Heteroatom Chemistry
Volume 8, Number 4, 1997

Silyl Enol Ethers as Protective Groups for Alkyl 4-Halo-3-oxobutanoates in the Arbuzov Reaction with Triethyl Phosphite

Andrew C. Grosse and Cornelis M. Moorhoff*

Department of Chemistry, University of Tasmania, GPO Box 252-75 Hobart, Tasmania, Australia 7001

Received 4 March 1997

ABSTRACT

Alkyl 4-bromo- and 4-chloro-3-oxobutanoates were protected as silyl enol ethers. The Arbuzov reaction of these new compounds with triethyl phosphite gave the corresponding silyl enol phosphonates in high yield. Facile deprotection of the silyl group with water gave alkyl 4-(diethoxyphosphinyl)-3-oxobutanoates in high yields. Protection of 1-methylethyl 4-bromo-3-oxobutanoate as the enol acetate followed by the subsequent reaction with triethyl phosphite gave the corresponding phosphonate in high yield. Deprotection with potassium 2-propoxide gave 1-methylethyl 4-(diethoxyphosphinyl)-3-oxobutanoate in good yield. © 1997 John Wiley & Sons, Inc.

INTRODUCTION

The Horner-Wadsworth-Emmons reaction of carbonyl compounds and either alkyl 4-(dialkoxyphosphinyl)-3-oxobutanoates **4** [1–7] or alkyl 4-(diphenylphosphinyl)-3-oxobutanoates **2** [8], as in Scheme 1, is a well-established procedure for the synthesis of alkyl δ,γ-unsaturated-β-ketoesters. However, this condensation procedure is often overshadowed by the problem of synthesizing these β-ketophosphinates **2** and β-ketophosphonates **4**.

Arbuzov erroneously assumed that the reaction between ethyl 4-bromo-3-oxobutanoate **1b** with triethyl phosphite gave pure β-ketophosphonate **4b** [9]. However, Jagodic found that, at room temperature, the reaction of ethyl 4-bromo-3-oxobutanoate **1b** and triethyl phosphite gave a mixture of β-ketophosphonate **4b** (Arbuzov product) and enol phosphate **5b** (Perkow product). At higher temperature, the ratio of β-ketophosphonate **4b** to enol phosphate **5b** increased, while at 0°C, only enol phosphate **5b** was obtained [10] (Scheme 1). Reacting the chloroester **1f** with triethyl phosphite gave exclusively enol phosphate **5g** [15].

Separation of a mixture of β-ketophosphonate **4b** and enol phosphate **5b** [11] or β-ketophosphonate **4c** and enol phosphate **5c** [12] was tedious and time-consuming. For example, repeated extraction of a mixture of β-ketophosphonate **4c** and enol phosphate **5c** in aqueous sodium bicarbonate solution with light petroleum ether and diethyl ether first extracted enol phosphate **5c**. Neutralizing the aqueous layer with 1M hydrochloric acid and extraction of the aqueous layer with dichloromethane gave phosphonate **4c**. However, due to partial hydrolysis of β-ketophosphonate **4c**, 1-(diethoxyphosphinyl)-2-oxopropane was also isolated [12]. Chromatography of a mixture of enol phosphate **5c** and β-ketophosphonate **4c** over silica gel required large quantities of silica gel and solvent; a mixture of light petroleum ether:diethyl ether (1:4) eluted enol phosphate **5c**, while a mixture of diethyl ether:2-propanol (9:1) eluted the β-ketophosphonate **4c**. However, the yield

*To whom correspondence should be addressed.

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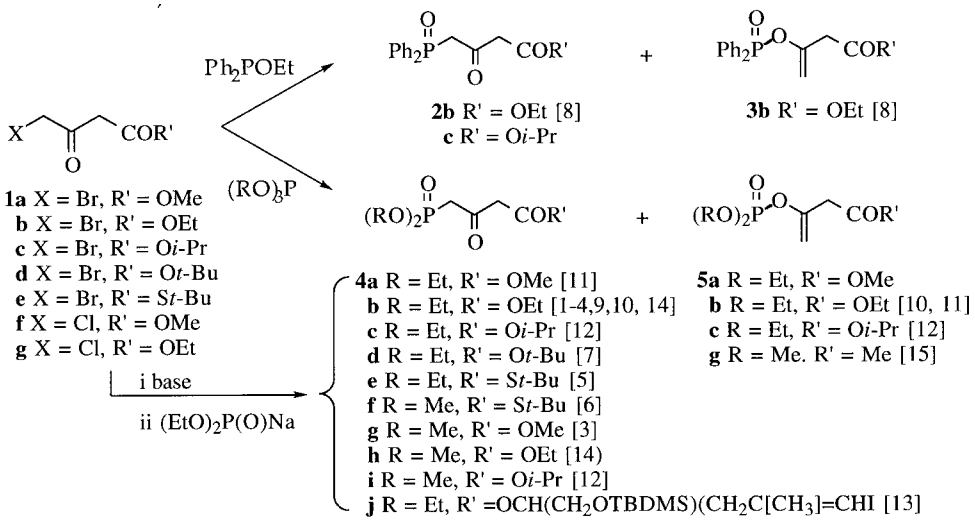


SCHEME 1

of pure *β*-ketophosphonate **4c** was at best about 35% [12].

Bodalski prepared the *β*-ketophosphonate **4b** in a yield of 50% by treating the sodium enolate of the bromoester **1b** with sodium diethyl phosphite [1] (Scheme 1). This route has since been used by many researchers to synthesize *β*-ketophosphonates **2b** [4], **2e** [5], **2f** [6], and **2j** [13] (Scheme 1), although the yields are not always very high, 50–80%. Treatment of the dianion of 1,1-dimethylethyl 3-oxobutanoate with diethylphosphorchloridate gave the phosphonate **4d** in a modest yield, 67% [7]. Generating the dianion of 1-(diethoxyphosphinyl)-2-oxopropane followed by treatment with ethyl chloromethanoate gave the phosphonate **4b** in a high yield [16], although the preparation of 1-(diethoxyphosphinyl)-2-oxopropane from halopropanone often gives a substantial amount of the Perkow product [17,18].

