CH_2Cl_2 (4 mL) was cooled to −78 °C, and DMSO (0.30 mL, 4.4 mmol) in CH_2Cl_2 (1 mL) was added slowly. The mixture was stirred at −78 °C for 2 min, and a solution of the alcohol (0.53 g, 1.8 mmol) in CH_2Cl_2 (5 mL) was added rapidly. The resulting mixture was stirred at −78 °C for 30 min, and triethylamine (1.4 mL, 1.0 g 10 mmol) was added. The mixture was stirred at −78 °C for 5 min and brought to 20 °C. Water (10 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The organic phases were dried (Na_2SO_4) and concentrated to give 0.64 g of an oil, which was purified by flash chromatography[23] (CH_2Cl_2, 10% EtOAc) to afford 0.47 g (89%) of **10**: mp 102–103 °C; IR ($CHCl_3$ cast) 1775 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 9.13 (s, 1 H, C*H*O), 7.1–7.6 (m, 10 H, Ar *H*), 3.8 (t, 2 H, NCH_2CH_2), 2.77 (t, 2 H, CH_2CHO); exact mass 293.1051 (293.1052 calcd for $C_{18}H_{15}NO_3$). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.72; H, 5.12; N, 4.78. Found: C, 73.50; H, 4.98; N, 4.64.

4,5-Diphenyl-3-(4-oxobutyl)-4-oxazolin-2-one (11). This was prepared from commercially available 4-aminobutyraldehyde diethyl acetal (1.0 mL, 0.94 g, 5.9 mmol), 4,5-diphenyl-1,3-dioxol-2-one[17] (1.4 g, 5.9 mmol), and Et_3N (1.0 mL, 0.7 g, 7.2 mmol). The residue obtained after the CF_3COOH step[17] was dissolved in THF/H_2O (3:1 v/v, 20 mL). The solution was stirred 20 min at 20 °C, and the THF was removed in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with water and brine. Drying (Na_2SO_4) and concentration gave 2.30 g of an oil, which was recrystallized from EtOAc/hexane to give 1.17 g (65%) of **11**: IR ($CHCl_3$ cast) 1754 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 9.6 (s, 1 H, C*H*O), 7.0–8.0 (m, 10 H, Ar *H*), 3.55 (t, 2 H, CH_2N), 2.47 (t, 2 H, CH_2CHO), 1.53 (m, 2 H, $CH_2CH_2CH_2$); exact mass 307.1218 (307.1209 calcd for $C_{19}H_{17}NO_3$). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.26; H, 5.80; N, 4.56. Found: C, 73.99; H, 5.80; N, 4.40.

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Diethyl 3-Iodopropynephosphonate: An Alkylative β-Keto Phosphonate Equivalent

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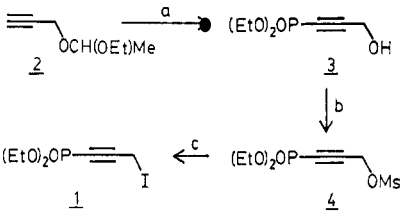
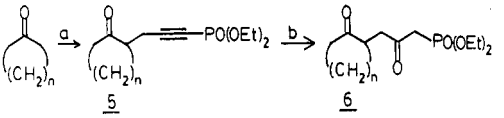
A wide range of natural products containing five-membered rings within their carbocyclic frameworks continue to be isolated and to challenge the imagination of synthetic chemists.[1] New strategies for their construction are constantly being developed; however, many of these methods require the establishment of a unique arrangement of functionalities in order to facilitate ring formation (i.e., vinylcyclopropane rearrangement,[2] Nazarov-type reactions,[3] α-alkynone cyclizations,[4] unsaturated diazoketone closures[5]). A straightforward approach to the introduction of a five-membered ring involves the alkylation of a ketone with an acetonyl equivalent, unmasking of the three-carbon appendage, and intramolecular cyclization. A variety of bromoacetone synthons have been developed for this purpose and utilized in the context of total synthesis.[6] For the most part, these reagents rely on an aldol reaction to close to the cyclopentenone ring. This process is often plagued with complications, such as base-catalyzed isomerization of initially formed products or anion exchange.[7] To improve the cyclization, the Wadsworth–Emmons reaction has become the method of choice, and two reagents have been developed for use in this manner: diethyl 3-bromo-2-ethoxypropenephosphonate[8] and bromoacetyl methylenetriphenylphosphorane.[9] Both reagents have

