A Simple Thiophosphate-Based Method for α-Alkylidenation of Lactones

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Abstract: A variety of α-alkylidene lactones has been synthesized using a one-pot procedure based on the reaction of readily available thiophosphates with aldehydes under basic, mild conditions.

Key words: α-alkylidene lactones, lactones, thiophosphates, aldol reactions, stereoselectivity

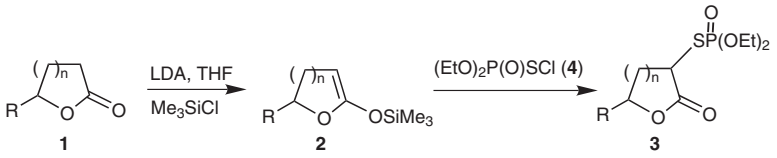
α-Alkylidene lactones can serve as useful intermediates in organic synthesis,[1] particularly for the synthesis of compounds exhibiting biological activity, i.e. natural cytotoxic obtusilactones.[1f–1h] Ethylidene lactones with six-membered rings are key intermediates in the synthesis of some pyrrolizidine alkaloids.[2] Several potentially cytotoxic lactones containing a long alkyl chain in alkylidene moiety have been isolated from plants belonging to the Lauraceae family.[3] Therefore α-alkylidene lactones have been a subject of intensive synthetic studies. Two general synthetic methods of these compounds have been devised. One method is based on the introduction of the alkylidene group on the α position of the lactone ring,[4] the second one involves a ring closure reaction from acyclic olefinic or acetylenic precursors.[5] Direct introduction of an α-alkylidene group to γ-butyrolactone which included base-catalyzed condensation of γ-butyrolactone with aldehyde,[4a–4d] reactions of aldehyde with anions of α-phosphonolactones,[4e–4g] α-triphenylphosphoranylidene lactones,[4h,i] α-silyl carbanions[4j,k], α-thiomethylene intermediates[4l,m] or *S*-(tetrahydro-2-oxo-3-furanyl)dithiocarbonate[4n,o] have been described in the literature. Although numerous methods have been reported[6] for the preparation of α-alkylidene lactones, the development of new, simple and stereoselective protocols for obtaining these compounds still presents a synthetic problem.

We have elaborated a new strategy for the stereoselective conversion of carbonyl compounds into unsaturated derivatives based on intermediates thio- and selenophosphates.[7] As part of a continuing program of research, based on our methodology, studies on the construction of exocyclic and endocyclic carbon–carbon double bonds were undertaken.[8] Recently, we have reported a one-pot procedure for α-methylenation of lactones including racemic frullanolide, and α-methylenation of cycloalkanones.[8a]

This paper describes an extension of our methodology to the synthesis of α-alkylidene γ- and δ-lactones. For this purpose a variety of the corresponding, new thiophosphates **3** have been synthesized. The compounds **3** were easily prepared from the appropriate lactones **1** adopting our previously described method[9] (Scheme 1). Treatment of **1** with trimethylsilyl chloride gave O-silylated lactones **2**.[10] Addition of readily available *O*,*O*-diethyl chlorothiophosphonate (**4**),[11] an excellent thiophosphorylating agent, afforded thiophosphates **3** in high yield and purity.

Next, the addition of thiophosphate anions, generating by the action of sodium hydride on lactones **3**, to various aldehydes was examined. This reaction proceeded at low temperature for 1 hour and then another hour at room temperature and led to the formation of α-alkylidene compounds **5** in good yields (Scheme 2, Table 1). It is noteworthy that the conversion of **1** into **5** can be performed using crude intermediate silyl enol ethers **2** and thiophosphates **3**.

A number of α-alkylidene lactones **5** were obtained as a mixture of *E*- and *Z*-diastereomers. These isomers were easily separated by flash chromatography (Table 1).



