Reaction of Phosphonate-Stabilized Carbanions with Cyclic Enones Bearing a β-Leaving Group

Malose J. Mphahlele and Tomasz A. Modro*

Centre for Heteroatom Chemistry, Department of Chemistry, University of Pretoria, Pretoria 0002, South Africa

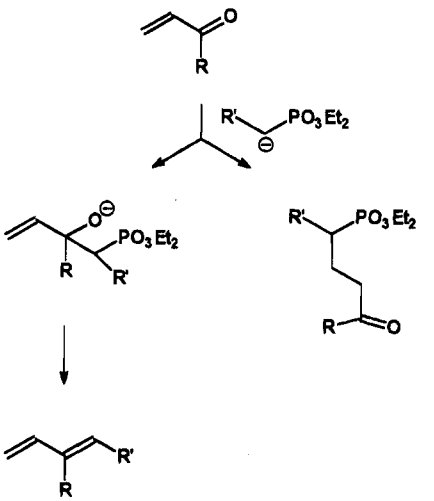
Received July 21, 1995[⊗]

Reaction between α-lithiated alkylphosphonic esters and α,β-unsaturated cyclopentenones and cyclohexenones carrying a heteroatom substituent Y in the β-position was studied. Complete chemoselectivity was observed as a function of substituent Y. For Y = OMe exclusive addition–elimination at the β-carbon was observed, yielding α,β-unsaturated δ-ketophosphonates. The β-chloro-substituted substrates (Y = Cl) derived from cyclohexenone reacted exclusively at the carbonyl carbon, yielding (2-hydroxyalkyl)phosphonates with the retained chlorovinyl function. The alcohols, depending on the conditions, could be dehydrated to two different products. The reaction of 3-chlorocyclopent-2-en-1-one with diethyl (lithiomethyl)phosphonate occurred at the β-carbon, but the ketophosphonate product was isolated in a stable enolic form.

Introduction

Reaction of phosphorus–stabilized carbanions with carbonyl substrates represents one of the major methods in synthetic organic chemistry.[1] In the case of α,β-unsaturated carbonyl compounds, the reaction can follow the addition to the carbonyl group (a route to dienes), or to the β-carbon, yielding a δ-ketophosphonate (Scheme 1). Literature reports[2] show that both reactions can take place, the regioselectivity being a complex function of the structure of both, the nucleophile and the electrophile, of the base or of the solvent. It was concluded that the increase in the delocalization of the negative charge in the nucleophile favors reaction at the β-carbon,[2c] but in the addition of triethyl phosphonoacetate to chalcone the regioselectivity was changed completely by the change of the base from NaH to EtONa.[2b] Amido esters of allylphosphonic acid react with cyclic enones exclusively at the β-carbon;[2d] however, the polyvinylogation of α,β-unsaturated aldehydes with carbanions derived from vinylogues of acetals of phosphonoacetaldehyde involves the exclusive addition to the carbonyl group.[2e] Zbiral and Ohler demonstrated exclusive carbonyl selectivity in the addition of diethyl (lithiomethyl)phosphonate (a poorly delocalized carbanion) to cyclic enones;[2g] a similar result was reported for the reaction of the diisopropyl analogue with α,β-unsaturated aldehydes.[2h] In one report,[2f] a saturated β-(2-phosphonoalkyl)-substituted cyclohexanone was obtained from cyclohexenone and β-copper–zinc phosphonate *via* Michael addition, but the unsaturated analogue, β-substituted cyclohexenone, could be prepared from 3-iodocyclohexenone *via* an addition–elimination process. In this respect, the latter reaction represented an extension of the preparation of 3-alkyl cyclic enones from β-halo-α,β-enones and organocuprates.[3] We have reported a similar addition–elimination mechanism for the reaction between lithiated diethyl prop-2-enylphosphonate and (*E*)-4-methoxybut-3-en-2-one yielding (after prototropic isomerization) diethyl 6-oxohepta-2,4-dienylphosphonate (Scheme 2).[4]

Scheme 1



In continuation of our interest in nucleophilic reactivity of phosphonic derivatives,[5] we decided to investigate the reaction of *localized* [6] phosphoryl-stabilized carbanions with cyclic enones bearing a potential leaving group in the β-position.

Results and Discussion

Four β-methoxy-substituted (**1a–d**) and three β-chloro-substituted (**2a–c**) cyclic enones were used as substrates

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1995.

(1) (a) Cadogan, J. I. G.; Ed. *Organophosphorus Reagents in Organic Synthesis*, Academic Press: London, 1979. (b) Maryanoff,; B. E. Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(2) (a) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. (b) Bergmann, E. D.; Solomonovici, A. *Tetrahedron* **1971**, *27*, 2675. (c) Cossentini, M.; Deschamps, B.; Anh, N. T.; Seyden-Penne, J. *Tetrahedron* **1977**, *33*, 409, 413. (d) Hua, D. H.; Chan-Yu-King, R.; McKie, J. A.; Myer, L. *J. Am. Chem. Soc.* **1987**, *109*, 5026. (e) Duhamel, L.; Guillemont, J.; Le Gallic, Y.; Ple, G.; Poirier, J-M.; Ramondec, Y.; Chabardes, P. *Tetrahedron Lett.* **1990**, *31*, 3129. (f) Retheford, C.; Chou, T.-S.; Schelkun, R. M.; Knochel, P. *Tetrahedron Lett.*, **1990**, *31*, 1833. (g) Ohler, E.; Zbiral, E. *Synthesis* **1991**, 3597. (h) Zon. J.; Leja, E. *Phosphorus, Sulfur, Silicon* **1992**, *71*, 179.

