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Studies on Organophosphorus Compounds 59. Regioselective Phosphorylation and Formylation of Propenylphosphonates—A Novel and Convenient Route to Propenylidenebisphosphonates and 1-Methoxycarbonylpropenylphosphonates

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ABSTRACT

Phosphorylation and formylation of 2-(or 1-)propenylphosphonates show high α-regioselectivity and give, under different conditions, 2-propenylidenebisphosphonates, 1-methoxycarbonyl-2-propenylphosphonates, ethenylidebenebisphosphonates, and 1-methoxycarbonylethenylphosphonates, respectively, in high yields.

INTRODUCTION

Methylenebis (phosphonic acid) (**1a**) and its derivatives are of considerable interest due to their biological activity and medicinal potential. These compounds demonstrate antiviral activity [1] and inhibition of osteoclastic bone resorption [2] and can serve as ligands for ^{99}Tc radiopharmaceuticals [3]. Ethenylidenebis (phosphonic acid) (**2**) and its analogues have also found utility as sequestering agents [4], as monomers for the preparation of polymeric flame retardants [5], and in medical applications [6]. However, few methods have been reported for the preparation of **2** and its derivatives (**3**) [4,7,8]. This discrepancy has stimulated our investigation of new routes to prepare **3**. We wish to report herein a novel, convenient general method for the synthesis of **3** by phosphorylation of 2-propenylphosphonates (**4**) and 1-propenylphosphonates (**5**).

RESULTS AND DISCUSSION

2-propenylphosphonates (allylphosphonates) (**4**) are versatile reagents which have attracted the interest of synthetic chemists. For example, alkylation [9], trimethylsilylation [9], rearrangement [10], and Horner-Emmons reactions [11] of 2-propenylphosphonates have been reported. Since the phosphorylation of alkylphosphonates serve as a convenient method for the preparation of alkylidenebisphosphonates [12], preparation of **3** via phosphorylation of propenylphosphonates could be envisaged.

Although the allylphosphonate anion (**10**) has usually been generated from 2-propenylphosphonate rather than from 1-propenylphosphonate, we have found that 1-propenylphosphonate can also be used to generate **10**. This expands the scope of such anions **10**.

We prepared 2-propenylphosphonates (**4a–d**) by the reaction of allyl halides with diethyl phosphite [13]. 1-Propenylphosphonates (**5e–g**) were

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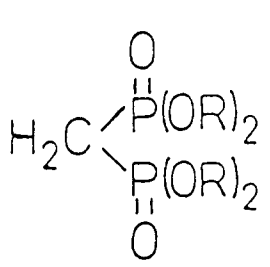
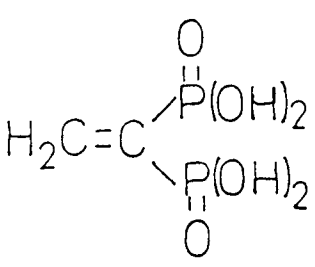


1 R=H(a)
R=Et(b)



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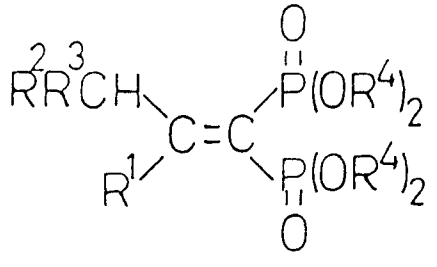


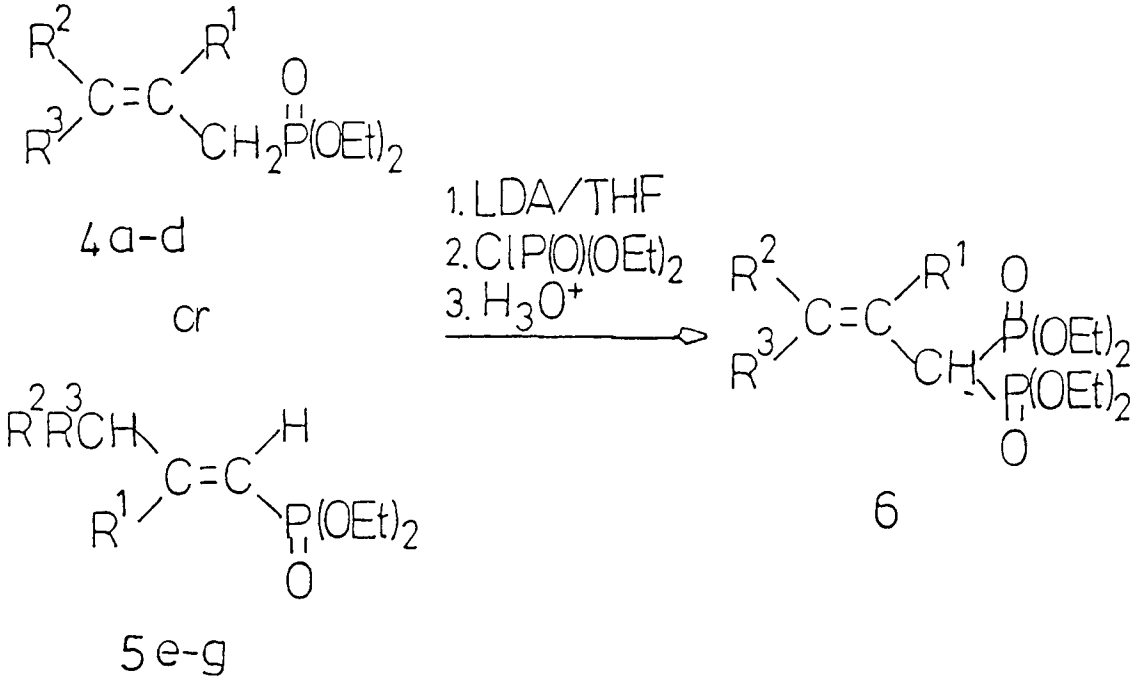
3 R^1, R^2, R^3=H,alkyl,aryl
R^4=Et

prepared by the Horner-Emmons reaction of methylenebisphosphonate (**1b**) with aldehydes or ketones [14]. The allylphosphonate anion (**10**) was generated by treatment of **4** or **5** with LDA. Phosphorylation of **10** with diethyl phosphorochloridate, followed by quenching with aqueous HCl, gave 2-propenylidenebisphosphonates **6** as the sole product. The only exception was observed with **4a** which gave 1-propenylidenebisphosphonate **3a** instead of **6a** as the reaction product. Due to the acidity of the allylic CH of the phosphorylation product **6**, two equivalents of base (LDA) were needed.