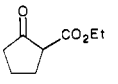
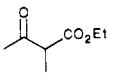
Scheme I[a]



[a] Reagents: (a) 1. *n*-BuLi/$ClPO(OEt)_2$, 2. 50% aqueous HOAc; (b) $MsCl/Et_3N$; (c) NaI.

Table I. Alkylation and Hydrolysis Results[a]



substrate	yield, % 5	6
n = 2	99	98
n = 3	99	97
n = 4	94	99
	98[b]	80
	96[b]	78

[a] Reagents: (a) $KN(SiMe_3)_2/BEt_3/1$; (b) $HgSO_4/10\%$ H_2SO_4/EtOH. [b] Alkylation conditions: NaH (1.1 equiv), substrate (1 M THF), 0 °C, 1 h, 1 (1 M THF), −78 °C, 30 min, room temperature 24 h.

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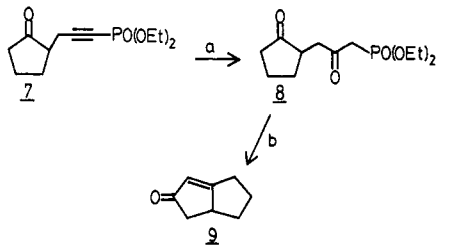
Scheme II[a]



7 8 9

[a] Reagents: (a) $HgSO_4$/10% H_2SO_4/EtOH; (b) n-Bu_4NOH/benzene/H_2O.

proven synthetically useful; however, these limited options may prove vexing in the context of total synthesis. Herein, we report our study of diethyl 3-iodopropynephosphonate as a phosphonate-containing acetonyl equivalent.

Phosphate 1 was prepared in four steps from the ethyl vinyl ether protected proparagyl alcohol 2 (Scheme I).[10] Treatment of 2 with n-butyllithium followed by reaction with diethyl chlorophosphate and acidic workup gave acetylenic phosphonate 3. The hydroxyl group was converted to iodide 1 by mesylation and displaced with sodium iodide. Diethyl 3-iodopropynephosphonate (1) was prepared by this method in 75% overall yield.

Next, the effectiveness of 1 as an acetonyl equivalent for the preparation of β-keto phosphonates was established (Table I). Treatment of ketone enolates, formed under the conditions described by Negishi,[11] with 1 gave the corresponding alkylation products 5. These acetylenic phosphonates were hydrolyzed with acidic mercury(II) sulfate to yield the expected β-keto phosphonates 6. Compounds containing a β-keto ester functionality also underwent alkylation and were hydrolyzed to the corresponding reagents in the same manner. In all cases studied, the acetylenic phosphonates hydrolyzed without formation of isomeric ketophosphonates.[12]

To demonstrate the cyclopentane annulation process, compound 8 was cyclized to pentalene 9 by the Heathcock procedure (Scheme II).[13] Thus, diethyl 3-iodopropynephosphonate can be utilized as an acetonyl equivalent for the annulation of five-membered rings.

Experimental Section

The NMR spectra were recorded on a Varian EM-390 or JEOL FX-90Q. Chemical shifts are expressed in parts per million downfield from Me_4Si. The infrared spectra were recorded on a Perkin-Elmer 1420 spectrophotomer. Mass spectra were obtained by chemical ionization with isobutane on a VG-7035 mass spectrometer.