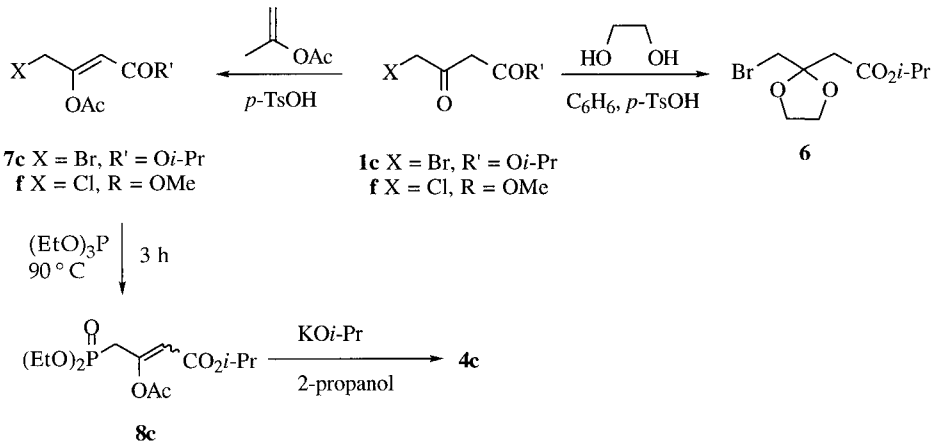
For the synthesis of natural products, we had a need for pure phosphonate **2c**, but we were disappointed at the low yield of **2c** prepared via conventional methods. In this article, we describe an improved general method for the preparation of alkyl 4-(dialkoxyphosphinyl)-3-oxobutanoates **2** from alkyl 4-halo-3-oxobutanoates **1**. The method that we employed was the Arbuzov reaction of the appropriate keto-protected alkyl 4-halo-3-oxobutanoates **1**, with triethyl phosphite. This method avoided the formation of the enol phosphate **5** (Perkow reaction). Deprotection gave alkyl 4-(diethoxyphosphinyl)-3-oxobutanoates **2** in high yield and purity.

RESULTS AND DISCUSSION

Protection of the keto group of **1** has been investigated previously. For example, protection of the keto group of **1g** as a methoxycarbonylhydrazono group (=N-NHCO$_2$Me), followed by the Arbuzov reaction with triethyl phosphite and subsequent deprotection, gave the phosphonate **4b** in 55% yield [14]. Derivatives of 4-(diethoxyphosphinyl)-3-oxobutanoates **4** have been prepared via 6-(diethoxyphosphinyl)-methyl-2,2-dimethyl-1,3-dioxen-4-one, though this is not a simple procedure [19]. Deprotection of methylenol ethers is not easy [20].

We first tried to protect the keto functionality of the bromoester **1c** as a ketal; however, the bromoketal **6** [21] failed to react with triethyl phosphite even in the presence of nickel salts [22]. The enol acetate esters were then prepared according to the literature [23]. Refluxing alkyl 4-halo-3-oxobutanoates **1c** or **1f** in excess 2-propenyl acetate in the presence of *p*-TsOH gave the 2*Z*-isomers **7c** [21] and **7f** in 80% and 94% yield, respectively (Scheme 2). Reaction of the bromoenol acetate **7c** with triethyl phosphite in $CDCl_3$ was very slow at room temperature and took 10 days at 65°C to complete. When this reaction was repeated without solvent at 90°C, the reaction had been completed within 3 hours to give an isomeric mixture of 2*E*- and 2*Z* 1-methylethyl 3-acetoxy-4-(diethoxyphosphinyl)-2-butenoate **8c** (1:4) in high yield, 95%. Deprotection of the enol acetylphosphonate **8c** with potassium isopropoxide in 2-propanol gave impure *β*-ketophosphonate **4c** in high yield, 95% (Scheme 2). The chloroenol acetate **7f** was unreactive toward triethyl phosphite. Prolonged heating led to deprotection of chloroenol acetate **7f** and to subsequent formation of the enol phosphate **5a**.

We recently prepared the silyl enol ethers **9c**, **10g**, and **10i** (Scheme 3) [21]. Preparation of the



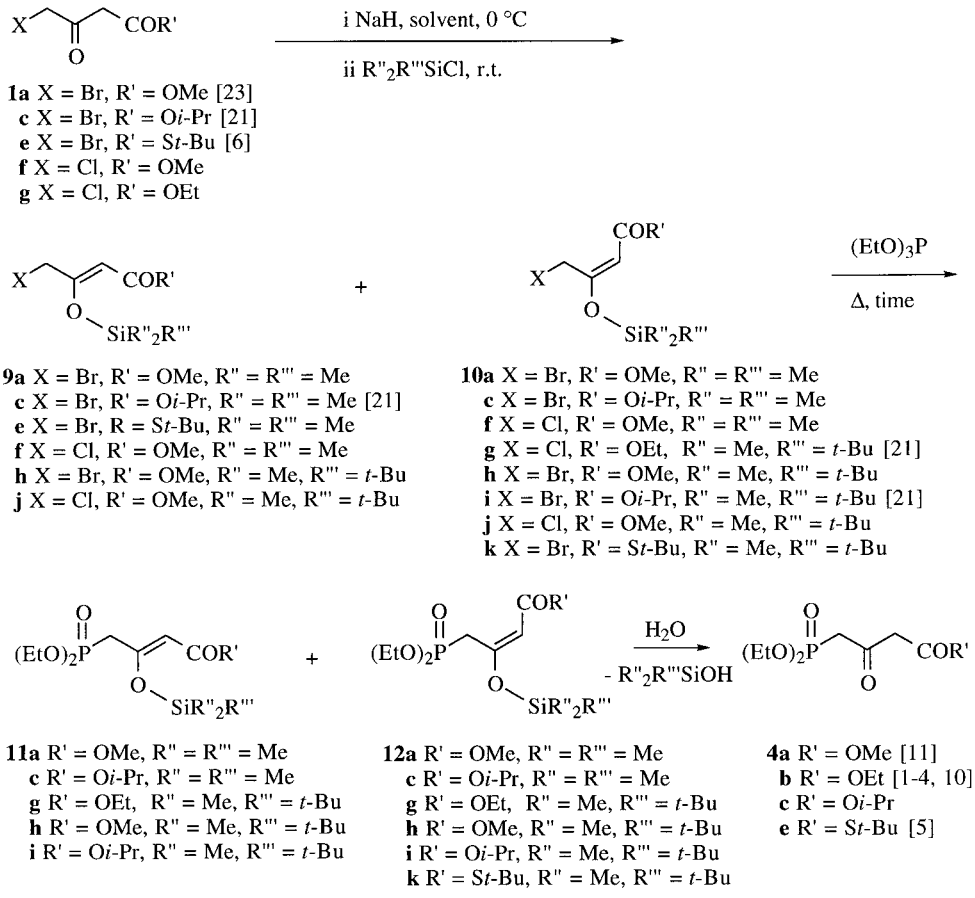
7c X = Br, R' = O*i*-Pr
f X = Cl, R = OMe