1, 2, 3	n	R	% Yield of 3
a	1	H	92
b	1	CH_3	96
c	1	C_7H_{15}	78
d	2	H	75

Scheme 1

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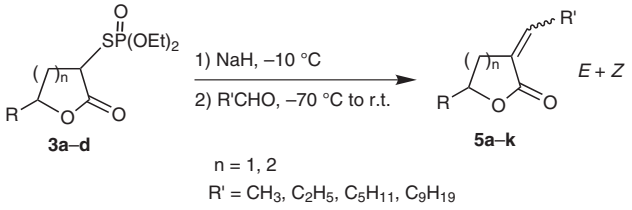
Table 1 Synthesis of α-Alkylidene γ- and δ-Lactones **5** from **3** and Various Aldehydes[a]

Entry	**5**	n	R	R′	*E*/*Z*[b]	Yield (%)[c]
1	**a**	1	H	CH_3	9:1	69
2	**a**	1	H	CH_3	1:1	55[d]
3	**b**	1	H	C_2H_5	10:1	82[e]
4	**c**	1	H	C_5H_{11}	2:1	92[e]
5	**d**	1	H	C_9H_{19}	1:1.6	79[f]
6	**e**	1	CH_3	CH_3	8:1	72
7	**f**	1	CH_3	C_9H_{19}	1:2	68[f]
8	**g**	1	C_7H_{15}	CH_3	2.5:1	67.7[g]
9	**h**	1	C_7H_{15}	C_9H_{19}	1:2.2	54[e] (**3**: 33)[h]
10	**i**	2	H	CH_3	1:1	55
11	**j**	2	H	C_2H_5	1.2:1	80
12	**k**	2	H	C_9H_{19}	1:2	48 (**3**: 42)[h]

[a] Conditions: **3** (1 equiv), NaH (1.2 equiv), Et_2O, –10 °C, 30 min, R′CHO (1 equiv), –70 °C, 1 h → r.t., 1 h.
[b] Determined by ^1H NMR spectra of crude reaction mixtures.
[c] Overall yield of both isomers.
[d] Conditions: –70 °C, 1 h → –20 °C, 1 h.
[e] Conditions: –70 °C, 1 h → r.t., 12 h.
[f] Conditions: –70 °C, 1 h → r.t., 48 h.
[g] Conditions: –70 °C, 1 h → –20 °C, 20 h.
[h] Determined by ^{31}P NMR spectra of crude reaction mixtures.



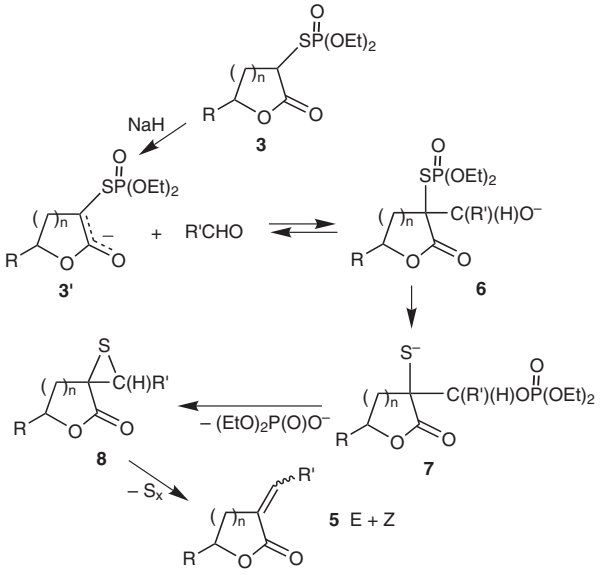
Scheme 2

The addition of thiophosphate **3a** to aldehydes containing a short carbon chain occurs with high stereoselectivity producing predominantly *E*-α-alkylidene γ-butyrolactones (entries 1, 3). Increasing amount of *Z*-isomer of α-alkylidene γ-butyrolactones is observed with the elongation of the alkyl chain of aldehyde (entries 4, 5). When the derivative of γ-valerolactone **3b** is used, the same trend of stereoselectivity is observed (entries 6, 7). Condensation of thiophosphorylated γ-undecanoic lactone **3c** with acetaldehyde as well as decanal affords a mixture of both *E*- and *Z*-diastereomers in a similar ratio (entries 8, 9). When these studies were extended to thiophosphate **3d** derived from δ-valerolactone, a drop in the stereoselectivity of reactions with acetaldehyde and propionaldehyde was noted (entries 10, 11).