All reactions were run in flame-dried vessels under an atmosphere of nitrogen except those in which water was present. All additions wherever possible were made via syringe through a septum, and all reactions were stirred with magnetic stirrers. Dry THF was obtained by distillations from sodium benzophenone ketyl. The base $KN(SiMe_3)_2$ was generated by the reaction of KH with 1.2 equiv of $HN(SiMe_3)_2$ in THF, according to a literature procedure.[14] All other reagents and solvents were obtained from commercial sources and purified by standard methods.

2-Propyn-1-yl 1-Ethoxyethyl Ether (2). To a solution of propargyl alcohol (28 mL, 0.48 mol) and ethyl vinyl ether (46 mL, 0.48 mol) at 0 °C was added dichloroacetic acid (0.5 mL). After the mixture had been stirred for 1 h, it was neutralized with solid K_2CO_3 and extracted with ether (3 × 50 mL). The combined organic layers were washed with water (2 × 50 mL), dried over Na_2SO_4, and evaporated to give 54.7 g (90%) of 2: bp 27–30 °C (10 mmHg); IR ($CHCl_3$) 3312, 3016, 2118 cm^{-1}; ^1H NMR ($CDCl_3$) 4.85 (q, J = 5, 9 Hz, 1 H), 4.2 (m, 2 H), 3.6 (m, 2 H), 2.4 (m, 1 H), 1.35 (d, J = 5 Hz, 3 H), 1.2 (t, J = 9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 98.2, 79.8, 73.7, 60.4, 53.1, 19.3, 14.9; MS, m/e (relative intensity) 128 (0.5), 113 (24.4), 83 (50.3), 73 (100). Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.49; H, 9.45.

Diethyl 3-Hydroxypropynephosphonate (3). To a −78 °C solution of 2 (11.85 g, 0.094 mol) in THF (97.5 mL) was added n-butyllithium (33.5 mL of 2.86 M in hexane, 0.094 mol). The solution was stirred for 30 min, at which time a solution of diethyl chlorophosphate (15 mL, 0.104 mol) in THF (112 mL) was added dropwise. The reaction was stirred at −78 °C for 30 min, quenched with acetic acid (82.6 mL) in water (77.4 mL), and stirred at room temperature for 12 h. The solution was neutralized with saturated Na_2CO_3, washed with EtOAc (3 × 75 mL), dried over Na_2SO_4, and evaporated to give 17 g (94%) of 3: bp 172–173 °C (0.3 mmHg); IR ($CHCl_3$) 3340, 3016, 2206, 1247, 1210 cm^{-1}; ^1H NMR ($CDCl_3$): 4.5 (br s, 1 H), 4.25–3.8 (m, 6 H), 1.25 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) 100.5 (d, J = 51.3 Hz), 73.8 (d, J = 299.1 Hz), 63.5 (d, J = 6.1 Hz), 50.4 (d, J = 4.9 Hz), 16.0 (d, J = 7.3 Hz); ^{31}P NMR (D_2O) −4.9; MS, m/e (relative intensity) 192 (100), 165 (11.9), 146 (11.8), 137 (11.3), 119 (10.2), 79 (7.3). Anal. Calcd for $C_7H_{13}O_4P$: C, 43.76; H, 6.82. Found: C, 44.40;, H, 7.19.