1c X = Br, R' = O*i*-Pr
f X = Cl, R = OMe

6

8c

SCHEME 2



1a X = Br, R' = OMe [23]
c X = Br, R' = O*i*-Pr [21]
e X = Br, R' = S*t*-Bu [6]
f X = Cl, R' = OMe
g X = Cl, R' = OEt

9a X = Br, R' = OMe, R" = R"' = Me
c X = Br, R' = O*i*-Pr, R" = R"' = Me [21]
e X = Br, R = S*t*-Bu, R" = R"' = Me
f X = Cl, R' = OMe, R" = R"' = Me
h X = Br, R' = OMe, R" = Me, R"' = *t*-Bu
j X = Cl, R' = OMe, R" = Me, R"' = *t*-Bu

10a X = Br, R' = OMe, R" = R"' = Me
c X = Br, R' = O*i*-Pr, R" = R"' = Me
f X = Cl, R' = OMe, R" = R"' = Me
g X = Cl, R' = OEt, R" = Me, R"' = *t*-Bu [21]
h X = Br, R' = OMe, R" = Me, R"' = *t*-Bu
i X = Br, R' = O*i*-Pr, R" = Me, R"' = *t*-Bu [21]
j X = Cl, R' = OMe, R" = Me, R"' = *t*-Bu
k X = Br, R' = S*t*-Bu, R" = Me, R"' = *t*-Bu

11a R' = OMe, R" = R"' = Me
c R' = O*i*-Pr, R" = R"' = Me
g R' = OEt, R" = Me, R"' = *t*-Bu
h R' = OMe, R" = Me, R"' = *t*-Bu
i R' = O*i*-Pr, R" = Me, R"' = *t*-Bu

12a R' = OMe, R" = R"' = Me
c R' = O*i*-Pr, R" = R"' = Me
g R' = OEt, R" = Me, R"' = *t*-Bu
h R' = OMe, R" = Me, R"' = *t*-Bu
i R' = O*i*-Pr, R" = Me, R"' = *t*-Bu
k R' = S*t*-Bu, R" = Me, R"' = *t*-Bu

4a R' = OMe [11]
b R' = OEt [1-4, 10]
c R' = O*i*-Pr
e R' = S*t*-Bu [5]

SCHEME 3

more labile trimethylsilyl enol ethers **9** was achieved by the following procedure. Deprotonation of alkyl 4-halo-3-oxobutanoates **1a**, **1c**, **1e**, and **1f** with sodium hydride in diethyl ether at 0°C was followed by reaction of the anion with trimethylsilyl chloride at room temperature [21]. After 1 to 5 hours, the major product was 2*Z*-silyl enol ether **9a**, **9c**, **9e**, and **9f** with up to 13% of 2*E*-silyl enol ether **10a**, **10c**, and **10f** (Scheme 3). We have now found that it is crucial to this preparation that the solvent and excess trimethylsilyl chloride are removed under strictly anhydrous conditions. The mixture of trimethylsilyl enol ethers **9** and **10** were directly vacuum distilled from the solvent-free reaction residue. Distillation slowly isomerized the 2*Z*-silyl enol ethers **9** to the 2*E*-trimethylsilyl enol ethers **10**. Reaction of the individual mixtures 2*Z*- and 2*E*-trimethylsilyl enol ethers **9a** + **10a** and **9c** + **10c** with triethyl phosphite for 24 hours at 60°C gave the trimethylsilyl enol phosphonates **11a** + **12a** and **11c** + **12c**, respectively, in high yield and purity. However, the trimethylsilyl group was soon removed by even the slightest moisture in air to give the desired *β*-ketophosphonates **4a** and **4c** in a quantitative yield. Trimethylsilanol had presumably evaporated.

The mixture of trimethylsilyl enol ethers **9f** and **10f** reacted sluggishly with triethyl phosphite for 7 days at 70°C. This unfortunately led to partial deprotection, and a mixture of silylenol phosphonates **11a** + **12a**, enol phosphate **5a**, and unreacted silyl enol ether **9f** + **10f** in a ratio of 40:27:33 was isolated (Scheme 3).

(1,1-Dimethylethyl)dimethylsilyl enol ethers **10g** [21], **10h**, **10i** [21], **10j**, and **10k** were prepared in a similar manner. However, it was found that diethyl ether was not a good solvent for reactions of the anion of each alkyl halobutanoate **1**. The anion was treated with excess resublimed (1,1-dimethylethyl)dimethylsilyl chloride in THF. In this case, as expected, the 2*E*-isomer **10** predominated, together with about 12% of the kinetically more favorable 2*Z*-isomers **9**. (1,1-Dimethylethyl)dimethylsilyl enol ethers **10h** and **10i** reacted with triethyl phosphite to give a high yield of the more stable silyl enol phosphonates **12h** and **12i**, respectively. These compounds also hydrolyzed with a little water to give the phosphonates **4a** and **4c**.

The corresponding silyl enol ether **10j** reacted very sluggishly with triethyl phosphite in either $CDCl_3$ (Table 1) or neat. Substantial deprotection again took place, leading to an unwanted amount of enol phosphate **5a**. In this case, it was easy to remove the enol phosphate **5a** by distillation. The resulting residue contained the mixture of silyl enol phosphonates **11h** and **12h**. Deprotection of the mixture of silyl enol phosphonates **11h** and **12h** was successfully carried out in aqueous HCl to give fairly pure *β*-ketophosphonate **4a**.