(3) Piers, E.; Nagakura, I. *J. Org. Chem.* **1975**, *40*, 2694.

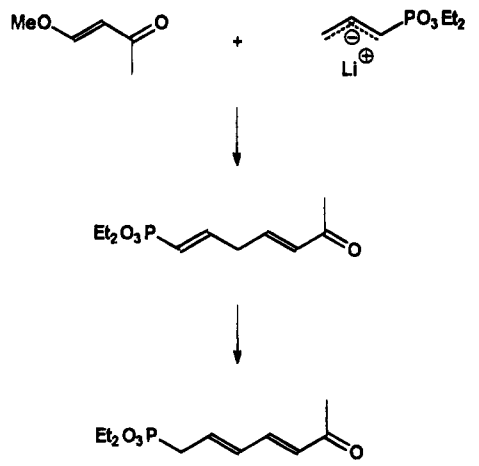
(4) Phillips, A. M. M.; Modro T. A. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1875.

(5) Muller, E. L.; Modro, A. M.; Modro, T. A. *Bull. Soc. Chim. Fr.* **1994**, *131*, 959, and preceeding papers of this series.

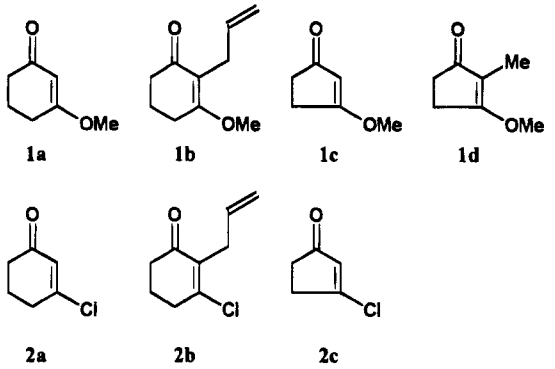
(6) The term *localized* is used here with respect to a carbanion which can react with an electrophile *via* only one carbon atom (α-carbon of the phosphonate). When an allylic phosphonate is used as a precursor, the carbanion formed can react with an electrophile *via* one of the two nucleophilic centers (α- and γ-carbons).[7] Reactions of such "*delocalized*" (ambident) carbanions with β-substituted α,β-unsaturated ketones will be reported in the following publication.

0022-3263/95/1960-8236$09.00/0

Scheme 2



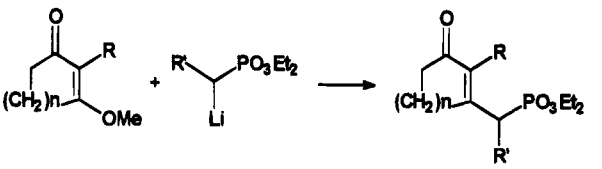
in reaction with lithiated diethyl methyl (**3a**) and ethyl (**3b**) phosphonates.



Methoxy derivatives **1** reacted with nucleophiles **3** exclusively at the β-carbon, yielding, according to the addition–elimination mechanism,[8] products **4**, resulting from the substitution of the methoxy group by the phosphonoalkyl nucleophile (Scheme 3). The reaction represents therefore a convenient route to 3-(phosphorylmethyl)cycloalkenones. Similar systems were prepared recently by different approaches, one that employed intramolecular Horner–Wittig reaction of bis-β-keto-phosphonates,[10] another involving oxidation of the alcohols obtained in the carbonyl addition of the P-stabilized carbanions to cycloalkenones.[2g]

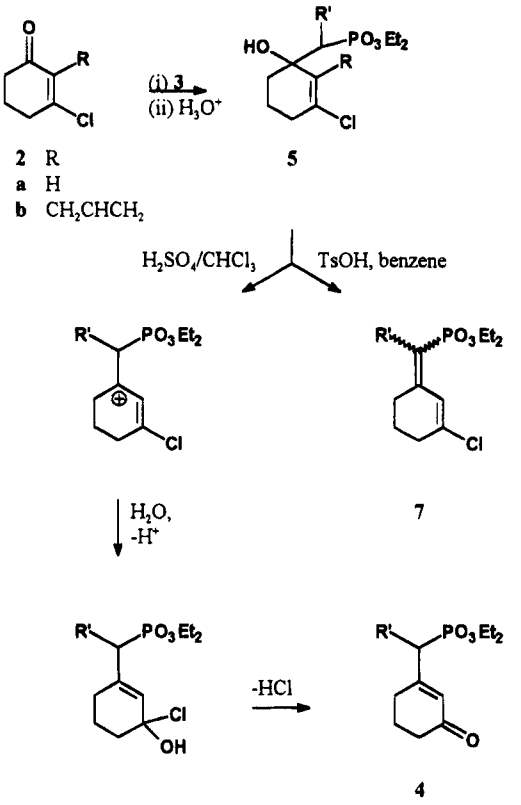
The reaction with 3-chlorocyclohexenones (**2a,b**) took a different course and involved an exclusive addition to the carbonyl group (Scheme 4). (2-Hydroxyalkyl)phosphonates **5** formed upon aqueous workup could be isolated and purified without any signs of decomposition. The observed rigorous and opposed regioselectivity in the nucleophilic addition of the phosphonate nucleophiles to substrates **1** and **2** suggests a strong effect of the β-heteroatom on the distribution of the electrophilic

