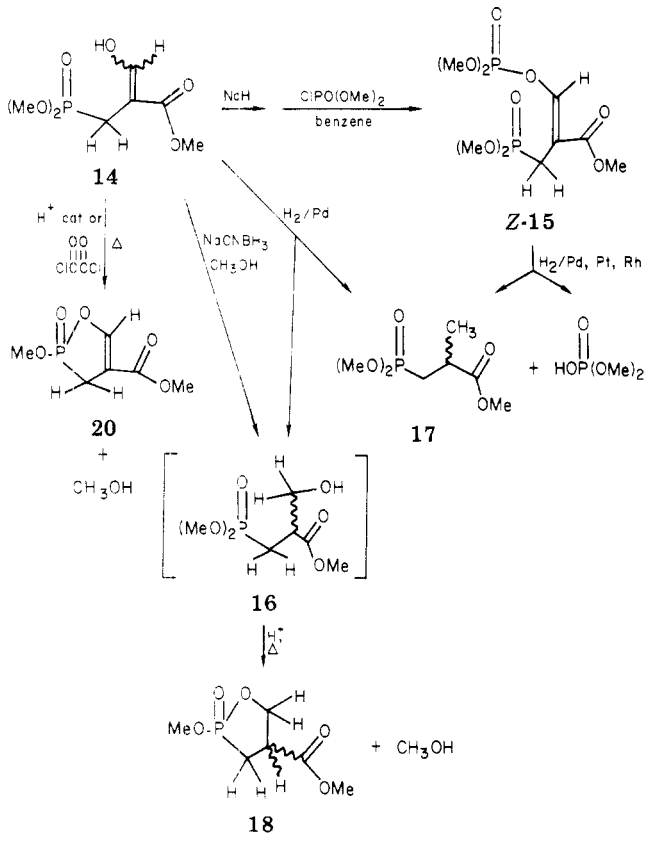
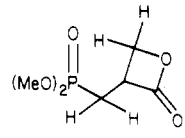
Scheme IV



further support for the predominance of the enol tautomer *Z*-**14**. IR absorptions at 3.68 and 6.15 μm are indicative of a strongly hydrogen-bonded hydroxyl group and the vinyl group, respectively.[16] Moreover, there is also a stretch at 8.64 μm which is indicative of a strongly hydrogen-bonded phosphoryl group. None of these absorptions was affected by dilution. Finally, at one point an 80:20 mixture of *Z*- and *E*-**14** was generated after distillation. As quantitatively predicted by estimating relative olefinic chemical shifts by the additive-increment method (see above), the *Z* isomer had an olefinic δ value 0.66 ppm greater than that for the corresponding *E* isomer.

When methyl ((dimethoxyphosphinyl)methyl)(hydroxymethylene)acetate (**14**) was subjected to catalytic hydrogenation with a palladium on charcoal catalyst, a mixture of two products was obtained in 84% yield, whose ^{1}H NMR spectrum suggested both a hydrogenation product, methyl (*RS*)-α-((dimethoxyphosphinyl)methyl)(hydroxymethyl)acetate (**16**), and a hydrogenolysis product, methyl (*RS*)-α-((dimethoxyphosphinyl)methyl)propionate (**17**), in a 95:5 ratio, respectively (Scheme IV). The identity of compound **17** in the mixture was confirmed by comparison of its ^{1}H NMR spectrum with that of authentic **17**.[17] The identity of compound **16** in the mixture was likewise confirmed by synthesis of **16** by an alternate route and comparison of its ^{1}H NMR spectrum.

As another synthetic approach to compound **16** (in 69% yield), compound **14**, undoubtedly reacting as its keto tautomer, was subjected to reduction by sodium cyanoborohydride in methanol in a manner similar to that of House et al.[18] A thermal, acid-catalyzed cyclization occurred to give the phostonate **18** in 72% yield on attempting to purify **16** via microdistillation, which was characterized both by the lack of a hydroxyl stretch in its IR spectrum and by its ^{1}H NMR spectrum. The phostonate structure of compound **18** is supported by the presence of a normal ester carbonyl stretch at 5.74 μm in its IR spectrum which would be lacking in a β-lactone, where carbonyl stretches typically occur at 5.5 μm.[19] The ^{1}H NMR spectrum also supports the phostonate structure **18**. Upon cyclization of compound **16**, there is a change in the methoxyphosphinyl resonance integrated intensity (δ 3.73, $^3J_{^{31}P-^1H}$ = 11 Hz) from that of a six-proton doublet to a pair of doublets whose integrated intensity corresponds to three protons ($^3J_{^{31}P-^1H}$ = 11 and 11.3 Hz), where each doublet presumably corresponds to one of two diastereomeric phostonates represented in structure **18**. Moreover, the carbomethoxy group singlet at δ 3.73 in compound **16** is still present in **18**, which clearly rules out alternative structure **19** where the carbomethoxy group would be lacking.