TABLE 1 Reaction of **10**; with Triethyl Phosphite

	9g + *$(EtO)_3P$ $CDCl_3$ at 70°C*	
	after 7 days	*after 14 days*
9g	50%	37%
11g	6%	3%
12g	33%	54%
5a	11%	12%

The reaction of silyl protected 1-methylethyl 4-bromo- **1c** and ethyl 4-chloro-3-oxobutanoates **1g** with ethoxydiphenylphosphine at 80°C for 12 hours gave the corresponding silyl protected diphenylphosphinates **13c** and **14g**, respectively, in high yield with minor amounts of the isomers **14c** and **13g**. Allowing moisture to hydrolyze **13c** gave pure **2c** in good yield and purity (Scheme 4).

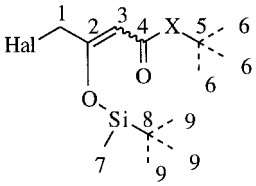
CONCLUSION

Protection of alkyl 4-bromo-3-oxobutanoates **1** as trimethylsilyl enol ethers followed by the Arbuzov reaction and subsequent cleavage of the intermediate mixture of silyl enol phosphonates **11** and **12** by moisture gave the corresponding *β*-ketophosphonates **4** in good to high yield and purity. The more stable (1,1-dimethylethyl)dimethylsilyl enol phosphonates **12** were easier to prepare and were obtained in higher purity than the trimethylsilyl enol phosphonates **11**, although they were less facile to cleave.

EXPERIMENTAL

^{1}H-NMR (δ, with TMS as an internal standard) and ^{13}C-NMR (δ) spectra in $CDCl_3$ were recorded on a Varian Gemini-200 spectrometer at 200 and 50.3 MHz, respectively. ^{31}P-NMR spectra were recorded on a Bruker instrument at 121.5 MHz and referenced to an external standard of 85% H_3PO_4. High-resolution chemical ionization spectra (CI) using ammonia and liquid secondary ion mass spectra (LSIMS) were obtained from a Kratos Concept ISQ instrument. Infrared spectra were obtained on a Hitachi 270-30 FTIR spectrophotometer (film, NaCl plates). Ultraviolet absorbance was measured as solutions in 96% EtOH on a Shimadzu UV-150 spectrophotometer. Microanalyses were obtained using a Carlo Erba, CHNS-O EA 1108 Elemental Analyser. Column chromatography was performed using Merck Si-60 (0.040–0.063 mm) silica gel. Methyl 3-oxobutanoate, ethyl 3-oxobutanoate, methyl 4-chloro-3-oxobutanoate **1f**, and ethyl 4-chloro-3-oxobutanoate **1g** were

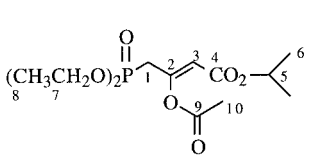
TABLE 2 ^{1}H Chemical Shifts (δ_H) of Compounds **9** and **10**[a,b]

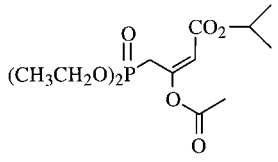
No.	**9a** *83%*	**10a** *17%*	**9f** *84%*	**10f** *16%*	**9e** *~100%*	**10h** *~100%*	**10j** *90%*	**9j** *10%*	**10k** *~100%*
						Hal = Cl, Br X = O, S			
1	3.80	4.49	3.91	4.60	3.74	4.49	4.60	3.90	4.40
3	5.41	5.19	5.42	5.21	5.58	5.18	5.18	5.41	5.41
5 or 6	3.68	3.70	3.69	3.70	1.48	3.70	3.67	3.65	1.50
7	0.33	0.32	0.32	0.32	0.34	0.28	0.25	0.25	0.27
9						0.98	0.95	0.97	0.97

[a]At 200 MHz in $CDCl_3$ and J_{PH} measured in Hz.
[b]Consult Scheme 3 for compounds.

obtained from Aldrich and distilled before use. Methyl 4-bromo-3-oxobutanoate **1a** and 1-methylethyl 4-bromo-3-oxobutanoate **1c** were prepared according to the literature [23]. Trimethylsilyl chloride was obtained from Aldrich and used without further purification. (1,1-Dimethylethyl)dimethylsilyl chloride was obtained from Aldrich and sublimed before use. Triethyl phosphite was dried and distilled before use.

Preparation of (2*E*)- *and* (2*Z*) *1-Methylethyl 3-acetoxy-4-*(*dimethoxyphosphinyl*)*-2-butenoate* **8c**. 1-Methylethyl 3-acetoxy-4-bromo-2-butenoate **8c** (9.03 g, 34 mmol) was added to triethyl phosphite (12.11 g, 73.0 mmol) at 110°C and stirred for 30 minutes. Triethyl phosphite and residual ethyl bromide were removed under reduced pressure and gave a residue (11.5 g) that was chromatographed on silica gel. Elution with ether gave a mixture of (2*E*) 1-methylethyl 3-acetoxy-4-(diethoxyphosphinyl)-2-butenoate **8c** and (2*Z*) 1-methylethyl 3-acetoxy-4-(diethoxyphosphinyl)-2-butenoate *8c* in a ratio of 1:4 (10.9 g, 99%) MS (CI): Calcd for $C_{13}H_{24}O_7P$ ($MH^+\cdot$) 323.1269. Found 323.1259. m/z 323 ($MH^+\cdot$, 100), 280 (60), 221 (70), 194 (100), 179 (30), 125 (40), 97 (25), 43 (60). (2*E*)-isomer: ^{1}H NMR (200 MHz, $CDCl_3$, 20°C): δ = 1.263 (6H, d, J = 6.2 Hz, 2xCH_3-6), 1.340 (6H, t, J = 7.1 Hz, 2xCH_3-8), 2.271 (3H, s, CH_3-10), 3.708 (2H, d, J_{PH} = 23.0 Hz, CH_2-1), 4.130 (4H, qm, 2xCH_2-8), 5.020 (1H, h, J = 6.2 Hz, CH-5), 5.788 (1H, d, J_{PH} = 3.6 Hz, CH-3). ^{31}P: δ = 21.5. (2*Z*)-isomer. ^{1}H NMR (200 MHz, $CDCl_3$, 20°C): δ = 1.239 (6H, d, J = 6.2 Hz, 2xCH_3-6), 1.340 (6H, t, J = 7.1 Hz, 2xCH_3-8), 2.238 (3H, s, CH_3-10), 2.894 (2H, d, J_{PH} = 22.1 Hz, CH_2-1), 4.130 (4H, qm, 2xCH_2-7), 5.020 (1H, h, J = 6.2 Hz, CH-5), 5.749 (1H, d, J_{PH} = 4.0 Hz, CH-3). ^{31}P: δ = 20.7.