Scheme 3

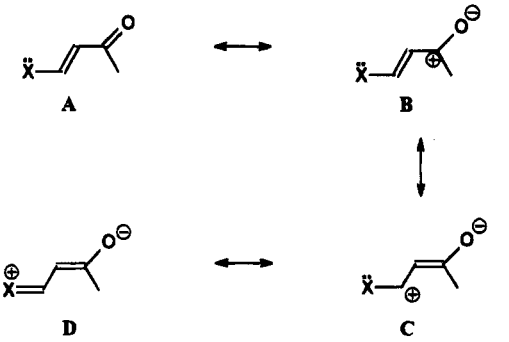


1	n	R	**3**	R'	**4**
a	2	H	**a**	H	
b	2	CH_2CHCH_2	**b**	Me	
c	1	H			
d	1	Me			

Scheme 4



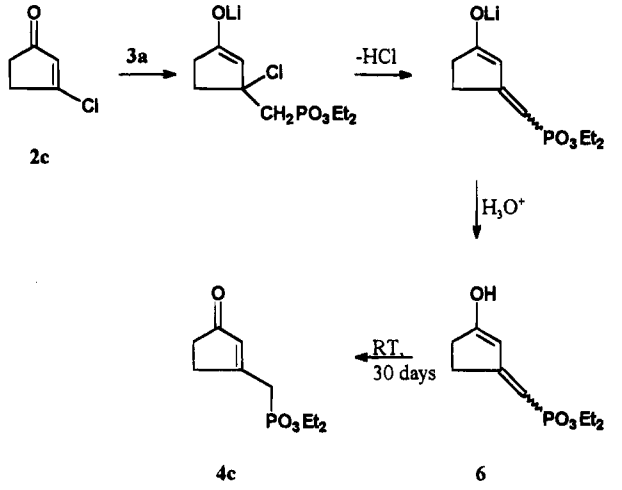
Scheme 5



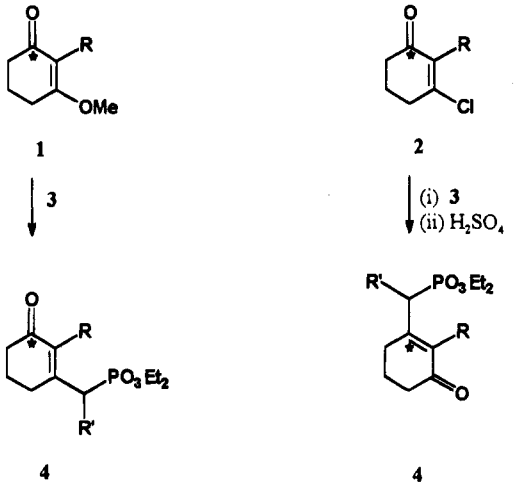
reactivity within the α,β-unsaturated system (Scheme 5). Because of significant difference in the inductive and resonance components of the electronic effects of the methoxy and chloro substituents (for Cl $\sigma_I = 0.47$, and $\sigma_R^\circ = -0.21$; for OMe $\sigma_I = 0.26$, and $\sigma_R^\circ = -0.41$[11]), we expect the contribution of the resonance hybrid **D** to be

(7) Muller, E. L.; Modro, T. A. *Bull. Soc. Chim. Fr.* **1993**, *130*, 668.
(8) As one referee pointed out, a bimolecular vinylic S_N type reaction cannot be completely excluded for the conversion **1** → **4**. Indeed, we have never observed any intermediate addition product, so, if it is formed, it collapses to the final product in a fast step. Analogous intermediates were, however, observed in the substitution of the methoxy group by thiolate ions in β-methoxy-α-nitrostilbene.[9] Because the MeO group (under basic conditions) is a much poorer leaving group than Cl, we believe that substrates **2**, rather than **1**, should be more reactive in the direct vinylic substitution.
(9) Bernasconi, C. F.; Killion, R. B.; Frassberg, J.; Rappoport, Z. *J. Am. Chem. Soc.* **1989**, *111*, 6862.
(10) Mikolajczyk, M.; Mikina, M. *J. Org. Chem.* **1994**, *59*, 6760.

Scheme 6



Scheme 7



much lower for X = Cl, hence lower electrophilic reactivity should be expected for substrates **2** at the β-carbon atom. It seems therefore that by selecting a specific substituent, β-hetero-substituted enones can serve as substrates for the preparation of unsaturated δ-ketophosphonates of the type **3** or 4-substituted 2-hydroxy-3-alkenylphosphonates (type **4**).

The behavior of 3-chlorocyclopentenone (**2c**) was exceptional. Its reaction with **3a** resulted in the attack at the β-carbon of **2c**, but the isolated product was shown to be an enolic form (**6**) of the corresponding ketophosphonate **4**. The enol was remarkably stable and tautomerized to the α,β-unsaturated ketone only after about one month at room temperature. Although the structure of the enol **6** was unambigously determined by spectroscopic methods (IR, ^1H, ^{13}C, ^{31}P NMR), the exact mechanism of its formation is not clear. It seems that for this substrate, the initial β-adduct undergoes 1,2-elimination of HCl rather than expulsion of chloride ion, yielding directly the enolate ion of **6** (Scheme 6). The stability of **6** is altogether not too surprising, as it represents a vinylogue of the diethyl (2-oxoethyl)phosphonate system, $Et_2O_3PCHRCHO$, which was demonstrated to exist mostly in a form of the (E) enolic tautomer, $Et_2O_3PCR{=}CHOH$.[12]