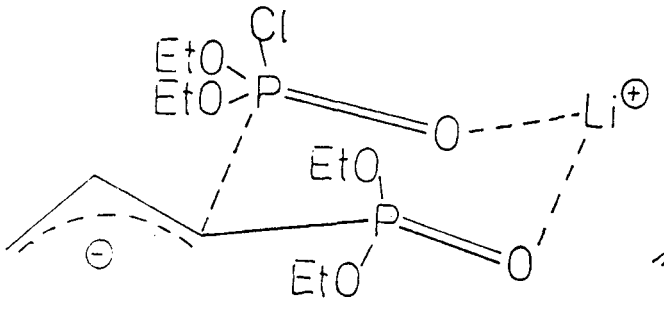
In Scheme 1, three important facts should be noted. The first is that both **4** and **5** lead to the same product **6**. Thus, the phosphonyl stabilized allyl anion **10** can be generated from either **4** or **5**. This result is in contradiction to the concept of a localized anion of allylphosphonate **10** [15,16].

The second is that the phosphorylation of allyl anion **10** occurs with regioselectivity at the α-carbon. While alkylation reactions of **10** also show α-regioselectivity, the reasons for this regioselectivity have not been satisfactorily explained [15,16].

On the basis of X-ray crystallographic analysis of lithiated alkylphosphonates [17] and theoretical calculations of lithiated allylphosphonic diamide [18], Denmark and co-workers have recently concluded that the lithium atom is bonded to phosphonyl oxygen, rather than to the carbon atom. This situation encourages us to postulate that during the phosphorylation of anion **10**, a chair conformation (7) is adopted in the transition state. In this structure, the two phosphonyl oxygens are strongly coordinated to the lithium atom and the phosphorylation at the α-carbon predominates in spite of steric factors while γ-phosphorylation of **10** seems impossible. The chair conformation **7** can be fur-



SCHEME 1



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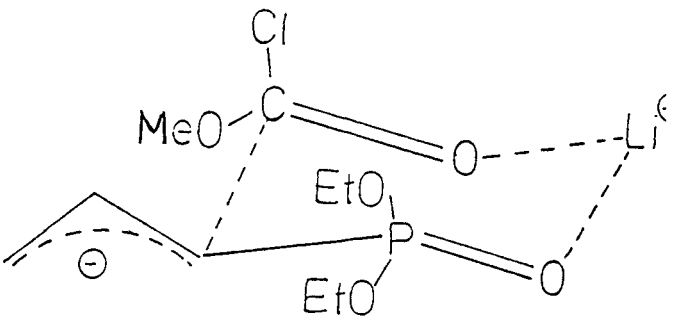

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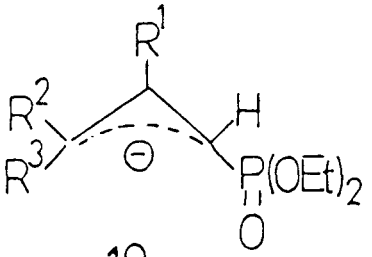
ther proved by carrying out the phosphorylation of **4a** in THF/HMPA (Scheme 2). When HMPA (hexamethylphosphoric triamide) was added to the reaction mixture, the lithium atom was coordinated by HMPA and the configuration **7** was destroyed. Thus, γ-phosphorylation became more accessible than α-phosphorylation due to steric factors, and phosphorylation product of anion **10** gives the allylanion **11** in the presence of a second equivalent of LDA in situ, protonation of **11** by strong acid yields **6** rather than **3**. This reflects the high negative charge density at the α-carbon which is stabilized by the adjacent two powerful electron-withdrawing phosphonyl groups.



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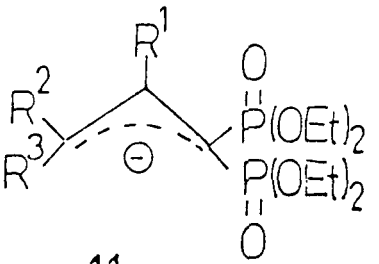

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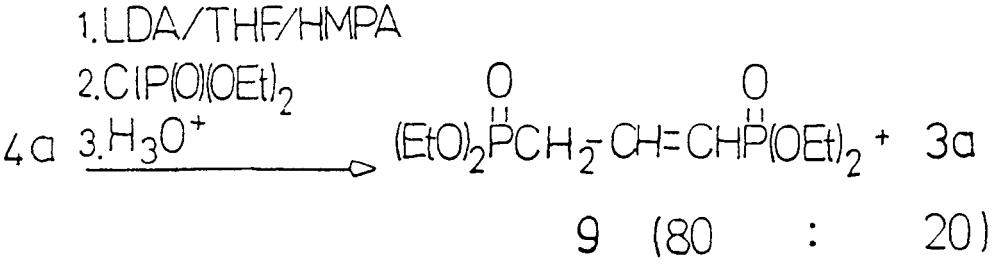
compound **9** [19] was isolated as the major product while **3a** was obtained as the minor one (**9**/**3a** = 80/20). This indicates that the electronic effect of anion **10** has only a minor effect on the regioselectivity, although it seems to be important in the alkylation reaction of anion **10**. The chair conformation can satisfactorily account for the α-regioselectivity observed and may possess a general role in the reaction of allylanion **10** with phosphonyl- or carbonyl-bearing compounds [20].

Third, we observe that instead of ethenylidenebisphosphonates **3**, 2-propenylidenebisphosphonates **6** are isolated in this reaction. As the α-

Protonation is kinetically controlled and results in the formation of **6**. The isolation of **3a** [21] instead of **6a** may result either from the large steric difference between the α and γ positions of anion **11** or from the fast rearrangement of **6a** as it is formed to **3a**. If **11** is quenched by addition of a weak acid, the reaction may be thermodynamically controlled and ethenylidenebisphosphonates **3** may be found. To test this hypothesis, we quenched the anion **11** by addition of ethanol, and under these conditions, compounds **3** were isolated in high yields. This further supports our hypothesis.



SCHEME 2

The above reactions are remarkably clean and provide high yields of the products. Table 1 shows the yields of the typical compounds **6** and **3** synthesized. Due to the easy availability of various substituted compounds **4** and **5**, these methods provide a general and convenient route to compounds **6** and **3**.