Diethyl 3-Iodopropynephosphonate (1). To a solution of 3 (4 g, 0.021 mol) and triethylamine (6.38 mL, 0.026 mol) in methylene chloride (139 mL) at 0 °C was added methanesulfonyl chloride (3.54 mL, 0.026 mol). The reaction was warmed to room temperature after 15 min, and stirring was continued for an additional 3 h. The solution was diluted with methylene chloride (100 mL), washed with 10% HCl (2 × 50 mL), saturated Na_2CO_3 (2 × 50 mL), and water (1 × 50 mL), dried over Na_2SO_4, and evaporated to give 5.47 g (97%) of 4: IR ($CHCl_3$) 3014, 2219, 1248 cm^{-1}; ^1H NMR ($CDCl_3$) 4.85 (d, J = 3 Hz, 2 H), 4.1 (m, 4 H), 3.05 (s, 3 H), 1.3 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) 91.2 (d, J = 50.1 Hz), 78.4 (d, J = 288.1 Hz), 63.2 (d, J = 6.1 Hz), 56.0 (d, J = 4.3 Hz), 37.9, 15.5 (d, J = 7.3 Hz); ^{31}P NMR ($CDCl_3$) −8.5; MS, m/e (relative intensity) 270 (100), 243 (9.8), 215 (8.7), 197 (3.6), 175 (6.0), 146 (21.7), 103 (7.8), 79 (5.4). Anal. Calcd for $C_8H_{15}O_6PS$: C, 35.56; H, 5.59. Found: C, 35.65; H. 5.65.

A solution of 4 (32.05 g, 0.116 mol), sodium iodide (24.88 g, 0.464 mol) and acetone (348 mL) was refluxed for 12 h. The solvent was evaporated, water (150 mL) added, and the resultant solution washed with ether (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give 28.39 g (81%) of 1: IR ($CHCl_3$) 3010, 2202, 1259 cm^{-1}; ^1H NMR ($CDCl_3$) 4.1 (m, 4 H), 3.6 (d, J = 4 Hz, 2 H), 1.2 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) 96.9 (d, J = 52.5 Hz), 75.3 (d, J = 257.6 Hz), 63.4 (d, J = 6.1 Hz), 16.1 (d, J = 7.3 Hz), −22.2 (d, J = 4.9 Hz); ^{31}P NMR ($CDCl_3$) +3.3; MS, m/e (relative intensity) 302 (100), 275 (7.5), 229 (7.7), 175 (24.0), 147 (19.8), 103 (44.2). Anal. Calcd for $C_7H_{12}O_3I$: C, 27.84; H, 4.00; I, 42.01. Found: C, 28.94; H, 4.20; I, 39.80.

General Alkylation Procedure. Preparation of 7. To a −78 °C solution of $KN(SiMe_3)_2$ (0.18 mL of 1 M in THF) was added cyclopentanone (0.018 mL, 0.181 mmol) in THF (0.17 mL), and the resultant mixture was stirred for 10 min at −78 °C and then 1 h at 0 °C. The reaction was cooled to −78 °C, triethylborane (0.18 mL of 1 M in THF) was added, and the resultant mixture was stirred for 30 min. After addition of 1 (50 mg, 0.165 mmol), the solution was stirred at −78 °C for 30 min and at room temperature for 12 h. The reaction mixture was diluted with 10% HCl (0.5 mL) and evaporated. The residue was washed with $CHCl_3$ (5 × 1 mL), dried through $MgSO_4$, and evaporated to give 43.4 mg (99%) of 7: IR ($CHCl_3$) 2205, 1738 cm^{-1}; ^1H NMR ($CDCl_3$) 4.0 (m, 6 H), 2.7–1.3 (m, 7 H), 1.9 (d, J = 4.5 Hz, 2 H), 1.2 (t, J

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= 7 Hz, 6 H); ^{13}C NMR (CCl_4) 214.6, 98.9 (d, J = 51.3 Hz), 72.6 (d, J = 299.1 Hz), 62.1 (d, J = 4.88 Hz), 46.8, 37.1, 28.8, 19.2 (d, J = 4.88 Hz), 16.2 (d, J = 6.1 Hz); ^{31}P NMR (CCl_4) -8.0; MS, m/e (relative intensity) 258 (11), 229 (15), 201 (11), 161 (99). Anal. Calcd for $C_{12}H_{19}O_4$: C, 56.00; H, 7.44. Found: C, 55.77; H, 7.43.