General Preparation of a Mixture of (2*Z*)- *and* (2*E*) *Alkyl 4-Halo-3-[*(*trimethylsilyl*)*oxy]-2-butenoates* **9** *and* **10**. Alkyl 4-halo-3-oxobutanoate **1** (25 mmol) in anhydrous diethyl ether (10 mL) was added within 10 minutes to an oil free suspension of sodium hydride (0.67 g, 28.0 mmol) in anhydrous diethyl ether (20 mL) at 0°C. A vigorous evolution of hydrogen gas occurred. The reaction mixture was stirred for another 10 minutes at 0°C and then treated with excess trimethylsilyl chloride and stirred for 5 hours at room temperature. A yellowish white gel formed. The solvent and excess trimethylsilyl chloride were cautiously removed under vacuum. The gel was then bulb-to-bulb distilled and gave a mixture of (2*Z*)- and (2*E*) alkyl 4-halo-3-[(trimethylsilyl)oxy]-2-butenoates **9** and **10**.

For methyl 4-bromo-3-[(trimethylsilyl)oxy]-2-butenoates **9a** and **10a** (5.95 g, 86.9%): Anal. calcd for $C_8H_{15}BrO_3Si$: C, 35.96; H, 5.66. Found: C, 35.94; H, 5.82. HRMS (EI) calcd for ($M^+\cdot$) $C_8H_{15}BrO_3Si$ m/z 265.9971; found 265.9958. MS; 266 ($M^+\cdot$, 1), 251 (85), 235 (10), 172 (100), 105 (20), 89 (45), 73 (65).

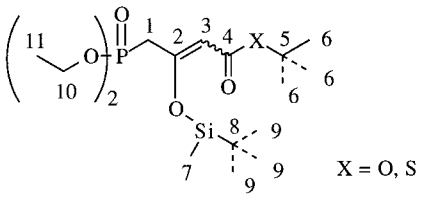
For (2*Z*)- and (2*E*) methyl 4-chloro-3-[(trimethylsilyl)oxy]-2-butenoate **9f** and **10f** (83.7%): Bp 75°C at 0.1 mm Hg. Anal. calcd for $C_8H_{15}ClO_3Si$: C,

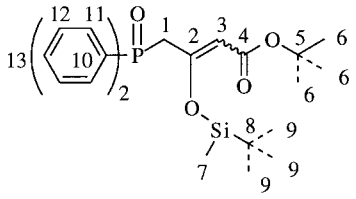
TABLE 3 ^{13}H Chemical Shifts (δ_C) of Compounds **9** and **10**[a,b]

No.	**9a** ~90%	**9f** ~84%	**10f** 16%	**9e** 100%	**10h** ~100%	**10j** 90%	**9j** 10%	**10k** ~100%
1	33.58	46.15	41.05	33.70	28.00	40.96	42.80	29.49
2	160.77	160.65	165.01	156.43	165.56	165.12	~165	~166.2
3	101.71	101.63	101.11	110.01	100.40	100.90	~100	109.29
4	165.22	165.33	166.85	188.39	166.82	166.77	~166	189.84
5	50.77	50.85	51.18	47.71	51.05	51.02	51.02	48.67
6				30.08				30.41
7	0.56	0.53	−0.03	0.76	−4.97	−4.94	−4.29	−4.25
8					~18	18.01	~18	18.65
9					25.31	25.26	25.65	25.92

[a]At 50.3 MHz in $CDCl_3$ and J_{PC} mesured in Hz.
[b]Consult Scheme 3 for compounds.

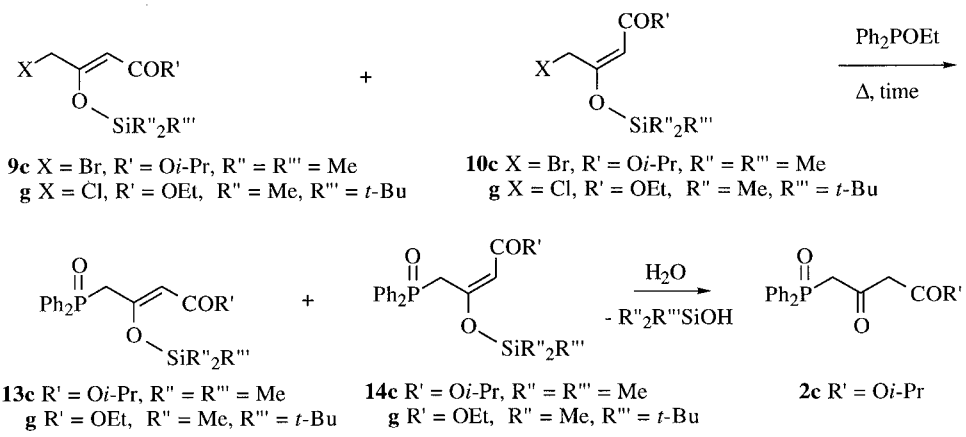
TABLE 4 ^{1}H Chemical Shifts (δ_H) of Compounds **11**, **12**, **13**, and **14**[a,b]





No.	**12a** ~100%	J_{PH}	**12c** 97%	J_{PH}	**11c** 3%	J_{PH}	**12i** 92%	J_{PH}	**11i** 8%	J_{PH}	**12k** ~100%	J_{PH}	**13c** ~100%	J_{PH}	**14g** 88%	J_{PH}
1	3.49	22.8	3.50	23.0	2.63	~23	3.50	23.2	2.64	22.5	3.44	23.0	4.17	14.5	4.12	14.9
3	5.12	2.4	5.08	3.3	5.19	~2	5.10	3.6	5.21	4.0	5.39	2.9	5.06	2.3	5.02	2.7
5	3.60		4.95		*c*		4.96		*c*				4.98		4.03	
6			1.18		*c*		1.19		*c*		1.43		1.21		1.15	
7	0.26		0.26				0.22				0.21		0.09		0.02	
9					*c*		0.92				0.91				0.84	
10	4.06	7.0	4.06	7.7	*c*		4.06	7.8	*c*		4.06	7.0				
11	1.25	~0	1.25	~0	*c*		1.25	~0	*c*		1.25					
Ph											7.9–7.7, 7.5–7.4				7.9–7.8, 7.4–7.3	

[a]At 200 MHz in $CDCl_3$ and J_{PH} measured in Hz.
[b]Consult Schemes 3 and 4 for compounds.
[c]Data not available.