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On microdistillation of compound **14**, a thermal, acid-catalyzed cyclization occurred to give the enol phostonate **20** in 76% yield (Scheme IV). Compound **20** was characterized both by its chemical-ionization mass spectrum, which gave a parent M + 1 peak, and by its ^{1}H NMR spectrum which showed a doublet of triplets for the vinyl proton and a doublet of doublets for the allylic proton. The relatively large $^3J_{^{31}P-^1H}$ value of 29.5 Hz is a manifestation either of the *Z* orientation of coupled nuclei[20] or of the predominance of the α mode of ^4J coupling. The large $^4J_{^1H-^1H}$ value of 2.1 Hz is typical of many small-ring compounds with restricted conformational mobility.[21] IR absorptions of compound **20** at 5.78 and 6.08 μm are consistent with an α,β-unsaturated vinyl ester.[31,32] In addition, the hydroxyl absorption at 3.68 μm in compound **14** is lacking in compound **20**, again consistent with cyclization to an enol phosphate. Another method of preparing compound **20** from **14** in 7% yield employed the use of oxalyl chloride in a manner similar to that of Clark and Heathcock.[22]

When the enol phosphate *Z*-**15** was subjected to catalytic hydrogenation, successively with Pt, Pd, and Rh catalysts, the sole products, isolated in 95% yield, were those of hydrogenolysis followed by hydrogenation (Scheme IV). The identity of the hydrogenolysis product, methyl (*RS*)-α-((dimethoxyphosphinyl)methyl)propionate (**17**), was confirmed by an unambiguous synthesis of **17**[17] and comparison of its ^{1}H NMR spectra. The inferred presence of dimethyl hydrogen phosphate as a co-product is supported by the observation of an acidic titratable proton at δ 11.2 in the ^{1}H NMR spectrum of the product mixture. These results contrast with those of Jacobson et al.[23] who observed the formation of diethyl isopropyl phosphate on

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(17) Pudovik, A. N.; Arbusov, B. A. *Zh. Obshch. Khim.* **1951**, *21*, 1837–1841.
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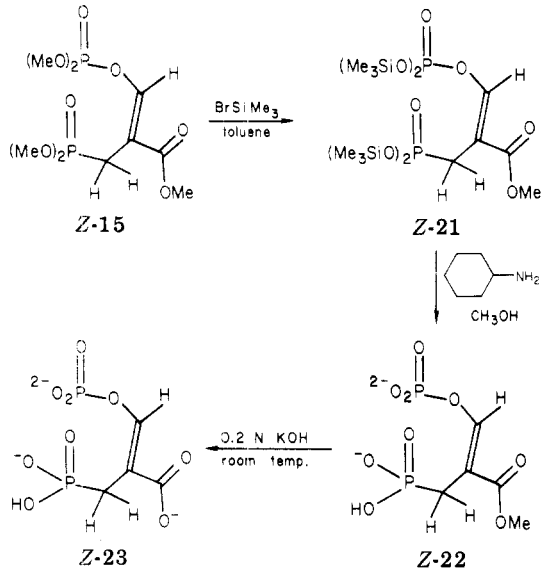
Scheme V



catalytic hydrogenation of dimethyl isopropenyl phosphate over a Pd catalyst.

When the enol phosphate *Z*-**15** was treated with a greater than fourfold excess of trimethylsilyl bromide in toluene at reflux, a viscous and highly moisture-sensitive oil was isolated in 82% yield which is believed to be the tetrasilyl ether *Z*-**21** (Scheme V). Precedent for the use of trimethylsilyl bromide in phosphonate transalkylation is provided by the work of several groups, Malatesta (1950) being one of the earliest.[24-26]

The tetrasilyl ether *Z*-**21** was then solvolyzed in a manner similar to that of Rudinskas and Hullar[27] to give a crude salt of the enol phosphate monocarboxymethyl ester (*Z*-**22**) in 95% yield. This crude salt was then treated with 5 theoretical equiv of 0.2 N potassium hydroxide overnight at room temperature to generate a mixture of the pentaacid *Z*-**23** and unreacted monocarboxymethyl ester *Z*-**22** in a 45:55 ratio, respectively.

This mixture was then desalted and applied to a (diethylamino)ethyl (DEAE)-cellulose anion-exchange column and eluted with a linear ammonium bicarbonate gradient. Two fractions that adsorbed UV light at 254 nm were collected, lyophilized, and then passed through a Dowex cation-exchange resin (Li^+ form) with water elution. The first UV-absorbing fraction to elute gave, after drying, an elemental analysis and a ^1H NMR spectrum that were consistent with its structure being the trilithium salt of the tetraacid enol phosphate monocarboxymethyl ester *Z*-**22**. The second UV-absorbing fraction to elute gave an elemental analysis and ^1H, ^{31}P, and ^{13}C NMR spectra that were all consistent with its structure being the tetralithium salt of the pentaacid *Z*-**23**. The overall yield for the purification and isolation of *Z*-**22** and *Z*-**23** was 75% based on starting crude *Z*-**15**.

The NMR data strongly support the fact that the enol phosphates *Z*-**22** and *Z*-**23** possess a single, unique geometry that is the same geometry as that of their precursors, *Z*-**15** and *Z*-**21**. For reasons already discussed in the tentative geometric assignment of *Z*-**15**, we tentatively assign the *Z* configuration to the enol phosphates *Z*-**22** and *Z*-**23**.