(2-Hydroxyalkyl)phosphonates **5** did not undergo the Horner–Wittig fragmentation to dienes under standard conditions (NaH in DMF[13]), yielding the unchanged substrates.[14] Substrates **5**, as tertiary alcohols, were found to be unstable under acidic conditions, but the course of their acid-catalyzed reaction depended on the applied conditions (Scheme 4). In benzene containing catalytic amounts of *p*-toluenesulfonic acid, **5a** was converted to the expected vinylic phosphonate **7**. After separation, two stereoisomers (*Z* and *E*) of **7** were obtained in pure form, and their configuration was tentatively assigned on the basis of the ^1H NMR chemical shift of the ring olefinic proton, 2′-H. A large difference in the chemical shift values was observed for that proton in two isomers ($\Delta\delta_H$ = 1.03 ppm), and the low-field shift was taken as a consequence of the deshielding effect of the phosphoryl substituent in the *Z* stereoisomer. When substrates **5** were treated in a chloroform solution with a drop of concd H_2SO_4, followed by the addition of water (or in neat trifluoroacetic acid), they gave, after the usual workup, ketophosphonates **4**, obtained previously from the methoxy-substituted substrates **1**. Formation of the ketophosphonates can be explained by the mechanism shown in Scheme 4; the reaction produces a **4** in which the carbonyl carbon is the carbon that carried the Cl atom in the substrate. That "different history" of two products **4** produced *via* two different pathways from different starting materials could be confirmed by experiments involving labeled substrates (Scheme 7).

Experimental Section

All solvents and commercially available reagents were purified by conventional methods before use. Reactions involving organolithium reagents were carried out in an atmosphere of dry nitrogen using flame-dried glassware. Melting points are uncorrected. For column chromatography, Merck Kieselgel 60 (0.063–0.200 mm) was used as a stationary phase. Mass spectra were recorded at an ionization potential of 70 eV. ^1H and ^{13}C NMR chemical shifts are given relative to the solvent ($CDCl_3$; ^1H: 7.24 ppm; ^{13}C: 77.0 ppm). ^{31}P NMR chemical shifts are given relative to 85% H_3PO_4 as external standard.

Diethyl methyl- and ethylphosphonate were prepared according to the literature procedure.[16]

2-(Prop-2-yl)cyclohexane-1,3-dione was prepared (55%) from cyclohexane-1,3-dione according to the literature procedure.[17]

3-Chlorocycloalkenones 2 were prepared from the corresponding cycloalkane-1,3-diones according to the literature procedures.[18,19]

3-Methoxycycloalkenones 1 were prepared according to the following general procedure developed in our laboratory. 3-Chlorocycloalkenone **2** (1 mol equiv) was added to a stirred suspension of anhydrous potassium carbonate (2 mol equiv) in dry methanol (2 mL/mmol of **2**), and the mixture was stirred

(11) Isaacs, N. S. *Physical Organic Chemistry*; Longman Scientific: Burnt Hill, Harlow, 1987; p 158.
(12) Petrova, J.; Zdravkova, Z. *Phosphorus, Sulfur, Silicon* **1993**, *81*, 89.
(13) Buss, A. D.; Cruse, W. C.; Kennard, O.; Warren, S. *J. Chem. Soc. Perkin Trans. 1* **1984**, 243.
(14) It is interesting to note that the related adduct of lithiated diethyl cyclohexen-2-ylphosphonate to cyclohexanecarboxaldehyde fragmented spontaneously yielding 34% of 3-(cyclohexylmethylidene)-cyclohexene.[15] It seems that the reversal of the relative positions of the phosphoryl substituent and the alkoxide oxygen has an effect on the rate of the elimination of the diethylphosphate ion.
(15) Gerber, J. P.; Modro, T. A. *Phosphorus, Sulfur, Silicon* **1994**, *88*, 99.
(16) *Organic Synthethes*; J. Wiley: New York, 1963, Coll. Vol. 4, p 326.
(17) Bullivant, M. J.; Pattenden, G. *J. Chem. Soc. Perkin Trans. 2* **1976**, 249.
(18) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 636.
(19) Piers, E.; Grierson, J. R.; Lau, C. K.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 210.

at room temperature for a period specific for each substrate. Water was added, and the solution was neutralized with 10% HCl and extracted with chloroform (3 × 30 mL/mmol of **1**). The chloroform solution was washed with water, dried ($MgSO_4$), filtered, and evaporated, and the crude product was purified as described below.

3-Methoxycyclohex-2-en-1-one (1a). Reaction time 1 h (75%): bp 80–82 °C (0.7 mm); mp 43–45 °C; ^{1}H NMR ($CDCl_3$) δ 1.94 (2H, dt, J = 6.3, 9.6 Hz), 2.30 (2H, t, J = 6.2 Hz), 2.36 (2H, t, J = 6.2 Hz), 3.64 (3H, s), 5.32 (1H, s); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 20.9, 28.5, 36.3, 55.3, 101.9, 178.6, 199.4; MS m/z 126 (M^+, 56), 98 (73), 69 (54), 68 (100), 40 (5). Anal. Calcd for $C_7H_{10}O_2$: C, 66.65 ; H, 7.99. Found: C, 66.55; H, 8.12.

3-Methoxy-2-(propen-2-yl)cyclohex-2-en-1-one (1b). Reaction time 24 h (50%): purified by column chromatography ($CHCl_3$–AcOEt, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.98 (2H, dt, J = 6.2, 9.0 Hz), 2.33 (2H, t, J = 6.7 Hz), 2.56 (2H, t, J = 6.2 Hz), 2.99 (2H, d, J = 6.1 Hz), 3.78 (3H, s), 4.87 (2H, m), 5.76 (1H, m); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 20.8, 24.9, 26.2, 36.3, 55.2, 113.8, 136.5, 150.2, 174.0, 198.1; MS m/z 166 (M^+, 38), 151 (100), 135 (45), 41 (72). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.95; H, 8.38.