SCHEME 4

TABLE 5 ^{13}C Chemical Shifts (δ_C) of Compounds **12**, **13**, and **14**[a,b]

No.	**12a** ~100%	J_{PC}	**12c** 97%	J_{PC}	**12i** 92%	J_{PC}	**12k** ~100%	J_{PC}	**13c** ~100%	J_{PC}	**14g** 88%	J_{PC}
1	30.88	133.9	30.95	134.2	31.63	134.6	32.70	137.8	35.79	64.7	36.20	64.0
2	162.60	12.1	162.13	12.2	162.69	12.2	159.52	12.2	163.17	10.4	164.04	10.5
3	99.19	8.4	100.21	10.8	100.67	8.3	108.44	9.1	100.83	~0	100.28	~0
4	166.50	2.8	165.74	3.0	166.33	3.0	189.22	2.5	166.70	2.3	167.32	2.4
5	49.82		65.71		66.14		47.60		66.34		59.19	
6			21.12		21.53		29.83		21.62		14.00	
7	−1.03		−0.87		−5.18		−3.64		−0.62		−5.29	
8					17.57		17.95				17.60	
9					24.98		25.31				25.03	
10	60.91	6.2	60.93	6.1	61.37	6.3	61.84	6.4	*c*		*c*	
11	15.41	6.7	15.52	6.4	15.89	6.4	16.25	6.6	130.67	9.3	130.68	9.3
12									127.97	11.9	127.92	11.8
13									131.24	~0	131.19	~0

[a]At 50.3 MHz in $CDCl_3$ and J_{PC} measured in Hz.
[b]Consult Schemes 3 and 4 for compounds.
[c]δ_C obscurred.

43.14; H, 6.79. Found: C, 43.20; H, 7.01. HRMS (EI) calcd for $C_8H_{15}ClO_3Si$ ($M^{+}\cdot$) m/z 222.0479; found 222.0476. MS; 222 ($M^{+}\cdot$, 6), 207 (100), 191 (20), 173 (50), 73 (70). ν_{max} (film) 2954 (m), 1725 (s), 1634 (s), 1438 (m), 1394 (m), 1253 (s), 1216 (s), 1170 (s), 1145 (s), 1041 (m), 993 (m), 848 (s), 668 (m) cm^{-1}.

General Preparation of (2*E*)- *and* (2*Z*) *Alkyl 4-Halo-3-*{[(*1,1,-dimethylethyl*)*dimethylsilyl*]*oxo*}*-2-butenoate* **9/10**. Alkyl 4-halo-3-oxobutanoate **1** (25 mmol) in anhydrous tetrahydrofuran (15 mL) was added within 15 minutes to an oil free suspension of sodium hydride (0.70 g, 29.2 mmol) in anhydrous tetrahydrofuran (30 mL) at 0°C. A vigorous evolution of hydrogen gas occurred. The reaction mixture was stirred for another 10 minutes at 0°C and then treated with (1,1-dimethylethyl)dimethylsilyl chloride (4.00 g, 26.5 mmol) in anhydrous tetrahydrofuran (10 mL) and stirred for 8–24 hours at room temperature. A yellowish white gel had formed. The reaction mixture was diluted with anhydrous dichloromethane and filtered through silica gel. The solvents were removed under vacuum. The gel was bulb-to-bulb distilled and gave alkyl 4-halo-3-{[(1,1-dimethylethyl)dimethylsilyl]oxy}-2-butenoate **9/10.**

For (2*E*) methyl 4-bromo-3-{[(1,1-dimethylethyl)dimethylsilyl]oxy}-2-butenoate **10h** (5.8 g, 73%): Anal. calcd for $C_{11}H_{21}BrO_3Si$: C, 42.72; H, 6.84. Found: C, 42.98; H, 6.98. HRMS (LSIMS) calcd for ($MH^{+}\cdot$) $C_{11}H_{22}BrO_3Si$ m/z 309.0519; found 309.0491. MS; 309 ($M^{+}\cdot$, 70), 293 (25), 277 (95), 251 (100), 220 (25).

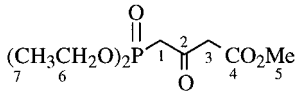
For (2*E*) methyl 4-chloro-3-{[(1,1-dimethylethyl)dimethylsilyl]oxy}-2-butenoate **10j** (69.7%): bp 100°C at 0.5 mm Hg. Solidified in refrigerator at −21°C. Anal. calcd for $C_{11}H_{21}ClO_3Si$: C, 49.89; H, 7.99. Found: C, 49.89; H, 8.38. HRMS (LSIMS) calcd for ($MH^{+}\cdot$) $C_{11}H_{22}ClO_3Si$ m/z 265.1027; found: 265.1029. MS; 265 ($MH^{+}\cdot$, 55), 233 (95), 207 (100), 147 (60). λ_{max} = 239 (ε = 12,500). ν_{max} (film) 2953 (s), 2860 (m), 1718 (s), 1628 (s), 1472 (m), 1351 (s), 1314 (s), 1257 (s), 1141 (s), 1042 (s), 970 (m), 897 (m), 811 (m) cm^{-1}.

For (2*E*) S-*t*-Butyl 4-bromo-3-{[(1,1-dimethylethyl)dimethylsilyl]oxy}-2-butenoate **10k** (85%): ν_{max} (film) 3062 (w), 2957 (s), 2858 (s), 1725 (m), 1658 (s), 1596 (s), 1472 (m), 1363 (s), 1342 (s), 1290 (s), 1131 (s), 1051 (s), 927 (m), 890 (s), 840 (s) cm^{-1}.

General Preparation of alkyl 4-(*Diethoxyphosphinyl*)*-3-oxobutanoate 4 via alkyl 4-*(*Diethoxyphosphinyl*)*-3-[*(*trimethylsilyl*)*oxy]-2-butenoate* **11/12**. Triethyl phosphite (166 mg, 1 mmol) was added neat to a solution of alkyl 4-bromo-3-[(trimethylsilyl)oxy]-2-butenoate **9/10** (1 mmol) in $CDCl_3$ (0.5 mL) and heated for 24 hours at 60°C. During the reaction, unreacted bromoester, triethyl phosphite, and ethyl bromide were observed in the ^1H-NMR spectra. After the reaction had been completed, excess triethyl phosphite, ethyl bromide, and $CDCl_3$ were removed under vacuum to give mainly crude (2*E*) alkyl 4-(diethoxyphosphinyl)-3-[(trimethylsilyl)oxy]-2-butenoate **12**.