The other base systems (LDA,[4o] K_2CO_3/18-crown-6[4g]) that might favor *E*- or *Z*-olefination of **3** have been explored and the effect of added metal salt ($ZnCl_2$) on the yields and *E*/*Z* ratios of α-alkylidene lactones **5** was studied. Unfortunately no improvement in stereoselectivity was observed.

The basic concept of the transformation of thiophosphate **3** into α-alkylidene lactone **5** is illustrated in Scheme 3.

The addition of thiophosphate anion **3′** to aldehydes provides the corresponding diastereomeric oxyanion **6**. Further conversion of this intermediate proceeds via a



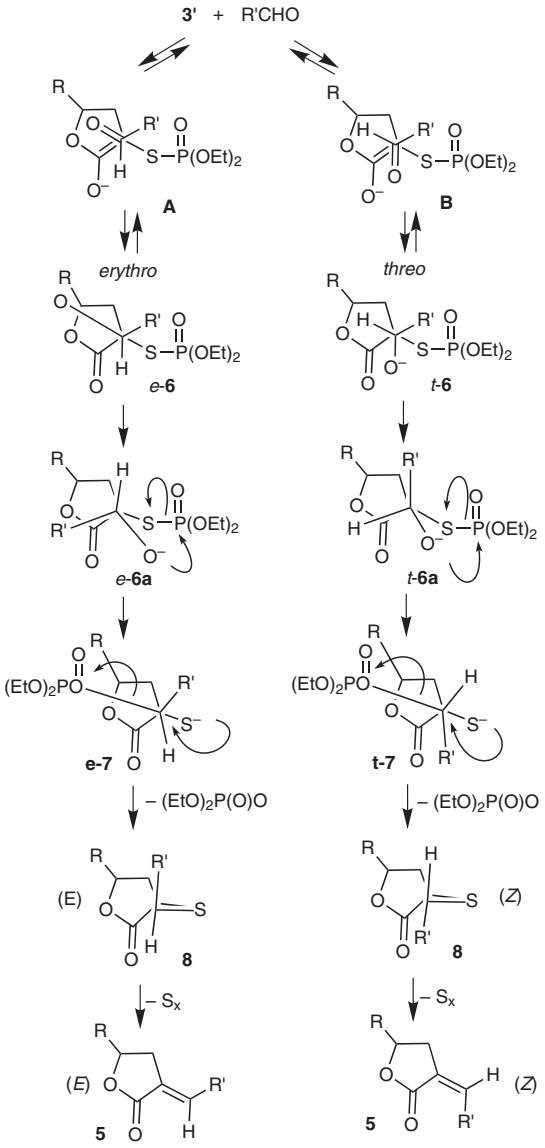
Scheme 3

rearrangement involving migration of phosphoryl group from sulfur to oxygen affording thiolate anion **7**. Subsequent cyclization of **7** with elimination of phosphate group leads to episulfide **8**. Finally a spontaneous desulfurization of **8** gives α-alkylidene lactone **5**. Examined reactions proceed with a good to moderate stereoselectivity. The main factors controlling of stereochemistry of α-alkylidene lactones are the size of alkyl substituent of the aldehyde, and the size of the substituent in the lactone ring, and the reaction time and temperature.

It is known that in kinetically controlled aldol-type reaction the stereoselection is attributed to the form of a transition state.[12] It is reported in the literature[13] that the reaction of lithium enolate of dioxalanones with aldehydes occurs through the conventional Zimmerman–Traxler transition state (TS)[14] with the hydrogen of the aldehyde rather than R′ group the facing the dioxalanone ring. According to the suggestion by Matsui[4o] the following transition state models **A** and **B** are considered (Scheme 4).