3-Methoxycyclopent-2-en-1-one (1c). Reaction time 1 h (80%): mp (ether-hexane, 1:1) 50–51 °C (lit.[20] mp 50.3–52.1 °C).

3-Methoxy-2-methylcyclopent-2-en-1-one (1d). Reaction time 18 h (74%): purified by bulb to bulb distillation; oven temp 75 °C (0.5 mm); mp (ether–hexane, 1:1) 59–61 °C; ^{1}H NMR ($CDCl_3$) δ 1.62 (3H, s), 2.43 (2H, m), 2.62 (2H, m), 3.94 (3H, s); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 5.85, 24.6, 33.3, 56.3, 150.1, 187.0, 206.1; MS m/z 126 (M^+, 100), 112 (42), 97 (51), 83 (68), 55 (58), 43 (60), 27 (54). Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.35; H, 8.10.

Reaction of 3-Methoxycycloalk-2-en-1-ones (1) with Lithiated Diethyl Alkylphosphonates (3). General Procedure. To a stirred solution of n-butyl lithium (1.6 M solution in hexane; 5.4 mL, 8.7 mmol) was added a solution of **3** (7.9 mmol) in THF (1 mL) dropwise at −65 °C. The solution was stirred at −65 °C for 30 min, and a solution of **1** (7.9 mmol) in THF (1 mL) was added dropwise. After 15 min at −65 °C the mixture was allowed to warm up to room temperature and was then stirred for another 15 min.The mixture was quenched with saturated aqueous ammonium chloride and extracted with chloroform (3 × 30 mL). The chloroform extract was washed with water (2 × 20 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The following products **4** were prepared.

Diethyl [(3-Oxo-1-cyclohexen-1-yl)methyl]phosphonate (4a, n = 2; R = R′ = H). Purified by bulb to bulb distillation (oven temp 125 °C (1 mm); lit.[2g] oven temp 120 °C (0.01 Torr)) (70%): ^{1}H NMR ($CDCl_3$) δ 1.30 (6H, t, J = 7.1 Hz), 1.99 (2H, dt, J = 6.2, 9.6 Hz), 2.35 (2H, t, J = 6.4 Hz), 2.46 (2H, dd, J = 4.7, 10.4 Hz), 2.73 (2H, d, J = 23.6 Hz), 4.08 (4H, dq, J = 7.2, 11.2 Hz), 5.94 (1H, J = 5.0 Hz); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 16.4 (d, J = 5.6 Hz), 22.6, 30.5, 36.3 (d, J = 135.1 Hz), 37.0, 62.4 (d, J = 6.6 Hz), 129.4 (d, J = 11.0 Hz), 156.1 (d, J = 10.9 Hz), 199.0; ^{31}P NMR ($CDCl_3$) δ 24.3; IR (CCl_4) ν_{PO} 1254.0, ν_{CO} 1679.5.

Diethyl [1-(3-Oxo-1-cyclohexen-1-yl)ethyl]phosphonate (4b, n = 2; R = H; R′ = Me). Purified by column chromatography ($CHCl_3$–AcOEt, 4:1) (62%): ^{1}H NMR ($CDCl_3$) δ 1.26 (6H, t, J = 7.0 Hz), 1.35 (3H, dd, J = 7.2, 18.0 Hz), 1.96 (2H, dt, J = 6.7, 9.5 Hz), 2.34 (2H, t, J = 6.7 Hz), 2.47 (2H, m), 2.73 (1H, dq, J = 7.3, 24.7 Hz), 4.06 (4H, dq, J = 7.0, 11.1 Hz), 5.95 (1H, d, J = 4.6 Hz); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 12.9 (d, J = 6.4 Hz), 16.1 (d, J = 5.6 Hz), 22.4, 28.9, 37.0, 40.1 (d, J = 134.9 Hz), 62.1 (two d, J = 5.4 Hz), 127.5 (d, J = 11.2 Hz), 161.9 (d, J = 7.9 Hz), 199.0; ^{31}P NMR ($CDCl_3$) δ 27.4; IR (CCl_4) ν_{PO} 1251.2, ν_{CO} 1678.1; MS m/z 260 (M^+, 21), 139 (56), 123 (32), 122 (100), 95 (22). Anal. Calcd for $C_{12}H_{21}O_4P$: C, 55.38; H, 8.13. Found: C, 55.04; H, 8.29.