In addition to bearing the same net charge at physiologic pH as do the nucleotide triphosphates, *Z*-**23** bears a certain structural resemblance to both 1,3- and 2,3-diphosphoglyceric acid. Both *Z*-**22** and *Z*-**23** seem quite stable in both the solid state and aqueous solution at pH's greater than 5 and may, therefore, prove to be useful biochemical probes of enzyme active-site topography along with the completely nonhydrolyzable analogues *E*- and *Z*-**4** and *E*- and *Z*-**9**.

Experimental Section

General. All melting and boiling points are uncorrected. NMR spectra were determined at 60 MHz with either a Varian Model A-60A or Perkin-Elmer R12B spectrometer and at 100 MHz with a Varian XL-100 with pulsed Fourier transform capabilities and a multinuclear probe accessory; δ values are relative to Me_4Si. IR spectra were recorded on a Beckman Acculab 4 spectrometer. Microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley.

General Procedure for Additions of Stabilized Phosphonate Carbanions to Dimethyl Acetylenedicarboxylate. The stabilized phosphonate carbanion (0.054 mol) in 10 mL of benzene is formed by adding the phosphonate dropwise to 2.58 g of 56% sodium hydride (washed twice with hexane) under nitrogen in 200 mL of benzene at 0 °C and is stirred at room temperature for 1 h. After the solution is cooled to 0 °C, 7 mL of dimethyl acetylenedicarboxylate (Aldrich) in 10 mL of benzene is added dropwise, and the reaction mixture is stirred for 2 h at room temperature. The mixture is then cooled to 0 °C, 50 mL of saturated, aqueous KH_2PO_4 is added, and the mixture is extracted with five 100-mL portions of ether. The ether extract is dried overnight over anhydrous Na_2SO_4 and filtered, and the solvent is removed in vacuo, leaving a dark viscous oil. This oil can best be purified by fractional distillation using a salt bath and a high vacuum. Smaller quantities can be adequately purified via bulb-to-bulb distillation. The following additions to dimethyl acetylenedicarboxylate have been carried out with this procedure.

Addition of Methyl (Dimethoxyphosphinyl)acetate (2) to Dimethyl Acetylenedicarboxylate. A mixture of two isomeric β,γ-unsaturated phosphonates (*E*- and *Z*-**3**) was obtained (6.5 g, 37% yield) in a 75:25 ratio on short-path distillation: bp 140–145 °C (0.02 mm); ^1H NMR ($CDCl_3$) δ (*Z*-**3**) 3.80 (m, 15 H), 4.32 (d, $^2J_{^{31}P-^1H}$ = 25.2 Hz, 1 H), 6.76 (d, $^4J_{^{31}P-^1H}$ = 4.6 Hz, 1 H); (*E*-**3**) 3.80 (m, 15 H), 5.86 (d, $^2J_{^{31}P-^1H}$ = 28.2 Hz, 1 H), 6.91 (d, $^4J_{^{31}P-^1H}$ = 3.6 Hz, 1 H). Anal. Calcd for $C_{11}H_{17}O_9P$: C, 40.75; H, 5.28. Found: C, 41.09; H, 5.36.

Bis(dimethoxyphosphinyl)methane (5) was prepared according to the method of Roy[28] and Nicholson et al.;[29] bp 80–85 °C (0.02 mm) (lit.[25] bp 87–90 °C (0.05 mm)).

Addition of Bis(dimethoxyphosphinyl)methane (5) to Dimethyl Acetylenedicarboxylate. A mixture of two isomeric β,γ-unsaturated phosphonates (*E*- and *Z*-**7**) was obtained (8.5 g, 45% yield) in a 35:65 ratio by short-path distillation: bp 155–160 °C (0.02 mm); ^1H NMR ($CDCl_3$) δ (*Z*-**7**) 3.95 (t, $^2J_{^{31}P-^1H}$ = 25.3 Hz, 1 H), 3.83 (m, 18 H), 6.85 (t, $^4J_{^{31}P-^1H}$ = 4.4 Hz, 1 H); (*E*-**7**) 3.83 (m, 18 H), 5.9 (t, $^2J_{^{31}P-^1H}$ = 27.0 Hz, 1 H), 6.89 (t, $^4J_{^{31}P-^1H}$ = 3 Hz, 1 H). Anal. Calcd for $C_{11}H_{20}O_{10}P_2$: C, 35.30; H, 5.38. Found: C, 35.00; H, 5.38.

Bis(diethoxyphosphinyl)methane (6) was prepared according to the method of Roy;[28] bp 85–90 °C (0.02 mm) (lit.[28] bp 90–94 °C (0.1 mm)).