Compounds **6** are reasonably stable once isolated. However, **6** can be rearranged at high temperature or by treatment with strong base (except hydroxide ion) to the corresponding **3**. This indicates that **3** is thermodynamically more stable than **6**. Compounds **3** are quite susceptible to attack by hydroxide ion and quickly decompose to give the corresponding compounds **5** [22].

For comparison, the carbomethoxylation of **4** and **5** has also been investigated (Scheme 3). α-Regioselectivity is also observed in the reaction. This can be rationalized by formation of the intermediate chair conformation **8** which is analogous to **7**. Quenching these reactions with strong acids yields 1-methoxycarbonyl-2-propenylphosphonates (**12**), whereas 1-methoxycarbonylethenylphosphonates (**13**) are isolated if the reaction is quenched with the weak acid ethanol (Table 1). These results are consistent with our understanding of the phosphonyl-stabilized allyl anion **10**.

The formylation of **4** and **5** leads to a general and convenient route to **12**, or **13**, for which only a few preparative methods have been reported [7,23,24]. These are novel derivatives of α-dialkoxyphosphonoacetate.

TABLE 1. Preparation of Compounds **3**, **6**, **12**, and **13**

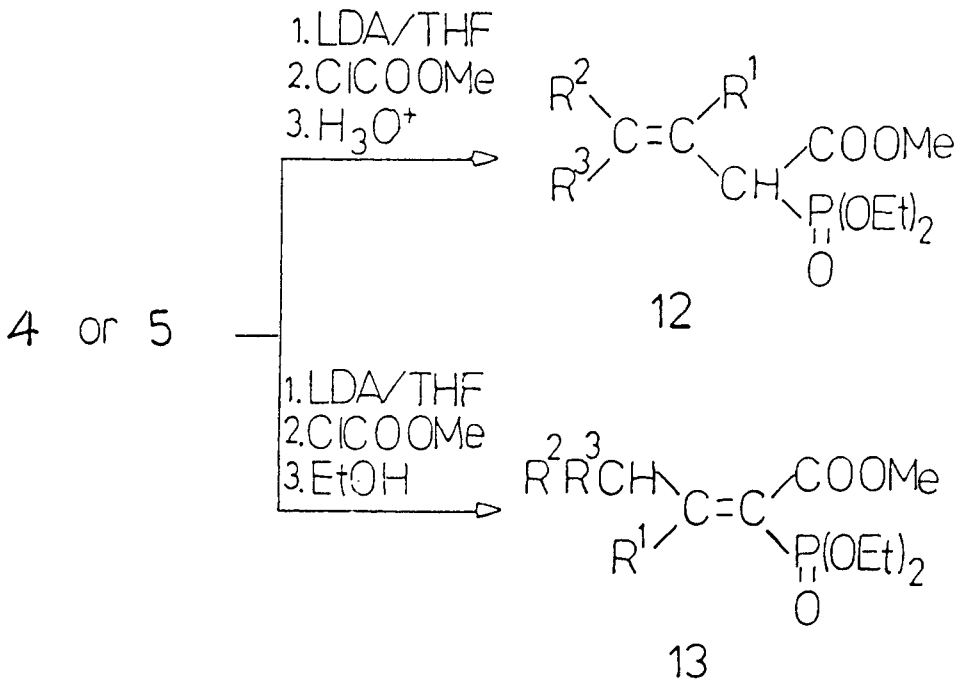
				Yield (%)*			
Entry	R^1	R^2	R^3	***3***	***6***	***12***	***13***
a	H	H	H	80	/	80	84
b	H	H	CH_3	81	85	88	90
c	H	CH_3	CH_3	80	90	92	95
d	CH_3	H	H	86	90	90	90
e	H	H	n-C_5H_{11}	82	87	80	80
f	C_6H_5	H	H	87	93	81	83
g	$(CH_2)_4$		H	72	86	90	77

*Isolated yield based on the corresponding **4** or **5**.

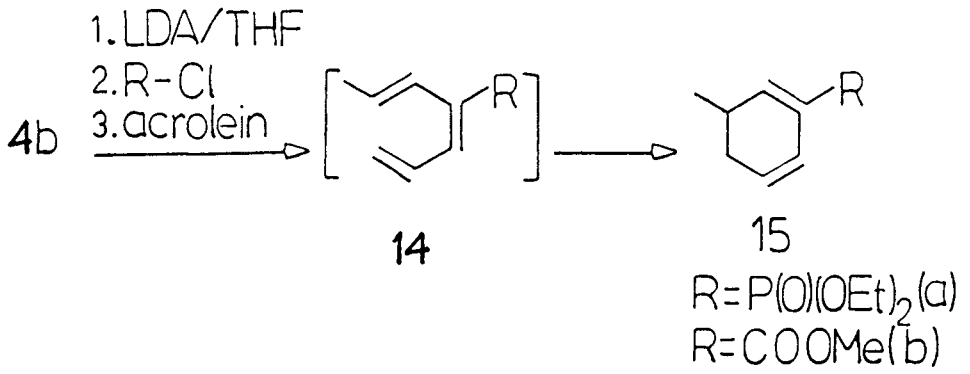
Besides the biological interest of compounds **3**, **6**, **12**, and **13**, they also have considerable synthetic utility. For example, cyclic dienes bearing phosphonate or acetate moieties can be achieved, as in Scheme 4.

Phosphonate **4b** undergoes phosphorylation or formylation with diethoxyphosphoryl chloride or methyl chloroformate in the presence of a base (LDA). By subsequent reaction with acrolein, a cyclic diene **15** [25] is obtained by a one-pot reaction. The reaction obviously proceeds via a triene intermediate (**14**) which results from the Horner-Emmons reaction of anion **11** with acrolein and quickly undergoes electrocyclization to provide **15**.

This example illustrates the synthetic application of propenylphosphonates **4** and **5**.



SCHEME 3



SCHEME 4

CONCLUSION

The α-regioselectivity in phosphorylation and formylation of the phosphonate-stabilized allyl anion **10** may be rationalized by the formation of the chair-conformational transition state which results from coordination of these lithium atoms with phosphoryl or carbonyl oxygens.