Diethyl {[3-Oxo-2-(propen-2-yl)-1-cyclohexen-1-yl]methyl}phosphonate (4c, n = 2, R = CH_2CHCH_2, R′ = H). Purified by column chromatography (AcOEt) (54%): ^{1}H NMR ($CDCl_3$) δ 1.30 (6H, t, J = 7.0 Hz), 1.95 (2H, dt, J = 6.2, 9.7 Hz), 2.21 (2H, t, J = 6.3 Hz), 2.54 (2H, dt, J = 5.5, 10.9 Hz), 2.81 (2H, d, J = 24.2 Hz), 3.13 (2H, d, J = 5.0 Hz), 4.09 (4H, dq, J =7.1, 10.6 Hz), 4.91 (1H, dd, J = 1.7, 5.9 Hz), 4.96 (1H, dd, J = 1.8, 2.7 Hz), 5.73 (1H, m); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 16.4 (d, J = 6.0 Hz), 22.2, 29.1, 31.9, 33.3 (d, J = 135.3 Hz), 37.7, 62.2 (d, J = 6.5 Hz), 114.7, 135.3, 135.6 (d, J = 12.5 Hz), 150.1 (d, J = 11.7 Hz), 197.9; ^{31}P NMR ($CDCl_3$) δ 25.2; IR (CCl_4) ν_{PO} 1253.1, ν_{CO} 1673.0; MS m/z 286 (M^+, 57), 152 (57), 149 (69), 148 (82), 147 (89), 133 (67), 105 (77), 91 (100), 41 (64), 29 (66). Anal. Calcd for $C_{14}H_{23}O_4P$: C, 58.73; H, 8.10. Found: C, 58.72; H, 8.15.

Diethyl [(3-Oxo-1-cyclopenten-1-yl)methyl]phosphonate (4d, n = 1, R = R′ = H).[2g,10] Purified by column chromatography ($CHCl_3$–AcOEt, 4:1) (65%): ^{1}H NMR ($CDCl_3$) δ 1.31 (6H, t, J = 7.1 Hz), 2.43 (2H, m), 2.73 (2H, m), 2.98 (2H, d, J = 23.2 Hz), 4.11 (4H, dq, J = 7.2, 11.0 Hz), 6.10 (1H, m); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 16.3 (d, J = 5.8 Hz), 31.8 (d, J = 136.7 Hz), 32.4 (d, J = 2.9 Hz), 35.5, 62.4 (d, J = 6.6 Hz), 133.1 (d, J = 9.7 Hz), 171.4 (d, J = 8.3 Hz), 207.0; ^{31}P NMR ($CDCl_3$) δ 23.2; IR (CCl_4) ν_{PO} 1257.7, ν_{CO} 1714.3; MS m/z 232 (M^+ , 99), 204 (61), 176 (81), 148 (99), 96 (63), 95 (99), 94 (99), 81 (79), 41 (94), 39 (100), 29 (99), 27 (97).

Diethyl [1-(3-Oxo-1-cyclopenten-1-yl)ethyl]phosphonate (4e, n = 1, R = H, R′ = Me). Purified by column chromatography (AcOEt–$CHCl_3$, 2:1) (69%): ^{1}H NMR ($CDCl_3$) δ 1.30 (6H, t, J = 7.0 Hz), 1.44 (3H, dd, J = 7.2, 17.9 Hz), 2.41 (2H, m), 2.60–3.10 (3H, m), 4.10 (4H, dq, J = 7.1, 11.1 Hz), 6.10 (1H, m); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 13.5 (d, J = 6.3 Hz), 16.4 (d, J = 5.7 Hz), 31.0, 35.2, 37.0 (d, J = 136.3 Hz), 62.5 (two d, J = 7.0 Hz), 131.7 (d, J = 9.3 Hz), 177.8 (d, J = 8.1 Hz), 209.2; ^{31}P NMR ($CDCl_3$) δ 26.3; IR (CCl_4) ν_{PO} 1217.1, ν_{CO} 1725.0; MS m/z 218 (29), 190 (29), 162 (33), 111 (63), 109 (99), 108 (100), 81 (67), 53 (61), 29 (72), 27 (69). Anal. Calcd for $C_{11}H_{19}O_4P$: C, 53.66; H, 7.78. Found: C, 53.55; H, 7.90.

Diethyl [(3-Oxo-2-methyl-1-cyclopenten-1-yl)methyl]phosphonate (4f, n = 1, R = Me, R′ = H). Purified by column chromatography ($CHCl_3$–acetone, 95:5) (55%): ^{1}H NMR ($CDCl_3$) δ 1.30 (6H, t, J = 7.1 Hz), 1.72 (3H, t, J = 2.1 Hz), 2.39 (2H, m), 2.66 (2H, m), 2.91 (2H, d, J = 24.0 Hz), 4.10 (4H, dq, J = 7.2, 11.1 Hz); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 8.22, 16.4 (d, J = 5.4 Hz), 30.4 (d, J = 137.0 Hz), 30.6, 34.2, 62.3 (d, J = 7.1 Hz), 150.2 (d, J = 9.2 Hz), 162.4 (d, J = 8.1 Hz), 208.3; ^{31}P NMR ($CDCl_3$) δ 24.3; IR (CCl_4) ν_{PO} 1256.8, ν_{CO} 1710.6; MS m/z 246 (M^+, 100), 218 (41), 190 (49), 162 (57), 109 (44), 108 (99), 80 (51), 79 (54). Anal. Calcd for $C_{11}H_{19}O_4P$: C, 53.66; H, 7.78. Found: C, 53.50; H, 7.95.

Diethyl [1-(3-Oxo-2-methyl-1-cyclopenten-1-yl)ethyl]phosphonate (4g, n = 1, R = R′ = Me). Purified by column chromatography (AcOEt–$CHCl_3$, 2:1) (65%): ^{1}H NMR ($CDCl_3$) δ 1.28 (6H, t, J = 7.1 Hz), 1.42 (3H, dd, J = 7.2, 18.8 Hz), 1.72 (3H, dd, J = 2.0, 3.0 Hz), 2.37 (2H, m), 2.65 (2H, m), 3.32 (1H, dq, J = 7.2, 24.0 Hz), 4.14 (4H, m); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 8.4, 12.3 (d, J = 6.6 Hz), 16.4 (d, J = 5.4 Hz), 26.8, 33.9, 34.7 (d, J = 137.9 Hz), 62.3 (two d, J = 7.0, 15.4 Hz), 149.7 (d, J = 9.3 Hz), 167.8 (d, J = 8.2 Hz), 207.5; ^{31}P NMR ($CDCl_3$) δ 27.9; IR (CCl_4) ν_{PO} 1332.3, ν_{CO} 1708.0; MS m/z 260 (M^+, 51), 123 (64), 122 (100), 95 (15), 29 (33). Anal. Calcd for $C_{12}H_{21}O_4P$: C, 55.38; H, 8.13. Found: C, 54.85; H, 8.15.