Addition of Bis(diethoxyphosphinyl)methane (6) to Dimethyl Acetylenedicarboxylate. A mixture of two isomeric β,γ-unsaturated phosphonates (*E*- and *Z*-**8**) was obtained (9.5 g, 44% yield) in a 60:40 ratio by short-path distillation: bp 165–170 °C (0.01 mm); ^1H NMR ($CDCl_3$) δ (*Z*-**8**) 1.33 (t, J = 7 Hz, 12 H), 3.8 (m, 6 H), 4.2 (m, J = 7 Hz, 8 H) (allylic t is buried, hence unassignable), 6.87 (t, $^4J_{^{31}P-^1H}$ = 4.4 Hz, 1 H); (*E*-**8**) 1.33 (t, J = 7 Hz, 12 H), 3.8 (m, 6 H), 4.2 (m, J = 7 Hz, 8 H), 5.77 (t, $^2J_{^{31}P-^1H}$ = 22.6 Hz, 1 H), 6.82 (t, $^4J_{^{31}P-^1H}$ = 3.0 Hz, 1 H). Anal. Calcd for

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$C_{15}H_{28}O_{10}P_2$: C, 41.86; H, 6.55. Found: C, 41.55; H, 6.47.

Hydrolysis of *E*- and *Z*-3. A 75:25 mixture of *E*- and *Z*-**3** (5.0 g) was heated at reflux for 2 h with 25 mL of 12 N HCl. On removal of the solvent, 1.75 g (55% yield) of a 75:25 mixture of β,γ-unsaturated phosphonic acids *E*- and *Z*-**4** was obtained on recrystallization from water: ^{1}H NMR (D_2O) δ (*E*-**4**) 3.5 (d, $^2J_{^{31}P-^1H}$ = 23.6 Hz, 2 H), 6.9 (d, $^4J_{^{31}P-^1H}$ = 6.2 Hz, 1 H); (*Z*-**4**) 3.01 (d, $^2J_{^{31}P-^1H}$ = 22.6 Hz, 2 H), 6.28 (d, $^4J_{^{31}P-^1H}$ = 5.0 Hz, 1 H). Anal. Calcd for $C_5H_7O_7P$: C, 28.59; H, 3.36. Found: C, 28.37; H, 3.39.

Purification and Characterization of *E*-4. *E*-**4** (1.05 g, 81% yield) was separated from *Z*-**4** by fractional crystallization from water of 1.75 g of a 75:25 mixture of *E*- and *Z*-**4**. *E*-**4** is less soluble in water and hence is the first to fall out of solution, leaving *Z*-**4** and any impurities in the mother liquor: mp 203–205 °C (for *E*-**4**); IR (Nujol) 3.45, 5.96, 7.94, 8.43, 9.82, 10.44 μm; ^{31}P NMR (D_2O, δ relative to external 20% trimethyl phosphate in D_2O, both samples locked sequentially on an external fluorinated sample) (*E*-**4**) −19.2; ^{13}C NMR [D_2O, δ relative to internal dioxane, sample was 50 μM ethylenediaminetetraacetic acid (EDTA) (*E*-**4**) 27.51 (d, $^1J_{^{31}P-^{13}C}$ = 130.4 Hz, 1 C), 129.38 (d, $^3J_{^{31}P-^{13}C}$ = 11.4 Hz, 1 C), 138.59 (d, $^2J_{^{31}P-^{13}C}$ = 12.7 Hz, 1 C), 168.73 (s, 1 C), 169.15 (s, 1 C).

Hydrolysis of *E*- and *Z*-8. A 60:40 mixture of *E*- and *Z*-**8** (5.0 g) was heated at reflux for 3 h with 25 mL of 12 N HCl. On removal of the solvent, 1.65 g (61% yield) of a 60:40 mixture of β,γ-unsaturated phosphonic acids *E*- and *Z*-**9** was obtained after recrystallization from water: ^{1}H-NMR (6 N DCl) δ (*E*-**9**) 5.63 (t, $^2J_{^{31}P-^1H}$ = 26.8 Hz, 1 H), 7.18 (t, $^4J_{^{31}P-^1H}$ = 3 Hz, 1 H); (*Z*-**9**) 4.15 (t, $^2J_{^{31}P-^1H}$ = 25 Hz, 1 H), 6.98 (t, $^4J_{^{31}P-^1H}$ = 4.2 Hz, 1 H). Anal. Calcd for $C_5H_8O_{10}P\cdot 0.75H_2O$: C, 19.78; H, 3.15. Found: C, 19.83; H, 3.34.

Several fractional recrystallizations from water gave a sample enriched in *E*-**9** in about a 95:5 ratio. *E*-**9** is less soluble in water than is *Z*-**9** and hence is easier to free from water-soluble impurities.

Diethyl β-(carboethoxy)ethylphosphonate (10) was prepared according to the method of Garner et al.;[30] bp 90–95 °C (1 mm) (lit.[30] bp 114–115 °C (2 mm)).