EXPERIMENTAL PART

Infrared spectra were obtained on a Perkin-Elmer 983 infrared spectrometer. ^{1}H NMR spectra were recorded on a XL-200 spectrometer. ^{31}P and ^{13}C NMR spectra were obtained with broad band decoupling on a FX-90Q spectrometer using TMS as the internal reference and 85% phosphoric acid as the external standard for ^{31}P NMR. The splitting in ^{13}C-NMR refers to the C-P coupling. CI-MS spectra were recorded on a Finnigan 4021 mass spectrometer. Butyllithium (1.6 M solution in Hexanes) was purchased from Aldrich Chemical Co. The other reagents were obtained from a commercial source (Shanghai Chemical Co.). Tetraethyl methylenebisphosphonate was prepared according to the literature [26]. Diisopropylamine was purified by treatment with CaH_2 and stored under nitrogen before use. Absolute ethanol was distilled by treatment with Mg.

*Tetraethyl (E)-2-butenylidenebisphosphonate (**6b**)*

General Procedure. Diisopropylamine (1.4 mL, 10 mmol) was added to dry, freshly distilled THF (20 mL) and the solution stirred for 1 minute under nitrogen in a 100 mL three-necked flask fitted with a rubber septum. The solution was cooled to −68°C, and then butyllithium (6.7 mL, 10 mmol) was added via the septum by the aid of a syringe and stirring was continued for 30 minutes. Diethyl 2-butenylphosphonate **4b** (0.96 g, 5 mmol) was then added dropwise at −68°C. After the complete addition, the solution was warmed to 0°C and maintained at that temperature for 10 minutes and then again cooled to −68°C, at which temperature diethyl phosphorochloridate (0.77 mL, 5.5 mmol) was added. After having been kept at −68°C for 30 minutes, the solution was allowed to warm to room temperature and stirred for 12 hours. Hydrochloric acid (1N) was added to the solution until the pH was slightly acidic. After the separation of the resulting two phases, the aqueous layer was extracted with CH_2Cl_2 (4 × 30 ml). The combined organic layer was dried with anhydrous sodium sulfate, and the solvent was removed under reduced pressure to give the crude product. This was purified by flash chromatography on silica with elution with acetone/petroether (1/2, v/v) to give the pure product **6b** as a colorless oil. Yield: 1.39 g (85%); IR (film) ν 1645, 1248, 1023, 969; CIMS: m/z 329 (M^++H); ^{1}H NMR ($CDCl_3$) δ 1.32, 1.34 (12H, 2t, J = 7, CH_3CH_2O), 1.78 (3H, dt, J = 1.5, 5, CH_3C=), 3.21 (1H, dt, J = 10, 24, CHP_2), 4.10 (8H, q, J = 7, CH_2O), 5.40–5.90 (2H, br, CH = CH); ^{31}P NMR ($CDCl_3$) δ 19.50 (s). ^{13}C NMR ($CDCl_3$) δ 15.82, 16.11 (2s, $4CH_3CH_2O$), 17.76 (s, CH_3C=), 42.58 (t, J = 134.1, CP_2), 62.18, 62.47, 62.81 (3s, $4CH_2O$), 118.1 (t, J = 10, $CHCP_2$), 132.6 (t, J = 13, $CHCH_3$). Anal. Calcd. for $C_{12}H_{26}O_6P_2$: C, 43.91; H, 7.99. Found: C, 43.75; H, 8.12.

*Tetraethyl 3-methyl-2-butenylidenebisphosphonate (**6c**)*

Colorless oil. IR (film) ν 1636, 1252, 1025, 969; CIMS: m/z 343 (M^++H); ^{1}H NMR ($CDCl_3$) δ 1.31, 1.33 (2 × 6H, 2t, J = 7, CH_3CH_2O), 1.70 (3H, dt, J = 1.2, 3.4, CH_3C=), 1.84 (3H, dt, J = 1.0, 4.3, CH_3C=), 3.47 (1H, dt, J = 11, 24, CHP_2), 4.20 (8H, m, CH_2O), 5.28 (1H, m, CH=); ^{31}P NMR ($CDCl_3$) δ 20.02 (s). Anal. Calcd. for $C_{13}H_{28}O_6P_2$: C, 45.62; H, 8.25. Found: C, 45.33; H, 8.35.

*Tetraethyl 2-methyl-2-propenylidenebisphosphonate (**6d**)*

Colorless oil. IR (film) ν 1638, 1251, 1027, 969; CIMS: m/z 329 (M^++H); 1H NMR ($CDCl_3$) δ 1.33, 1.34 (2 × 6H, 2t, J = 7, CH_3CH_2O), 1.97 (3H, s, CH_3C=), 3.18 (1H, t, CHP_2), 4.20 (8H, m, CH_2O), 5.20 (2H, br, CH_2=); ^{31}P NMR ($CDCl_3$) δ 18.99 (s). Anal. Calcd. for $C_{12}H_{26}O_6P_2$: C, 43.91; H, 7.99. Found: C, 43.78; H, 8.08.

*Tetraethyl (E)-2-octenylidenebisphosphonate (**6e**)*

Colorless oil. IR (film) ν 1644, 1248, 1024, 969; CIMS: m/z 385 (M^++H); ^{1}H NMR ($CDCl_3$) δ 0.82–1.00 (9H, br, n-C_4H_9), 1.32 (12H, t, J = 7, CH_3CH_2O), 1.66 (2H, m, CH_2-C=), 3.20 (1H, dt, J = 10, 24, CHP_2), 4.17 (8H, m, CH_2O), 5.40 (2H, br, CH = CH); ^{31}P NMR ($CDCl_3$) δ 19.45 (s). Anal. Calcd. for $C_{16}H_{34}O_6P_2$: C, 50.00; H, 8.92. Found: C, 49.91; H, 9.03.

*Tetraethyl 2-phenyl-2-propenylidenebisphosphonate (**6f**)*

Colorless oil. IR (film) ν 3035, 1622, 1251, 1024, 971; CIMS: m/z 391 (M^++H); ^{1}H NMR ($CDCl_3$) δ 1.24 (12H, t, J = 7, CH_3), 3.67 (1H, t, J = 26, CHP_2), 4.13 (8H, m, CH_2O), 5.62, 5.86 (2 × 1H, m, CH_2=), 7.30 (5H, m, C_6H_5); ^{31}P NMR ($CDCl_3$) δ 18.87 (s). Anal. Calcd. for $C_{17}H_{28}O_6P_2$: C, 52.31; H, 7.23. Found: C, 52.32; H, 7.34.