Reaction of 3-Chlorocyclohex-2-en-1-ones (2) with Lithiated Diethyl Alkylphosphonates (3). The procedure was identical to that described for the reaction between enones **1** and nucleophiles **3**. The following products **5** were prepared.

Diethyl [(1-Hydroxy-3-chloro-2-cyclohexen-1-yl)methyl]phosphonate (5a, R = R′ = H) (from 2a and 3a). Purified by column chromatography (AcOEt) (70%): ^{1}H NMR ($CDCl_3$) δ 1.33 (6H, m), 1.67 (2H, m), 1.90 (2H, m), 2.07 (2H, dd, J = 8.9, 17.6 Hz), 2.28 (2H, m), 4.11 (4H, m), 5.91 (1H, s); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 16.3 (d, J = 6.2 Hz), 19.9, 32.7, 36.0 (d, J = 9.7 Hz), 37.9 (d, J = 135.2 Hz), 61.9 (two d, J = 7.2 Hz), 69.4, 129.3 (d, J = 11.6 Hz), 135.9 (d, J = 27.1 Hz); ^{31}P NMR ($CDCl_3$) δ 29.1; IR (CCl_4) ν_{PO} 1230.9, ν_{OH} 3432.1; MS m/z 264 ($M^+ - H_2O$, 25), 208 (11), 152 (51), 125 (100), 97

(20) House, H. O.; Rasmusson, G. H. *J. Org. Chem.* **1963**, *28*, 27.

(35), 91 (87). Anal. Calcd for $C_{11}H_{20}ClO_4P$: C, 46.73; H, 7.13. Found: C, 46.74; H, 7.24.

Diethyl {[1-Hydroxy-2-(propen-2-yl)-3-chloro-2-cyclohexen-1-yl]methyl}phosphonate (5b, R = CH_2CHCH_2, R' = H) (from **2b** and **3a**). Purified by column chromatography ($CHCl_3$–AcOEt, 4:1) (75%): ^{1}H NMR ($CDCl_3$) δ 1.29 (6H, t, J = 7.1 Hz), 1.59–2.46 (8H, set of m), 3.10 (2H, d, J = 6.0 Hz), 4.08 (4H, m), 5.02 (2H, m), 5.84 (1H, ddt, J = 2.4, 6.5, 8.4 Hz); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 16.3 (d, J = 5.9 Hz), 19.8, 32.8, 34.0, 35.1 (d, J = 133.0 Hz), 61.8 (two d, J = 6.9, 38.2 Hz), 72.4 (d, J = 3.2 Hz), 115.5, 133.7, 135.0 (d, J = 16.9 Hz), 136.0; ^{31}P NMR ($CDCl_3$) δ 29.5; IR (CCl_4) ν_{PO} 1230.6, ν_{OH} 3425.1; MS m/z 305 ($M^+ - H_2O$, 14), 249 (9), 167 (32), 152 (22), 131 (100), 130 (40), 129 (56), 91 (34), 41 (22). Anal. Calcd for $C_{14}H_{24}ClO_4P$: C, 52.10; H, 7.49. Found: C, 52.06; H, 7.55.

Diethyl [1-(1-Hydroxy-3-chloro-2-cyclohexen-1-yl)ethyl]phosphonate (5c, R = H, R' = Me) (from **2a** and **3b**). Purified by column chromatography (AcOEt–hexane, 3:2) (76%); pair of diastereoisomers (2:1): ^{1}H NMR ($CDCl_3$) δ major stereoisomer: 1.16 (3H, dd, J = 7.5, 17.7 Hz), 1.30 (6H, m), 1.50 - 2.30 (7H, m), 4.30 (4H, m), 5.99 (1H, s); minor stereoisomer: 1.09 (3H, dd, J = 7.3, 17.3 Hz), 1.30 (6H, m), 1.50 - 2.30 (7H, m), 4.30 (4H, m), 5.70 (1H, s); proton-decoupled ^{13}C NMR ($CDCl_3$) δ major stereoisomer: 10.5 (d, J = 5.1 Hz), 16.4 (d, J = 5.7 Hz), 19.6, 30.6 (d, J = 3.2 Hz), 32.7 (d, J = 6.7 Hz), 41.5 (d, J = 133.6 Hz), 61.9 (two d, J = 7.1, 12.3 Hz), 72,0, 127.3 (d, J = 6.0 Hz), 137.2; minor stereoisomer: 10.9 (d, J = 5.1 Hz), 16.4 (d, J = 5.7 Hz), 19.3, 30.6 (d, J = 3.2 Hz), 33.5 (d, J = 10.1 Hz), 41.8 (d, J = 134.6 Hz), 61.9 (two d, J = 7.1, 12.3 Hz), 72,0, 128.7 (d, J = 18.6 Hz), 137.2; ^{31}P NMR ($CDCl_3$) δ (both stereoisomers).32.6; IR (CCl_4) ν_{PO} 1221.2, ν_{OH} 3412.2; MS m/z 277 (M^+ - H_2O, 4), 152 (47), 131 (100), 125 (80), 29 (48). Anal. Calcd for $C_{12}H_{21}ClO_4P$: 48.74; H, 7.16. Found: C, 48.16; H, 7.37.