Phosphorylation of the Sodium Enolate Anion of Ethyl ((Diethoxyphosphinyl)methyl)(hydroxymethylene)acetate (11). **10** (2.2 g) was dissolved in 15 mL of benzene (dried over molecular sieves) and added rapidly to 0.64 g of 56% sodium hydride (washed twice with hexane) with stirring under N_2. Ethyl formate (16 mL; Aldrich) was rapidly added, and the mixture was stirred at room temperature for 3 h under N_2. The mixture was then cooled to 0 °C, freshly distilled diethyl phosphorochloridate (1.2 g; Aldrich) dissolved in 10 mL of benzene was then added dropwise at 0 °C, and the mixture was allowed to stir for 3 h at room temperature. The reaction mixture was then filtered through a medium-fritted sintered-glass filter under N_2, and the solvent removed in vacuo. Short-path distillation [bp 160–165 °C (0.2 mm)] gave 2.5 g (83% yield) of enol phosphate *Z*-**12**: ^{1}H NMR ($CDCl_3$) δ 2.34 (m, 15 H), 2.94 (d, $^2J_{^{31}P-^1H}$ = 21.6 Hz, 2 H), 4.12 (m, 10 H), 7.68 (apparent t, $^4J_{^{31}P-^1H}$ = $^3J_{^{31}P-^1H}$ = 6.4 Hz, 1 H). Anal. Calcd for $C_{14}H_{28}O_9P_2$: C, 41.80; H, 7.02. Found: C, 41.87; H, 6.98.

Dimethyl β-(carbomethoxy)ethylphosphonate (13) was prepared according to the method of Pudovik and Kitaev;[31] bp 95–103 °C (1 mm) (lit.[31] bp 137–138 °C (10 mm)).

Crossed-Claisen Condensation of Dimethyl β-(Carbomethoxy)ethylphosphonate (13) with Methyl Formate. **13** (15.7 g) was dissolved in 150 mL of dimethoxyethane (freshly distilled from sodium hydride) and added rapidly to 4.5 g of 56% sodium hydride (washed twice with hexane) with stirring under N_2. Methyl formate (109 mL; Aldrich) was rapidly added, and the mixture was allowed to stir at room temperature for 3 h under N_2. The mixture was then cooled to 0 °C and 50 mL of saturated aqueous KH_2PO_4 was added, followed by extraction with five 100-mL portions of CH_2Cl_2. The CH_2Cl_2 extract was dried overnight on Na_2SO_4 and filtered, and the solvent was removed in vacuo at room temperature to leave a viscous yellow oil which solidified on standing overnight at 0 °C. Recrystallization from CH_2Cl_2 gave 13.8 g (77% yield) of methyl ((dimethoxyphosphinyl)methyl)(hydroxymethylene)acetate (**14**): mp 78–79 °C (white plates); IR (neat) 3.68, 5.94, 6.15, 7.23, 8.64, 9.85 μm; ^{1}H NMR ($CDCl_3$) δ 2.92 (d, $^2J_{^{31}P-^1H}$ = 20.4 Hz, 2 H), 3.76 (d, J = 11 Hz, 6 H), 3.70 (s, 3 H), 7.83 (d, $^4J_{^{31}P-^1H}$ = 5.2 Hz, 1 H), 9.18 (br s, 1 H). Anal. Calcd for $C_7H_{13}O_6P$: C, 37.51; H, 5.85. Found: C, 37.78; H, 5.89.

Microdistillation of a sample of **14** at bp 105–110 °C (0.1 mm) gave an 80:20 mixture of presumably *Z*- and *E*-**14** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ (*Z*-**14**) 2.92 (d, $^2J_{^{31}P-^1H}$ = 20.4 Hz, 2 H), 3.76 (d, J = 11 Hz, 6 H), 3.70 (s, 3 H), 7.83 (d, $^4J_{^{31}P-^1H}$ = 5.2 Hz, 1 H), 9.83 (br s, 1 H); (*E*-**14**) 2.71 (d, $^2J_{^{31}P-^1H}$ = 19.2 Hz, 2 H), 3.76 (d, J = 11 Hz, 6 H), 3.70 (s, 3 H), 7.17 (br s, 1 H), 9.83 (br s, 1 H); ^{1}H NMR (D_2O) δ (presumably 65:35 *Z*-*E*) (*Z*-**14**) (*E*-**14**) 2.93 (d, $^2J_{^{31}P-^1H}$ = 20 Hz, 2 H), 3.70 (s, 3 H), 3.72 (d, J = 11 Hz, 6 H), 7.87 (d, $^4J_{^{31}P-^1H}$ = 5.2 Hz, 1 H); (*E*-**14**) 2.27 (d, $^2J_{^{31}P-^1H}$ = 18.1 Hz, 2 H), 3.73 (s, 3 H), 3.72 (d, J = 11 Hz, 6 H), 5.08 (s, 1 H).

Thermal Cyclization of Methyl ((Dimethoxyphosphinyl)methyl)(hydroxymethylene)acetate (14). **14** (2.0 g) was heated at reflux under vacuum (150 °C bath at 0.8 mm) for 1.5 h in a 15-mL pear-shaped flask equipped with a magnetic stirrer and reflux condenser. After cooling, the reaction mixture was distilled, bp 80–85 °C (0.05 mm), to give 1.3 g (76% yield) of an enol phosphonate (**20**). A ^{1}H NMR spectrum ($CDCl_3$) of the distillate suggested the presence of approximately 3% of an impurity which could account for the fact that the elemental analysis for hydrogen deviates slightly from theoretical: ^{1}H NMR ($CDCl_3$) δ 2.78 (d of d, $^2J_{^{31}P-^1H}$ = 13.7 Hz, $^4J_{^1H-^1H}$ = 2.1 Hz, 2 H), 3.71 (s, 3 H), 3.76 (d, $^3J_{^{31}P-^1H}$ = 11 Hz, 3 H), 7.50 (d of t, $^3J_{^{31}P-^1H}$ = 29.5 Hz, $^4J_{^1H-^1H}$ = 2.1 Hz, 1 H); IR (neat) 5.78, 6.08, 6.96, 8.42, 9.67 μm. Anal. Calcd for $C_6H_9O_5P$: C, 37.52; H, 4.74. Found: C, 37.29; H, 5.19.