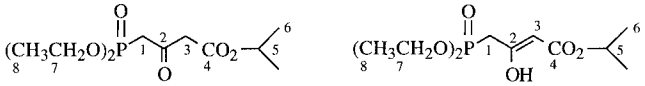
For (2*E*) methyl 4-(diethoxyphosphinyl)-3-[(trimethylsilyl)oxy]-2-butenoate **12a**: HRMS (EI) calcd for ([MH-$SiMe_3$]$^{+}\cdot$) $C_9H_{18}O_6P$ m/z 253.0877; found 253.0841. MS; 253 ([MH-$SiMe_3$]$^{+}\cdot$, 100), 221 (40).

This reaction mixture was left in air for 7 days to give methyl 4-(diethoxyphosphinyl)-3-oxobutanoate **4a** (0.24 g, 100%) [11]. Anal. calcd for $C_9H_{17}O_6P$: C, 42.86; H, 6.79. Found: C, 43.32; H, 7.08. HRMS (CI) calcd for $C_9H_{18}O_6P$ (MH^+) m/z 153.0841; found: 253.0877.



For (2*E*) 1-methylethyl 4-(diethoxyphosphinyl)-3-[(trimethylsilyl)oxy]-2-butenoate **12c** (0.33 g, 94.3%): HRMS (EI) calcd for ($[MH\text{-}SiMe_3]^+\cdot$) $C_{11}H_{22}O_6P$ m/z 281.1159; found: 281.1154. MS; 281 ($[MH\text{-}SiMe_3]^+\cdot$, 100), 239 (20), 221 (25), 195 (30), 183 (80). ν_{max} (film) 2981 (s), 1741 (s), 1718 (s), 1622 (m), 1445 (m), 1393 (m), 1255 (s), 1143 (m), 1108 (s), 1031 (s), 970 (s), 848 (s) cm^{-1}.

(2*E*) 1-methylethyl 4-(diethoxyphosphinyl)-3-[(trimethylsilyl)oxo]-2-butenoate **12c** (0.29 g, 0.82 mmol) was dissolved in $CDCl_3$ and then left in air for 7 days to give 1-methylethyl-4-(diethoxyphosphinyl)-3-oxobutanoate **4c** (0.27 g, 100%). Anal. calcd for $C_{11}H_{21}O_6P$: C, 47.15; H, 7.55. Found: C, 47.08; H, 7.67. HRMS (CI) calcd for $C_{11}H_{22}O_6P$ ($MH^+\cdot$) m/z 281.1159; found: 281.1154. MS (LSIMS): 281 ($MH^+\cdot$, 100), 239 (20), 221 (25), 195 (30), 183 (80). ^1H NMR (200 MHz, $CDCl_3$, 20°C): δ = 1.262 (6H, d, J = 6.3 Hz, 2xCH_3-6), 1.348 (6H, t, J = 7.2 Hz, 2xCH_3-8), 3.271 (2H, d, J_{PH} = 22.7 Hz, CH_2-1), 3.642 (2H, s, CH_2-3), 4.164 (4H, dq, J_{PH} = 7.4 Hz, J_{HH} = 7.2 Hz, CH_2-7), 5.058 (1H, h, J = 6.3 Hz, CH-5). Enol (9%): 2.788 (2H, d, J_{PH} = 22.3 Hz, CH_2-1), 5.122 (1H, s, CH-3), 12.301 (1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$, 20°C): δ = 15.83 (J_{PC} = 6.2 Hz, 2xCH_3-8), 21.24 (2xCH_3-6), 41.95 (J_{PC} = 127.0 Hz, CH_2-1), 49.55 (J_{PC} = ~0 Hz, CH_2-3), 62.39 (J_{PC} = 6.6 Hz, 2xCH_2-7), 68.71 (CH-5), 165.91 (C-4), 194.39 (J_{PC} = 6.0 Hz, C-2).



Reaction of Triethyl phosphite with Ethyl 4-Chloro-3-{[(1,1-dimethylethyl)dimethylsilyl]oxy}-2-butenoate **10g**. Redistilled triethyl phosphite (650 mg, 3.91 mmol) was added to ethyl 4-chloro-3-[(1,1-dimethylethyl)dimethylsilyloxy]-2-butenoate **10g** (279 mg, 1 mmol) at room temperature under anhydrous conditions and then heated for 24 hours at 100°C. Excess triethyl phosphite was removed under vacuum to give a mixture of ethyl 3-[(diethoxyphosphinyl)oxy]-3-butenoate **5b** (36%) and methyl 3-{[(1,1-dimethylethyl)dimethylsilyl]oxy}-4-(diethoxyphosphinyl)-2-butenoate **12g** (64%). Bulb-to-bulb distillation at 120°C, 0.2 mm Hg, removed the enol phosphate **5b**, and the residue contained the phosphonate **12g**. MS (LSIMS); m/z ($MH^+\cdot$, 367) (100), 335 (60), 309 (30), 249 (20). ν_{max} (film) 2940 (s), 2920 (s), 2840 (m), 1730 (m), 1680 (s), 1600 (s), 1450 (m), 1370 (m), 1280 (s), 1240 (vs), 1120 (vs), 1010 (vs), 940 (s), 790 (s) cm^{-1}.

General Procedure for the Reaction of Triethyl Phosphite and Alkyl 4-Bromo-3-{[(1,1-dimethylethyl)dimethylsilyl]oxy}-2-butenoate **10i** *and* **10k**. Redistilled triethyl phosphite (1.1 mmol) was added to alkyl 4-bromo-3-{[(1,1-dimethylethyl)dimethylsilyl]oxy}-2-butenoate **10i** (~1 mmol) at room temperature under anhydrous conditions and then heated for 12 hours at 70°C. Excess triethyl phosphite was removed under vacuum to give (2*E*) alkyl 4-(diethoxyphosphinyl)-3-{[(1,1-dimethylethyl)dimethylsilyl]oxy}-2-butenoate **12**.