General Hydrolysis Procedure. Preparation of 8. To solution of 7 (0.183 g, 0.70 mmol), $HgSO_4$ (51.9 mg, 0.18 mmol), and EtOH (2 mL) at 0 °C was added 10% H_2SO_4 (0.69 mL), and the resultant reaction mixture was stirred at room temperature for 48 h. The solvent was evaporated and the residue washed with $CHCl_3$ (3 × 2 mL), dried through $MgSO_4$, and evaporated to give 0.188 g (98%) of 8: IR ($CHCl_3$) 1732, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) 4.1 (m, 4 H), 3.05 (d, J = 21 Hz, 2 H), 2.6-1.4 (m, 9 H), 1.2 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) 211, 200.2 (d, J = 4.9 Hz), 62.8 (d, J = 7.3 Hz), 44.9, 43.8, 42.6 (d, J = 126.9 Hz), 37.4, 29.3, 20.9, 16.4 (d, J = 6.1 Hz); ^{31}P NMR ($CDCl_3$) +19.6, +31.9 (enol); MS, m/e (relative intensity) 276 (15), 248 (10), 220 (55), 179 (39), 152 (82), 125 (57). Anal. Calcd for $C_{12}H_{21}O_5P$: C, 52.17; H, 7.66. Found: C, 52.08; H, 7.67.

Bicyclo[3.3.0]oct-1-en-3-one (9). To a solution of 8 (29 mg, 0.11 mmol) in benzene/water (2 mL, 1:1, v/v) at room temperature was added a solution of tetrabutylammonium hydroxide (0.3 mL, 0.18 mmol, 40 wt % in water). The resulting mixture was vigorously stirred for 2 h, and the layers separated. The aqueous phase was extracted with Et_2O (2 × 2 mL), and the combined organic layers were dried with $MgSO_4$, evaporated, and chromatographed (Et_2O) to give 11 mg (90%) of 9: IR ($CHCl_3$) 1700, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) 5.9 (s, 1 H), 2.4-3.2 (m, 4 H), 1.6-2.4 (m, 4 H), 0.8-1.6 (m, 1 H); ^{13}C NMR ($CDCl_3$) 210.6, 190.8, 124.9, 46.9, 42.4, 31.2, 26.3, 25.6; MS, m/e (relative intensity) 122 (100), 81 (0.5).

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Registry No. 1, 110271-58-4; 2, 18669-04-0; 3, 7653-22-7; 4, 110271-59-5; 5 (n = 2), 110294-72-9; 5 (n = 3), 110271-62-0; 6 (n = 2), 110271-61-9; 6 (n = 3), 110271-63-1; 7, 110271-60-8; 8, 77861-34-8; 9, 72200-41-0; $C(O)CH(CO_2Et)CH_2CH_2CH_2$, 611-10-9; $H_3CC(O)CH(CO_2Et)CH_3$, 609-14-3; $C(O)C(CO_2Et)(CH_2C{\equiv}CP(O)(OEt)_2)CH_2CH_2CH_2$, 110271-64-2; $C(CO)C(CO_2Et)CH_2C(O)CH_2P(O)(OEt)_2)CH_2CH_2CH_2$, 110271-65-3; $H_3CC(O)C(CO_2Et)(CH_2C{\equiv}CP(O)(OEt)_2)CH_3$, 110271-66-4; $H_3CC(O)C(CO_2Et)(CH_2C(O)CH_2P(O)(OEt)_2)CH_3$, 110271-67-5; cyclopropanone, 5009-27-8; cyclobutanone, 1191-95-3; cyclopentanone, 120-92-3; propargyl alcohol, 107-19-7; ethyl vinyl ether, 109-92-2; diethyl chlorophosphate, 814-49-3.