Treatment of 14 with Oxalyl Chloride To Give the Enol Phostonate (20). A modification of the general method of Clark and Heathcock[22] was used. To 1.0 g of **14** was added 0.56 g of oxalyl chloride (Aldrich) with stirring, neat, under N_2, until a homogeneous solution was achieved (10 min). The mixture was then evacuated at room temperature (0.5 mm) for 0.5 h and then microdistilled at 80–85 °C (0.05 mm) to give 0.06 g (7% yield) of the enol phostonate **20** whose ^{1}H NMR spectrum ($CDCl_3$) was identical with that of **20** prepared by thermal cyclization. A chemical-ionization mass spectrum of **20** prepared via the oxalyl chloride route gave the expected parent M + 1 peak of 193. A 2M + 1 peak at 385 was also observed.

Methyl (*RS*)-α-((dimethoxyphosphinyl)methyl)-propionate (17) was prepared according to the method of Pudovik and Arbusov:[17] bp 97–105 °C (0.02 mm) [lit.[17] bp 137–138 °C (10 mm)]; ^{1}H NMR ($CDCl_3$) δ 1.22 (d, J = 7 Hz, 3 H), 1.5–3 (complex m, 3 H), 3.65 (d, J = 11 Hz, 6 H), 3.62 (s, 3 H).

Catalytic Hydrogenation of 14. **14** (1.0 g) was dissolved in 25 mL of methanol and subjected to 3 atm pressure of H_2 in a Parr apparatus for 24 h, the time necessary to achieve complete uptake of hydrogen with 5.0 g of palladium on charcoal catalyst. Filtration to remove the catalyst and removal of the solvent in vacuo gave 0.85 g (84% yield) of a viscous oil whose ^{1}H NMR spectrum ($CDCl_3$) suggested a hydrogenation product, methyl (*RS*)-α-((dimethoxyphosphinyl)methyl)(hydroxymethyl)acetate (**16**), and a hydrogenolysis product, methyl (*RS*)-α-((dimethoxyphosphinyl)methyl)propionate (**17**), in a 95:5 ratio, respectively. The identity of **17** in the mixture was made by comparison with the ^{1}H NMR spectrum ($CDCl_3$) of authentic **17** (see above). The identity of **16** in the mixture was likewise confirmed by synthesis of **16** by another route (see below) and comparison of its ^{1}H NMR spectrum ($CDCl_3$).

Preparation of Methyl (*RS*)-α-((Dimethoxyphosphinyl)methyl)(hydroxymethyl)acetate (16) by Sodium Cyanoborohydride Reduction of 14. **14** (0.5 g) was dissolved in 25 mL of methanol, and 2.0 g of sodium cyanoborohydride (Aldrich) was added with stirring. After the solution was stirred for 3 h at room temperature, a drop of methyl orange indicator was added along with 10 mL of water. The pH was then lowered to 3 repeatedly with the dropwise addition of 1 N HCl until the orange color failed to disappear over a 1-h period. The reaction mixture was then thoroughly extracted with five 75-mL portions of CH_2Cl_2. After the solution was dried overnight over Na_2SO_4 and filtered, the CH_2Cl_2 was removed in vacuo, leaving a white semicrystalline solid whose ^{1}H NMR spectrum ($CDCl_3$) was

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(31) Pudovik, A. N.; Kitaev, Y. P. *Zh. Obshch. Khim.* **1952**, *22*, 467–477.

identical with that of **16** obtained via the catalytic hydrogenation route (0.36 g, 69% yield): ^{1}H NMR ($CDCl_3$) δ 1.9–3.15 (complex m, 5 H), 3.73 (d, $^3J_{^{31}P-^1H}$ = 11 Hz, 6 H), 3.73 (s, 3 H), 4.52 (br s, 1 H); IR (neat) 2.98, 5.76, 7.00, 8.21, 9.82, 12.05 μm. In an attempt to purify **16** for elemental analysis, thermal cyclization to phostonate **18** occurred.

Thermal Cyclization of Methyl (*RS*)-α-((Dimethoxyphosphinyl)methyl)(hydroxymethyl)acetate (16). Slow microdistillation of 0.3 g of **16** at low vacuum gave 0.18 g (72% yield) of phostonate **18** as a viscous, colorless oil: bp 165–170 °C (3 mm); IR (neat) 5.74, 6.88, 7.48, 8.08, 9.74, 11.76 μm; ^{1}H NMR ($CDCl_3$) δ 1.8–2.45 (complex m, 2 H), 1.8–3.5 (complex m, 1 H), 3.9–4.55 (complex m, 2 H), 3.5–3.9 (complex m, 6 H). Anal. Calcd for $C_6H_{11}O_5P$: C, 37.12; H, 5.71. Found: C, 36.79; H, 5.82.