Enol of Diethyl [(3-Oxo-1-cyclopenten-1-yl)methyl]phosphonate (6). Reaction between 3-chlorocyclopent-2-en-1-one (**2c**) (0.5 g, 4.3 mmol) and **3a** was carried out as described above. After the usual workup, the product was purified by column chromatography ($CHCl_3$–AcOEt, 4:1) and afforded **6** (0.288 g, 25%): ^{1}H NMR ($CDCl_3$) δ 1.27 (6H, t, J = 7.0 Hz), 2.60–2.80 (4H, m),4.00 (4H, dq, J = 7.0, 11.0 Hz), 5.19 (1H, d, J = 16.2 Hz), 7.05 (1H, s); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 16.3 (d, J = 6.5 Hz), 32.3 (d, J = 22.1 Hz), 36.3, 61.3 (d, J = 5.0 Hz), 102.6 (d, J = 192.8 Hz), 129.4 (d, J = 7.2 Hz), 151.4, 164.6 (d, J = 5.9 Hz); ^{31}P NMR ($CDCl_3$) δ 18.8; IR (CCl_4) ν_{PO} 1245.9, $\nu_{C=C}$ 1613.9, ν_{OH} 3421.2. After one month at 5 °C, the product rearranged completely to **4d**, showing NMR (^{1}H, ^{13}C, ^{31}P) and IR spectra identical to those of the independently prepared **4d**.

Dehydration of Alcohols 5. Method A. Concentrated sulfuric acid (0.095 g per mmol of **5**) was added dropwise at room temperature to a stirred solution of **5** in dry chloroform (6 mL per mmol of **5**). After 5 min water (4 mL per mmol of **5**) was added dropwise, and aqueous phase was separated and extracted with chloroform (3 × 6 mL per mmol of **5**). The combined chloroform solution was washed with 5% aqueous $NaHCO_3$ and with water, dried ($CaCl_2$), filtered, and evaporated. The residue was purified by column chromatography (AcOEt) yielding pure **4**.

4a (from **5a**) (80%): NMR (^{1}H, ^{13}C, ^{31}P) and IR spectra identical to those obtained for the product prepared from **1a** and **3a**.

4b (from **5c**) (75%): NMR (^{1}H, ^{13}C, ^{31}P) and IR spectra identical to those obtained for the product prepared from **1a** and **3b**.

When **5c** was incubated in trifluoroacetic acid-*d* (0.5 mL/70 mg of **5c**) for 5 min, ^{31}P NMR spectrum indicated complete conversion of the substrate to a mixture of **4b** and two other products, probably the diastereomeric trifluoroacetates of **5c**. A drop of D_2O was added, and the solution was left at room temperature for 12 h. The NMR (^{1}H and ^{31}P) spectra of the solution showed the exclusive formation of **4b** as the only product.

Method B. A solution of alcohol **5a** (1.0 g, 3.7 mmol) and *p*-toluenesulfonic acid (0.035 g, 0.2 mmol) in dry benzene (50 mL) was heated under reflux for 24 h using Dean–Stark conditions. Water (10 mL) was added, the aqueous phase was extracted with benzene (3 × 10 mL), and the combined benzene solution was washed with water, dried ($MgSO_4$), and evaporated. The residue was separated by column chromatography (Et_2O) and afforded the following products.

***(Z)*-Diethyl [(3′-Chlorocyclohexen-2′-ylidene)methyl]phosphonate (7a)**: 0.244 g (25%); ^{1}H NMR ($CDCl_3$) δ 1.30 (6H, t, J = 7.1 Hz), 1.83 (2H, m), 2.36 (2H, m), 2.47 (2H, t, J = 6.1 Hz), 4.05 (4H, dq, J = 7.2, 11.0 Hz), 5.23 (1H, d, J = 15.7 Hz), 7.28 (1H, s); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 16.3 (d, J = 6.5 Hz), 23.0 , 32.4 (d, J = 22.2 Hz), 33.6, 61.5, 110.1 (d, J = 187.5 Hz), 124.3 (d, J = 9.3 Hz), 135.7, 150.2; ^{31}P NMR ($CDCl_3$) δ 17.4; MS m/z 264 (M^+, 28), 236 (14), 208 (35), 155 (76), 127 (18), 91 (100). Anal. Calcd for $C_{11}H_{18}ClO_3P$: C, 49.91; H, 6.85. Found: C, 49.50; H, 7.00.

***(E)*-Diethyl [(3′-Chlorocyclohexen-2′-ylidene)methyl]phosphonate (7b)**: 0.049 g (5%); ^{1}H NMR ($CDCl_3$) δ 1.30 (6H, t, J = 7.1 Hz), 1.83 (2H, two t, J = 6.2, 9.5 Hz), 2.45 (2H, t, J = 6.1 Hz), 2.74 (2H, t, J = 9.5 Hz), 4.05 (4H, dq, J = 7.2, 11.0 Hz), 5.27 (1H, d, J = 16.5 Hz), 6.25 (1H, s); ^{31}P NMR ($CDCl_3$) δ 18.6.

Acknowledgment. Financial assistance from the University of Pretoria and the Foundation for Research Development is gratefully acknowledged.

JO951330I