*Tetraethyl (1-cyclohexenyl)methylenebisphosphonate (**6g**)*

Colorless oil. IR (film) ν 1652, 1253, 1026, 967; CIMS: m/z 369 (M^++H); ^{1}H NMR ($CDCl_3$) δ 1.31, 1.33 (2 × 6H, 2t, J = 7, CH_3), 1.40–1.72 (4H, br, CH_2 of cyclohexenyl), 2.00–2.22 (4H, br, CH_2 of cyclohexenyl), 3.00 (1H, t, J = 26, CHP_2), 4.16 (8H, m, CH_2O), 5.98 (1H, br, CH=); ^{31}P NMR ($CDCl_3$) δ 19.70 (br). Anal. Calcd. for $C_{15}H_{30}O_6P_2$: C, 48.91; H, 8.21. Found: C, 48.76; H, 8.39.

*Tetraethyl 1-butenylidenebisphosphonate (**3b**)*

General Procedure. Diisopropylamine (1.4 mL, 10 mmol) was added to dry, freshly distilled THF (20 mL), and the solution was cooled to −68°C. Butyllithium (6.7 mL, 10 mmol) was added under nitrogen, and stirring was continued for 30 minutes. Diethyl 2-butenylphosphonate **4b** (0.96 g, 5 mmol) was then added dropwise. After the complete addition, the solution was warmed to 0°C and maintained at this temperature for 10 minutes and then again cooled to −68°C, at which temperature, diethyl phosphorochloridate (0.77 mL, 5.5 mmol) was added. After having been kept at −68°C for 30 minutes, the solution was warmed to room temperature and stirred for 12 hours. Absolute ethanol (10 mL) was added and the solution stirred for 3 hours. Anhydrous TsOH (5.2 g, 30 mmol) was added to quench the reaction. The resulting mixture was concentrated under vacuum and purified by flash chromatography on silica with elution with acetone/petroether (1/1.5, v/v) to give the pure product **3b** as a colorless oil, 1.32 (81%); IR (film) ν 1598, 1240, 1026, 970; CIMS: m/z 329 (M^++H); ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, t, J = 7, CH_3CH_2C=), 1.35 (12H, t, J = 7, CH_3CH_2O), 2.40 (2H, dtq, J = 3, 6, 7, CH_2C=), 4.16 (8H, m, CH_2O), 7.65 (1H, ddt, J = 6, 27, 48); ^{31}P NMR ($CDCl_3$) δ 16.14 (d, J = 50.3), 12.30 (d, J = 50.3). Anal. Calcd. for $C_{12}H_{26}O_6P_2$: C, 43.91; H, 7.99. Found: C, 43.60; H, 8.32.

*Tetraethyl 1-propenylidenebisphosphonate (**3a**)*

Colorless oil. IR (film) ν 1595, 1239, 1026, 970; CIMS: m/z 315 (M^++H); ^{1}H NMR ($CDCl_3$) δ 1.35 (12H, t, J = 7, CH_3CH_2O), 2.29 (3H, dt, J = 3, 7, CH_3-C=), 4.16 (8H, m, CH_2O), 7.66 (1H, ddq, J = 7, 28, 48, CH=); ^{31}P NMR ($CDCl_3$) δ 12.38 (d, J = 52.8), 16.02 (d, J = 52.8). ^{13}C NMR ($CDCl_3$) δ 15.90, 16.20 (2s, $4CH_3CH_2O$), 18.22 (dd, J = 8, 19, CH_3-C=), 61.78, 62.02, 62.05, 62.26 (4s, $4CH_2O$), 123.4 (dd, J = 145, 169, CP_2), 164.1 (s, CH). Anal. Calcd. for $C_{11}H_{24}O_6P_2$: C, 42.05; H, 7.70. Found: C, 41.88; H, 7.92.

*Tetraethyl 3-methyl-1-butenylidenebisphosphonate (**3c**)*

Colorless oil. IR (film) ν 1595, 1240, 1025, 969; CIMS: m/z 343 (M^++H); ^{1}H NMR ($CDCl_3$) δ 0.90 (6H, d, J = 6, CH_3CH), 1.35 (12H, t, J = 7, CH_3CH_2O), 2.50 (1H, m, $CHCH_3$), 4.18 (8H, m, CH_2O), 7.60 (1H, ddd, J = 7, 28, 49, CH = CP_2); ^{31}P NMR ($CDCl_3$) δ 12.35 (d, J = 52.0), 16.18 (d, J = 52.0). Anal. Calcd. for $C_{13}H_{28}O_6P_2$: C, 45.62; H, 8.25. Found: C, 45.34; H, 8.45.

*Tetraethyl 2-methyl-1-propenylidenebisphosphonate (**3d**)*

Colorless oil. IR (film) ν 1615, 1240, 1025, 965; CIMS: m/z 329 (M^++H); ^{1}H NMR ($CDCl_3$) δ 1.26 (12H, t, J = 7, CH_3CH_2O), 2.25 (6H, s, CH_3C=), 4.10 (8H, m, CH_2O); ^{31}P NMR ($CDCl_3$) δ 19.65 (s). Anal. Calcd. for $C_{12}H_{26}O_6P_2$: C, 43.91; H, 7.99. Found: C, 43.64; H, 8.23.

*Tetraethyl 1-octenylidenebisphosphonate (**3e**)*

Colorless oil. IR (film) ν 1600, 1241, 1024, 970; CIMS: m/z 385 (M^++H); ^{1}H NMR ($CDCl_3$) δ 0.85–1.05 (11H, br, n-C-H_{11}), 1.32 (12H, t, J = 7, CH_3CH_2O), 2.50 (2H, m, CH_2C=), 4.15 (8H, m, CH_2O), 7.54 (1H, ddt, J = 7, 27, 50, CH = CP_2); ^{31}P NMR ($CDCl_3$) δ 12.60 (d, J = 54.7), 16.29 (d, J = 54.7). Anal. Calcd. for $C_{16}H_{34}O_6P_2$: C, 50.00; H, 8.92. Found: C, 49.77; H, 9.22.

*Tetraethyl 2-phenyl-1-propenylidenebisphosphonate (**3f**)*

Colorless oil. IR (film) ν 3042, 1700, 1363, 1218, 1028, 961; CIMS: m/z 391 (M^++H); ^{1}H NMR ($CDCl_3$) δ 1.32 (12H, m, CH_3CH_2O), 2.50 (3H, dd, J = 1, 3.4, CH_3-C=), 4.10 (8H, m, CH_2O), 7.40 (5H, m, C_6H_5); ^{31}P NMR ($CDCl_3$) δ 17.12 (d, J = 3.6), 17.94 (d, J = 3.6). Anal. Calcd. for $C_{17}H_{28}O_6P_2$: C, 52.31; H, 7.29. Found: C, 52.16; H, 7.55.