Dimethyl phosphorochloridate was prepared according to the method of Fiszer and Michalski;[32] bp 55–58 °C (2 mm) [lit.[32] bp 80 °C (18 mm)].

Phosphorylation of Sodium Enolate Anion of Methyl ((Dimethoxyphosphinyl)methyl)(hydroxymethylene)acetate (14). *Z*-**15** 80:20 mixture of presumably *Z*- and *E*-**14** (2.0 g) was dissolved in benzene and added dropwise with stirring under N_2 at 0 °C to 0.43 g of 56% sodium hydride (twice hexane washed) in 200 mL of benzene, and the solution was allowed to stir for 5 h at room temperature. Freshly distilled dimethyl phosphorochloridate (1.2 g) dissolved in 10 mL of benzene was then added dropwise at 0 °C, and the solution was allowed to stir for 3 h at room temperature. The reaction mixture was then filtered through a medium-fritted glass filter and the solvent removed in vacuo. Short-path distillation, bp 150–155 °C (0.01 mm), gave 2.77 g (94% yield) of the enol phosphate *Z*-**15**: IR (neat) 5.64, 6.13, 6.59, 7.76, 8.71, 9.54 μm; ^{1}H NMR ($CDCl_3$) δ 2.94 (d, $^2J_{^{31}P-^1H}$ = 21.8 Hz, 2 H), 3.82 (m, J = 11 Hz, 15 H), 7.69 (apparent t, $^4J_{^{31}P-^1H}$ = $^3J_{^{31}P-^1H}$ 6.2 Hz, 1 H). Anal. Calcd for $C_9H_{18}O_9P_2$: C, 32.54; H, 5.46. Found: C, 32.64; H, 5.44.

Catalytic Hydrogenation of Enol Phosphate *Z*-15. *Z*-**15** (0.5 g) was dissolved in 25 mL of ethyl acetate and subjected to 3 atm of H_2 in a Parr apparatus for 3 h in separate runs with each of the following catalysts: (1) 100 mg of platinum oxide, (2) 0.5 g of 5% palladium on charcoal, and (3) 0.5 g of 5% rhodium on alumina. A ^{1}H NMR spectrum ($CDCl_3$) was obtained after removal of the catalyst and the solvent. In each case, the crude product showed an acidic proton at δ 11.2. The three spectra obtained were virtually superimposable, suggesting identical products in each run; ^{1}H NMR ($CDCl_3$) δ 1.22 (d, J = 7 Hz, 3 H), 1.5–3 (complex m, 3 H), 3.65 (m, J = 11 Hz, 15 H), 11.19 (s, 1 H). The identity of the products was confirmed by comparison of their ^{1}H NMR spectra ($CDCl_3$) with that of authentic methyl (*RS*)-α-((dimethoxyphosphinyl)methyl)propionate (**17**).

Transalkylation of Enol Phosphate (*Z*-15) with Excess Trimethylsilyl Bromide. *Z*-**15** (1 g) was heated at reflux for 1 h in toluene with trimethylsilyl bromide (3 mL; Pfaltz and Bauer) under N_2. The reaction mixture was then cooled to room temperature and the solvent and low-boiling byproducts were removed in vacuo at room temperature, leaving a viscous, yellow oil. This oil was then microdistilled to give the tetrasilyl ether *Z*-**21**, bp 145–150 °C (0.01 mm), as an extremely hygroscopic, colorless oil (1.39 g, 82% yield: ^{1}H NMR ($CDCl_3$) δ 0.25 (complex m, 36 H), 2.87 (d, $^2J_{^{31}P-^1H}$ = 22.4 Hz, 2 H), 3.73 (s, 3 H), 7.68 (d of d, J = 6.2 Hz, J = 7.1 Hz, 1 H). Anal. Calcd for $C_{17}H_{42}O_9P_2Si_4$: C, 36.15; H, 7.50. Found: C, 35.66; H, 7.29. The hygroscopic nature of this product presumably accounts for the slightly low carbon analysis.

Solvolysis of Tetrasilyl Ether *Z*-21. The general procedure of Rudinskas and Hullar[27] was followed to solvolyze *Z*-**21**. *Z*-**21** (0.35 g) was dissolved in 10 mL of dry ether and added dropwise at 0 °C to freshly distilled cyclohexylamine (2 mL; Aldrich) in 5 mL of dry methanol with stirring under N_2. The solvolysis mixture was then concentrated repeatedly in vacuo at room temperature with sequential additions of anhydrous methanol. The mixture was then dissolved in 5 mL of anhydrous methanol, and dry ether was added dropwise until precipitation occurred. The solutions were then centrifuged and the supernatants decanted. The white crystalline precipitate was then redissolved in anhydrous methanol and reprecipitated with ether. The tetracyclohexylammonium salt was then dried in vacuo to give an impure white microcrystalline powder (*Z*-**22**) (0.396 g, 95% yield): ^{1}H NMR (D_2O, δ relative to external Me_4Si) 1.0–2.2 (complex m, 40 H), 2.65 (d, $^2J_{^{31}P-^1H}$ = 20 Hz, 2 H), 2.9–3.4 (complex m, 4 H), 3.7 (s, 3 H), 7.83 (d of d, J = 4.9, J = 8 Hz, 1 H). This salt of *Z*-**22** was not further purified at this time but was saponified in its crude form, as follows, where it was isolated and characterized as its trilithium salt.