Reactivity Difference of Cis-Trans Pairs: Different Behavior of Stilbene Oxides and Activated Stilbene Imines[1,2]

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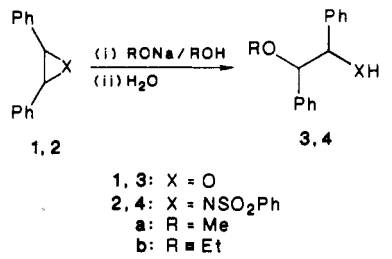
Recently[3,4] the hypothesis was put forward that nucleophilic ring opening of aziridines with a tervalent nitrogen proceeds most easily in the planar transition state of nitrogen inversion. Apart from theoretical considerations (increased ring strain, favorable steric and stereoelectronic conditions), this hypothesis was based[3] on experiments described by Gaertner[5] and on a reactivity comparison[3,6] of aziridines with cyclopropanes possessing similar strength of activation, i.e., similar basicity of their leaving groups. We present now simple experiments that harmonize well with this hypothesis.

Scheme I



A pair of cis-trans isomeric 2,3-disubstituted aziridines was considered suitable as probe for the hypothesis, since the trans isomer will invert faster than the cis isomer, even much faster if the two substituents are rather large. The trans isomer has two indistinguishable invertomers, and in both invertomers the nitrogen pyramid may be flattened for steric reasons. The cis isomer will exist practically exclusively as trans invertomer with a steep pyramid. This preferred trans invertomer of the cis isomer is confronted with a high inversion barrier. Inversion of the cis isomer can therefore be expected to be slower than inversion of the trans isomer.

To avoid possible complications in the intended study by nonsymmetry, identical substituents for positions 2 and 3 should be preferred and, in order to obtain sufficient reactivity, the aziridine should carry an activating group on the nitrogen atom. Pyramidal nitrogen conformation and nitrogen inversion are retained in activated aziridines, although their inversion process is faster than that of aziridine bases.[7] Therefore, we thought it might be informative to make a cis-trans reactivity comparison of such an aziridine pair with the two oxirane counterparts. The two oxiranes[8] and the two aziridines[9] can be expected to react in an S_N2 mechanism, provided the activated aziridines do not switch to an SET mechanism.[4,10] The latter possibility is very unlikely in alkoxide attack[3] on sulfonyl-activated aziridines.[4,10]

Fortunately, we found in a paper of Blum et al.[11] the experimental detail that *cis*-stilbene oxide reacts faster (3-h reflux in aqueous acetone) than *trans*-stilbene oxide (48 h) with sodium azide. Therefore we performed simple experiments to find out which isomer of 1 and of 2 reacts faster with sodium methoxide or sodium ethoxide (Scheme I).

(1) Reactions with Aziridines. 43.
(2) Part 42: Buchholz, B.; Stamm, H. *Chem. Ber.* **1987**, *120*, 1239.
(3) Buchholz, B. Stamm, H. *Isr. J. Chem.* **1986**, *27*, 17.
(4) Stamm, H.; Sommer, S.; Woderer, A.; Wiesert, W.; Mall, T.; Assithianakis, P. *J. Org. Chem.* **1985**, *50*, 4946.
(5) Gaertner, V. R. *J. Heterocycl. Chem.* **1971**, *8*, 177.
(6) Footnote 20 in ref 4.
(7) Lehn, J. M. *Fortschr. Chem. Forsch.* **1970**, *15*, 313. One of the reviewers proposed we consider an alternative explanation based on a trigonal-planar nitrogen conformation in the ground state of 2. Such a ground state does not harmonize with X-ray results of other *N*-sulfonylaziridines. Compare: Massa, W.; Birkhahn, M.; Landmann, B.; Hoffmann, R. W. *Chem. Ber.* **1983**, *116*, 404 and the literature cited therein.
(8) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737.
(9) See, e.g., preceeding papers of this series.
(10) Stamm, H.; Assithianakis, P.; Buchholz, B.; Weiss, R. *Tetrahedron Lett.* **1982**, 5021.
(11) Ittah, Y.; Sasson, Y.; Shohak, I.; Tsaroom, S.; Blum, J. *J. Org. Chem.* **1978**, *43*, 4271.

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