*Tetraethyl Cyclohexylidenemethylenebisphosphonate (**3g**)*

Colorless oil. IR (film) ν 1595, 1241, 1025, 969; CIMS: m/z 369 (M^++H); ^{1}H NMR ($CDCl_3$) δ 1.05 (2H, br, 4'-CH_2), 1.35 (12H, t, J = 7, CH_3), 1.55 (4H, br, 3'- and 5'-CH_2), 2.45 (4H, br, 2'- and 6'-CH_2), 4.18 (8H, m, CH_2O); ^{31}P NMR ($CDCl_3$) δ 19.30 (s). Anal. Calcd. for $C_{15}H_{30}O_6P_2$: C, 48.91; H, 8.21. Found: C, 48.95; H, 8.55.

*Tetraethyl 1,3-propenylenedisphosphonate (**9**)*

Diethyl 2-propenylphosphonate **4a** (0.89 g, 5 mmol) was added dropwise at −68°C to an LDA solution prepared by the action of butyllithium (6.7 mL, 10 mmol) on diisopropylamine (1.4 mL, 10 mmol) in THF (20 mL) in situ. After the complete addition, the solution was warmed to 0°C and stirred for 10 minutes. HMPA (10 mL) was added, and the mixture stirred for 10 minutes. The solution was then cooled to −55°C (too low a temperature may cause the precipitation of HMPA), and diethyl phosphorochloridate (0.77 mL, 5.5 mmol) was added. After having been kept at −55°C for 30 minutes, the solution was warmed to room temperature and stirred for 3 hours. Hydrochloric acid (1N) was added until the pH was slightly acidic. The mixture was extracted with CH_2Cl_2 (5 × 40 mL). The combined organic phase was dried with anhydrous sodium sulfate, and the solvent was removed under vacuum to give the mixture of **3a** and **9** (0.98 g, 60%, **3a**/**9** = 20/80, determined by ^{31}P NMR). Chromatography on silica with elution with acetone/petroether (1/2, v/v) gave pure **9** as the mixture of Z/E isomers (Z/E = 50/50) without further isolation. Colorless oil; ^{31}P NMR ($CDCl_3$) δ 19.34, 21.66 (P–CH); 30.50, 31.60 (P–CH_2). Other data were identical with those reported in the literature [19].

*Diethyl (E)-1-methoxycarbonyl-2-butenylphosphonate (**12b**)*

General Procedure. Diethyl 2-butenylphosphonate **4b** (0.96 g, 5 mmol) was added dropwise at −68°C to an LDA solution prepared by the action of butyllithium (6.7 mL, 10 mmol) on diisopropylamine (1.4 mL, 10 mmol) in THF (20 mL) in situ. After the complete addition, the solution was warmed to 0°C and stirred for 10 minutes and then again cooled to −68°C, at which temperature methyl chloroformate (0.43 mL, 5.5 mmol) was added dropwise. The solution was stirred for 30 minutes at −68°C and warmed to room temperature and stirred for an additional 4 hours. Hydrochloric acid (1N) was added until the pH was slightly acidic. The resulting two phases were separated, the aqueous layer extracted with ether (4 × 30 mL), the combined organic phase dried with anhydrous sodium sulfate, and concentrated in vacuo to give the crude product. This was purified by flash chromatography on silica with elution with acetone petroether (1/1.5, v/v) to give the pure **12b** as a colorless oil. Yield: 1.10 g (88%); IR (film) ν 3035, 1738, 1622, 1256, 1026, 967; CIMS: m/z 251 (M^++H); ^{1}H NMR ($CDCl_3$) δ 1.30 (6H, t, J = 7, CH_3CH_2O), 1.74 (3H, dd, J = 5, 5.2, CH_3C=), 3.70 (1H, dd, J = 7, 25, CHP), 3.74 (3H, s, CH_3O), 4.15 (4H, m, CH_2O), 5.66 (2H, m, CH = CH); ^{31}P NMR ($CDCl_3$) δ 19.26; ^{13}C NMR ($CDCl_3$) δ 15.86, 16.11 (2s, $2CH_3CH_2O$), 17.64 (d, J = 3.3, CH_3-C=), 49.72 (d, J = 133, CP), 52.14 (s, CH_3O), 62.66, 62.95 (2s, $2CH_2O$), 120.0 (d, J = 11, CHCP), 131.4 (d, J = 13, $CHCH_3$), 167.9 (d, J = 4.4, CO). Anal. Calcd. for $C_{10}H_{19}O_5P$: C, 48.01; H, 7.65. Found: C, 47.89; H, 7.56.

*Diethyl (E)-1-methoxycarbonyl-2-propenylphosphonate (**12a**)*

Colorless oil. IR (film) ν 1736, 1635, 1254, 1026, 968; CIMS: m/z 237 (M^++H); ^{1}H NMR ($CDCl_3$ δ 1.30 (6H, t, J = 7), CH_3CH_2O), 3.74 (1H, dd, J = 8, 28, CHP), 3.75 (3H, s, CH_3O), 4.15 (4H, m, CH_2O), 5.30 (2H, m, CH_2=), 6.00 (1H, m, CH=); ^{31}P NMR ($CDCl_3$) δ 18.46. Anal. Calcd. for $C_9H_{17}O_5P$: C, 45.77; H, 7.26. Found: C, 45.49; H, 7.28.

*Diethyl 1-methoxycarbonyl-3-methyl-2-butenylphosphonate (**12c**)*

Colorless oil. IR (film) ν 3035, 1737, 1640, 1254, 1027, 965; CIMS: m/z 265 (M^++H); ^{1}H NMR ($CDCl_3$) δ 1.30 (6H, t, J = 7, CH_3CH_2O), 1.75 (3H, dd, J = 1.2, 3.5, CH_3C=), 1.83 (3H, dd, J = 1.1, 4.0, CH_3C=), 3.75 (3H, s, CH_3O), 3.78 (1H, dd, J = 7, 25, CHP), 4.16 (4H, m, CH_2O), 5.70 (1H, m, CH=); ^{31}P NMR ($CDCl_3$) δ 19.80. Anal. Calcd. for $C_{11}H_{21}O_5P$: C, 50.00; H, 8.01. Found: C, 49.77; H, 8.30.