Saponification of Enol Phosphate Monocarboxymethyl Ester (*E*-22) with Aqueous Potassium Hydroxide. The crude salt of *Z*-**22** (0.15 g) was dissolved in 5.6 mL of 0.2 N potassium hydroxide and stirred overnight at room temperature. The solvent was then removed in vacuo at room temperature, and the mixture was then applied to a DEAE-cellulose anion-exchange column (bicarbonate form) and desalted by elution with an aqueous ammonium bicarbonate gradient. All UV-absorbing fractions were then pooled, lyophilized to dryness, and again applied to a DEAE-cellulose column (bicarbonate form). The column was then eluted with a linear aqueous ammonium bicarbonate gradient (0 to 0.7 M at 2 mL/min). The two peaks which absorbed at 256 nm were successively lyophilized to dryness. The first peak to elute, presumably unreacted compound *Z*-**22**, was applied to a Dowex cation-exchange column (Bio-Rad, lithium form) and eluted with water. The UV-absorbing eluate, compound *Z*-**22**, was then lyophilized and dried in vacuo to give 0.036 g of a white powder: ^{1}H NMR (D_2O, δ relative to external Me_4Si) (*Z*-**22**) 2.65 (d, $^2J_{^{31}P-^1H}$ = 20 Hz, 2 H), 3.7 (s, 3 H), 7.83 (d of d, J = 4.9, J = 8 Hz, 1H). Anal. Calcd for $C_5H_7Li_3O_9P_2 \cdot 1.25H_2O$: C, 18.98; H, 3.03; P, 19.58. Found: C, 19.26; H, 3.14; P, 19.48.

The second UV-absorbing peak to elute from the DEAE-cellulose column, presumed to be *Z*-**23**, was similarly converted to the lithium form and lyophilized to dryness to give compound *Z*-**23** as 0.032 g of a white powder. The total isolated yield of *Z*-**22** and *Z*-**23** from crude *Z*-**22** is 96%. The overall yield for the isolation of *Z*-**22** and *Z*-**23** is 75% based on starting *Z*-**15**. *Z*-**23**: ^{1}H NMR (D_2O, δ relative to external Me_4Si) 2.7 (d, $^2J_{^{31}P-^1H}$ = 20.5 Hz, 2 H), 7.4 (d of d, J = 7.05, J = 5.1 Hz, 1 H); ^{31}P NMR (D_2O, δ relative to external 20% trimethyl phosphate; both samples locked sequentially on an external fluorinated sample) 0.824 (s, 1 P), −17.54 (s, 1 P); ^{13}C NMR (D_2O, δ relative to internal dioxane) 26.14 (d, $^1J_{^{31}P-^{13}C}$ = 128.88 Hz, 1 C), 113.24 (apparent t, 1 C), 148.01 (d of d, J = 9.98 Hz, J = 3.14 Hz, 1 C), 177.42 (s, 1 C). Anal. Calcd for $C_4H_4Li_4O_9P_2 \cdot 3.25H_2O$: C, 13.95; H, 3.07; P, 17.99. Found: C, 14.17; H, 3.18; P, 17.80.

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Registry No. 2, 51298-31-8; (*E*)-**3**, 73574-39-7; (*Z*)-**3**, 73574-40-0; (*E*)-**4**, 73574-41-1; (*Z*)-**4**, 73574-42-2; **5**, 16001-93-7; **6**, 1660-94-2; (*E*)-**7**, 73574-43-3; (*Z*)-**7**, 73574-44-4; (*E*)-**8**, 73574-45-5; (*Z*)-**8**, 73574-46-6; (*E*)-**9**, 73574-47-7; (*Z*)-**9**, 73574-48-8; **10**, 3699-67-0; (*Z*)-**12**, 73574-49-9; **13**, 18733-15-8; (*E*)-**14**, 73574-50-2; (*Z*)-**14**, 73574-51-3; (*Z*)-**15**, 73574-52-4; (*RS*)-**16**, 73574-53-5; (*RS*)-**17**, 73574-54-6; (*RS*)-**18**, 73574-55-7; **20**, 73574-56-8; (*Z*)-**21**, 73574-57-9; (*Z*)-**22** tetracyclohexylammonium salt, 73574-59-1; (*Z*)-**22** trilithium salt, 73574-60-4; (*Z*)-**23** tetralithium salt, 73574-61-5; dimethyl acetylenedicarboxylate, 762-42-5; methyl formate, 107-31-3; dimethyl phosphorochloridate, 813-77-4.

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