For (2*E*) 1-methylethyl 4-(diethoxyphosphinyl)-3-{[(1,1-dimethylethyl)dimethylsilyl]oxy}-2-butenoate **12i** (390 mg, 99%): Anal. calcd for $C_{17}H_{35}O_6PSi$: C, 51.76; H, 8.94. Found: C, 51,61; H, 8.87. HRMS (LSIMS) calcd for $C_{17}H_{36}O_6PSi$ ($MH^+\cdot$) m/z 395.2019; found: 395.2025. MS (LSIMS): 395 ($MH^+\cdot$, 100), 337 (35), 298 (20), 281 (50), 267 (25). ν_{max} (film) 2980 (s), 2932 (s), 2860 (m), 1705 (s), 1621 (s), 1473 (m), 1393 (m), 1366 (m), 1328 (m), 1304 (s), 1256 (s), 1138 (s), 1107 (s), 1029 (s), 966 (m), 828 (s), 811 (s) cm^{-1}.

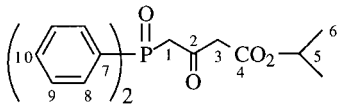
The silyl enol phosphonate **12i** was left for 2 days in the air and hydrolyzed to (1,1-dimethylethyl)dimethylsilanol and 1-methylethyl 3-oxo-4-(diethoxyphosphinyl)butanoate *4c* (100%).

For (**2***E*) S-*t*-butyl 4-(diethoxyphosphinyl)-3-{[(1,1-dimethylethyl)dimethylsilyl]oxy}-2-butenoate ν_{max} (film) 2960 (s), 2930 (s), 2860 (m), 1726 (m), 1658 (s), 1590 (s), 1474 (m), 1392 (s), 1363 (s), 1259 (s), 1162 (s), 1056 (s), 1028 (s), 968 (s), 916 (s), 842 (s) cm^{-1}.

Reaction of 1-Methylethyl 4-Bromo-2-[(trimethylsilyl)oxo]-2-butenoate **9c** *and Ethyl Diphenylphosphinite*. Ethyl diphenylphosphinite (230 mg, 1 mmol) was added neat to 1-methylethyl 4-bromo-2-[(trimethylsilyl)oxy]-2-butenoate **9c/10c** (295 mg, 1 mmol) at room temperature and then heated for 5 hours at 75°C. The residue was distilled to give 1-methylethyl 4-(diphenylphosphinyl)-3-[(trimethylsilyl)oxy]-2-butenoate **13c/14c.** ν_{max} (film) 3057 (m),

2980 (m), 2936 (w), 1714 (s), 1620 (s), 1592 (m), 1438 (s), 1403 (m), 1375 (m), 1317 (m), 1254 (m), 1201 (s), 1153 (s), 1105 (s), 1031 (m), 971 (m), 858 (s), 752 (s), 717 (s), 695 (s) cm^{-1}.

The reaction mixture was allowed to hydrolyze to give pure 1-methylethyl 4-(diphenylphosphinyl)-3-oxobutanoate **2c**. HRMS (EI) calcd for $C_{19}H_{21}O_4P$ m/z 344.1177; found: 344.1186. MS (EI): 344 ($M^{+}\cdot$, 10), 285 (20), 258 (30), 219 (40), 201 (100), 77 (45), 45 (65). ν_{max} (film) 3057 (s), 2982 (m), 2935 (w), 1736 (s), 1714 (s), 1660 (m), 1438 (s), 1403 (m), 1375 (m), 1319 (m), 1256 (m), 1196 (s), 1146 (m), 1106 (s), 728 (m), 695 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 20°C): δ = 1.216 (6H, d, J = 6.3 Hz, 2xCH_3-6), 3.699 (2H, s, CH_2-3), 3.796 (2H, d, J_{PH} = 14.6 Hz, CH_2-1), 5.009 (1H, h, J = 6.3 Hz, CH-5), 7.8–77 (4H, m, Ph), 7.55–7.44 (6H, m, Ph). ^{13}C NMR (50 MHz, $CDCl_3$, 20°C): δ = 21.31 (2xCH_3-6), 46.62 (J_{PC} = 56.3 Hz, CH_2-1), 68.58 (CH-5), 50.75 (J_{PC} = ~0Hz, CH_2-3), 128.46 (J_{PC} = 12.1 Hz, 4xCH-9), (C-7, obscurred), 130.48 (J_{PC} = 9.9 Hz, 4xCH-8), 132.02 (J_{PC} = 2.8 Hz, 2xCH-10), 166.157 (J_{PC} = ~0 Hz, C-4), 195.50 (J_{PC} = 5.5 Hz, C-CH-2).



Reaction of Methyl 4-Chloro-2-{[(1,1-dimethylethyl)dimethylsilyl]oxy}-2-butenoate **10j** with Diphenylphosphinite. Ethyl diphenylphosphinite (230 mg, ~1 mmol) was added neat to methyl 4-chloro-2-{[(1,1-dimethylethyl)dimethylsilyl]oxy}-2-butenoate **10j** (225 mg, 1 mmol) at room temperature, and the mixture was then heated for 12 hours at 80°C. The residue was distilled to give a mixture of methyl 2-{[(1,1-dimethylethyl)dimethylsilyl]oxy}-4-(diphenylphosphinyl)-2-butenoate **14g** (87.5%), **13g** (2.3%), and the enol phosphinate **3g** (10.2%). The enol phosphinate **3g** was removed by bulb-to-bulb distillation. Anal. calcd for **14g** $C_{24}H_{33}O_4PSi$: C, 63.44; H, 7.02. Found: C, 63.25; H, 6.35. MS (LSIMS): m/z 331 ([M-$C_6H_{15}Si]^+$, 100), 285 (80), 247 (40), 219 (20), 201 (70). ν_{max} (film) 3058 (m), 2955 (m), 1741 (m), 1714 (m), 1616 (m), 1438 (m), 1403 (m), 1308 (m), 1254 (m), 1201 (s), 1149 (m), 1130 (s), 729 (m), 717 (m), 696 (s) cm^{-1}.

ACKNOWLEDGMENTS

We thank Dr Graham Rowbottom for elemental analyses and Dr. Noel Davies for mass spectral analyses. Financial assistance from the Australian Research Council is gratefully acknowledged.

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