*Diethyl 1-methoxycarbonyl-2-methyl-2-propenylphosphonate (**12d**)*

Colorless oil. IR (film) ν 3045, 1738, 1641, 1254, 1026, 965; CIMS: m/z 251 (M^++H); ^{1}H NMR ($CDCl_3$) δ 1.32 (6H, t, J = 7, CH_3CH_2O), 1.96 (3H, s, CH_3C=), 3.75 (1H, d, J = 24, CHP), 3.76 (3H, s, CH_3O), 4.18 (4H, m, CH_2O), 5.16 (2H, m, CH_2=); ^{31}P NMR ($CDCl_3$) δ 18.99. Anal. Calcd. for $C_{10}H_{19}O_5P$: C, 48.01; H, 7.65. Found: C, 47.76; H, 7.77.

*Diethyl (E)-1-methoxycarbonyl-2-octenylphosphonate (**12e**)*

Colorless oil. IR ($CDCl_3$) ν 3035, 1737, 1623, 1256, 1025, 965; CIMS: m/z 307 (M^++H); ^{1}H NMR ($CDCl_3$) δ 0.80–1.10 (9H, br, n-C_4H_9), 1.32 (6H, t, J = 7, CH_3CH_2O), 1.80 (2H, m, CH_2C=), 3.70 (1H, dd, J = 7, 24, CHP), 3.75 (3H, s, CH_3O), 4.15 (4H, m, CH_2O), 5.68 (2H, m, CH=CH); ^{31}P NMR ($CDCl_3$) δ 19.20. Anal. Calcd. for $C_{14}H_{27}O_5P$: C, 54.90; H, 8.88. Found: C, 54.84; H, 8.89.

*Diethyl 2-phenyl-1-methoxycarbonyl-2-propenylphosphonate (**12f**)*

Colorless oil. IR (film) ν 3025, 1736, 1641, 1254, 1029, 969; CIMS: m/z 313 (M^++H); ^{1}H NMR ($CDCl_3$) δ 1.26 (6H, dt, J = 5, 7, CH_3CH_2O), 3.77 (3H, s, CH_3O), 4.15 (4H, m, CH_2O), 4.25 (1H, d, J = 24, CHP), 5.65, 5.87 (2H, 2d, J = 5, CH_2=), 7.38 (5H, m, C_6H_5); ^{31}P NMR ($CDCl_3$) δ 18.78. Anal. Calcd. for $C_{15}H_{21}O_5P$: C, 57.70; H, 6.78. Found: C, 57.44; H, 6.98.

*Diethyl (1-cyclohexenyl)-1-methoxycarbonylmethylphosphonate (**12g**)*

Colorless oil. IR (film) ν 1735, 1255, 1025, 966; CIMS: m/z 291 (M^++H); ^{1}H NMR ($CDCl_3$) δ 1.30 (6H, t, J = 7, CH_3CH_2O), 1.46–1.74 (4H, br, 5′ and 4′-CH_2), 2.00–2.26 (4H, br, 3′ and 6′-CH_2), 3.60 (1H, d, J = 24, CHP), 3.74 (3H, s, CH_3O), 4.16 (4H, m, CH_2O), 5.88 (1H, m, CH=); ^{31}P NMR ($CDCl_3$) δ 19.80. Anal. Calcd. for $C_{13}H_{23}O_5P$: C, 53.79; H, 7.99. Found: C, 53.51; H, 8.12.

*Diethyl (E)-1-methoxycarbonyl-1-butenylphosphonate (**13b**)*

General Procedure Diethyl 2-butenylphosphonate **4b** (0.96 g, 5 mmol) was added dropwise at −68°C to an LDA solution prepared by the action of butyllithium (6.7 mL, 10 mmol) on diisopropylamine (1.4 mL, 10 mmol) in THF (20 mL) in situ. After the complete addition, the solution was allowed to warm to 0°C and stirred for 10 minutes and then again cooled to −68°C, at which temperature, methyl chloroformate (0.43 mL, 5.5 mmol) was added dropwise for 30 minutes. The solution was warmed to room temperature and stirred for an additional 4 hours. Absolute ethanol (4 mL) was added and the mixture stirred for 1 hour. Anhydrous TsOH (5.2 g, 30 mmol) was added to quench the reaction. The mixture was concentrated in vacuo and purified by flash chromatography on silica with elution with acetone/petroether (1/1, v/v) to give pure **13b** as a colorless oil. Yield: 1.12 g (90%). IR (film) ν 1722, 1620, 1254, 1027, 967; CIMS: m/z 251 (M^++H); ^{1}H NMR ($CDCl_3$) δ 1.24 (3H, t, J = 7, CH_3CH_2C=), 1.32 (6H, t, J = 7, CH_3CH_2O), 2.00 (2H, m, CH_2C=), 3.80 (3H, s, CH_3O), 4.18 (4H, m, CH_2O), 6.92 (1H, dt, J = 8, 22, CH=); ^{31}P NMR ($CDCl_3$) δ 13.70; ^{13}C NMR ($CDCl_3$) δ 13.85 (s, CH_3CH_2C), 15.90, 16.13 (2s, $2CH_3CH_2O$), 30.80 (s, CH_2CH=), 52.25 (s, CH_3O), 62.92, 63.04 (2s, $2CH_3CH_2O$), 122.1 (d, J = 150, CP), 168.2 (s, CH=), 168.4 (s, COO). Anal. Calcd. for $C_{10}H_{19}O_5P$: C, 48.01; H, 7.65. Found: C, 47.68; H, 7.99.

*Diethyl (E)-1-methoxycarbonyl-1-propenylphosphonate (**13a**)*

Colorless oil. IR (film) ν 1723, 1625, 1260, 1025, 966; CIMS: m/z 237 (M^++H); ^{1}H NMR ($CDCl_3$) δ 1.30 (6H, t, J = 7, CH_3CH_2O), 2.12 (3H, dd, J = 4, 7, CH_3C=), 3.76 (3H, s, CH_3O), 4.16 (4H, m, CH_2O), 7.26 (1H, dq, J = 7, 23, CH=); ^{31}P NMR ($CDCl_3$) δ 13.70. Anal. Calcd. for $C_9H_{17}O_5P$: C, 45.77; H, 7.26. Found: C, 45.49; H, 7.55.

*Diethyl (E)-1-methoxycarbonyl-3-methyl-1-butenylphosphonate (**13c**)*

Colorless oil. IR (film) ν 1725, 1622, 1253, 1025, 967; CIMS: m/e 265 (M^++H); ^{1}H NMR ($CDCl_3$) δ 0.92 (6H, d, J = 7, CH_3CH), 1.32 (6H, t, J = 7, CH_3CH_2O), 2.36 (1H, m, CH), 3.75 (3H, s, CH_3), 4.18 (4H, m, CH_2O), 7.25 (1H, dd, J = 7, 27, CH=); ^{31}P NMR ($CDCl_3$) δ 14.10. Anal. Calcd. for $C_{11}H_{21}O_5P$: C, 50.00; H, 8.01. Found: C, 49.89; H, 7.92.

*Diethyl 1-methoxycarbonyl-2-methyl-1-propenylphosphonate (**13d**)*

Colorless oil. IR (film) ν 1722, 1623, 1269, 1025, 965; CIMS: m/z 251 (M^++H); ^{1}H NMR ($CDCl_3$) δ 1.32 (6H, t, J = 7, CH_3CH_2O), 1.94 (3H, d, J = 2, CH_3C=), 2.18 (3H, d, J = 4, CH_3C=), 3.80 (3H, s, CH_3O), 4.16 (4H, m, CH_2O); ^{31}P NMR ($CDCl_3$) δ 12.36. Anal. Calcd. for $C_{10}H_{19}O_5P$: C, 48.01; H, 7.65. Found: C, 47.83; H, 7.87.

*Diethyl (E)-1-methoxycarbonyl-1-octenylphosphonate (**13e**)*

Colorless oil. IR (film) ν 1722, 1621, 1254, 1027, 965; CIMS: m/z 307 (M^++H); ^{1}H NMR ($CDCl_3$) δ 0.80–1.29 (11H, br, n-C_5H_{11}), 1.32 (6H, t, J = 7, CH_3CH_2O), 2.24 (2H, m, CH_2C=), 3.80 (3H, s, CH_3O), 4.18 (4H, m, CH_2O), 7.30 (1H, dt, J = 7, 28, CH=); ^{31}P NMR ($CDCl_3$) δ 13.55. Anal. Calcd. for $C_{14}H_{27}O_5P$: C, 54.90; H, 8.88. Found: C, 54.77; H, 8.99.

*Diethyl (E)-1-methoxycarbonyl-2-phenyl-1-propenylphosphonate (**13f**)*

Colorless oil. IR (film) ν 1720, 1617, 1573, 1251, 1026, 968; CIMS: m/z 313 (M^++H); ^{1}H NMR ($CDCl_3$) δ 1.35 (6H, t, J = 7, CH_3CH_2O), 2.48 (3H, d, J = 3,

CH_3C=), 3.85 (3H, s, CH_3O), 4.18 (4H, m, CH_2O), 7.32 (5H, m, C_6H_5); ^{31}P NMR ($CDCl_3$) δ 12.07. Anal. Calcd. for $C_{15}H_{21}O_5P$: C, 57.70; H, 6.78. Found: C, 57.54; H, 6.98.

*Diethyl 1-methoxycarbonyl-cyclohexylidenemethylphosphonate (**13g**)*

Colorless oil. IR (film) ν 1722, 1625, 1253, 1027, 968; CIMS: m/z 291 (M^++H); ^1H NMR ($CDCl_3$) δ 1.02 (2H, br, 4'-CH_2), 1.32 (6H, t, J = 7, CH_3C), 1.45–1.90 (4H, br, 3'- and 5'-CH_2), 2.32 (4H, br, CH_2C=), 3.75 (3H, s, CH_3O), 4.18 (4H, m, CH_2O); ^{31}P NMR ($CDCl_3$) δ 12.78. Anal. Calcd. for $C_{13}H_{23}O_5P$: C, 53.79; H, 7.99. Found: C, 53.50; H, 8.21.

*Diethyl 3-methyl-1,5-cyclohexadiene-1-phosphonate (**15a**)*

Diethyl 2-butenylphosphonate **4b** (0.96 g, 5 mmol) was added dropwise at −68°C to an LDA solution prepared by the reaction of butyllithium (6.7 mL, 10 mmol) with diisopropylamine (1.4 mL, 10 mmol) in THF (20 mL) in situ. After the complete addition, the solution was warmed to 0°C and stirred for 10 minutes and then again cooled to −68°C, at which temperature diethyl phosphorochloridate (0.77 mL, 5.5 mmol) was added. The solution was stirred at −68°C for 30 minutes and then at room temperature for 12 hours. Acrolein (0.41 mL, 6 mmol) was added to the solution at −20°C, and stirring continued at −20°C for 2 hours and then at room temperature for 2 hours. Hydrochloric acid (1N) was added until the pH was slightly acidic. After the separation of the resulting two phases, the aqueous layer was extracted with ether (5 × 40 mL) and the combined organic phase dried with anhydrous sodium sulfate and concentrated in vacuo to leave the crude product, which was purified by vacuum distillation to give pure 15a as a colorless liquid; bp 120°C/0.4 Torr. Yield: 0.75 g (65%). The spectral data were identical with those reported in the literature [25b].

*Methyl 3-methyl-1,5-cyclohexadiene-1-carboxylate (**15b**)*

Diethyl 2-butenylphosphonate **4b** (0.96 g, 5 mmol) was added dropwise at −68°C to an LDA solution prepared by the action of butyllithium (6.7 mL, 10 mmol) on diisopropylamine (1.4 mL, 10 mmol) in THF (20 mL) in situ. The solution was warmed to 0°C and stirred for 10 minutes and then cooled to −68°C, at which temperature methyl chloroformate (0.43 mL, 5.5 mmol) was added dropwise. The solution was stirred at −68°C for 30 minutes and then room temperature for 4 hours. Acrolein (0.41 mL, 6 mmol) was added to the solution at −30°C, and stirring continued for 3 hours. Hydrochloric acid (1N) was added until the pH was slightly acidic. The resulting two phases were separated, the aqueous layer extracted with ether (4 × 3 mL) and the combined organic phase dried with anhydrous sodium sulfate and concentrated in vacuo to leave the crude product. This was purified by vacuum distillation to give the pure **15b** as a colorless liquid; bp 45°C/0.2 Torr. Yield: 0.36 g (60%). The spectral data were identical with those reported in the literature [25a].

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