From TS **A**, an *erythro* oxyanion intermediate ***e*-6** and from TS **B**, a *threo* oxyanion intermediate ***t*-6**, both favored for the steric reasons, are formed respectively. In this aldol type condensation under the kinetically controlled reaction conditions (low temperature) both diastereomers *E* and *Z* should be formed. Indeed treatment of thiophosphate **3a** with acetaldehyde and sodium hydride in diethyl ether at low temperature afforded the *E*- and *Z*-olefins **5a** in a 1:1 ratio. After warming the reaction mixture to 0 °C or to room temperature it proceeds with *E*-stereoselectivity. On the other hand, reactions of thiophosphates **3a**–**d** with the aldehyde containing a long alkyl chain, afford *Z*-α-alkylidene lactones **5** predominantly. That means the examined reactions proceed via *erythro* or *threo* **6** and **7** to give **5** under thermodynamically controlled reaction conditions. The marginal effect of the metal salt on the stereoselectivity of alkylidene compounds was noticed. These results can be rationalized by considering that a retro-aldolization of oxyanion intermediates **6** to substrates can compete with their rearrangement to thiolates anions **7**. The *erythro* ***e*-7** – precursor of *E*-olefin is more favored when the steric interaction between R′ group and carbonyl moiety of lactone is minimized in it. The *threo* intermediate ***t*-7**, which provides *Z*-olefin seems to be favored if R′ of aldehyde and R substituent in lactone ring are long chain alkyl groups. Therefore one can assume that the temperature and also steric factors influence the *E*/*Z* ratio of the final α-alkylidene lactones.

In summary we have demonstrated that application of our methodology with the use of corresponding thiophosphates, provides a general, simple and convenient route to α-alkylidene γ- and δ-lactones, via a single and double carbon–carbon bond forming reaction. The conversion of lactones into their α-alkylidene derivatives can be performed in one-pot procedure. It is noteworthy that *Z*-stereoselectivity is achieved for α-alkylidene lactones containing a long alkyl chain. Therefore this method is a valuable alternative to previous methods described for the synthesis of these compounds.



Scheme 4

Chemicals (aldehydes, lactones) and solvents were obtained from commercial sources (Fluka, Aldrich) and distilled or dried according to standard methods. Petroleum ether (PE) refers to the fraction boiling at 60–90 °C. Enol silyl ethers **1a**–**d** were prepared as described.[10] All reactions were carried out in an atmosphere of dry argon. Chromatographic purification was performed on silica gel columns (Merck, Kieselgel 70–230 mesh) with indicated eluent. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker AC 200 Spectrometer. IR spectra were measured on an Ati Mattson Infinity FT IR 60. MS spectra (EI, CI, and HRMS) were recorded on a Finnigan MAT 95 spectrometer. Microanalysis obtained on a Carbo Erba CHNS-OEA 1108 Elemental Analyzer. The products were characterized by comparison of their data with those of known samples or by their spectral data.

α-Alkylidene Lactones 5 from Lactones 1; General Procedure

A solution of SO_2Cl_2 (2 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the stirred solution of *O*,*O*,*O*-triethyl phosphorothioate (376

mg, 1.9 mmol) in CH_2Cl_2 (20 mL) at –30 °C, and the stirring was continued for 20 min at r.t. After removal of about 50% of solvent, the crude $(EtO)_2P(O)SCl$ (**4**) formed was added with stirring to a solution of freshly prepared (from the corresponding lactone by the action of LDA, TMSCl in THF at –70 °C) *O*-silyl enol ether **2** (2.2 mmol) in CH_2Cl_2 (40 mL) at –70 °C. The mixture was stirred and allowed to warm slowly to r.t. The solvent and trimethylsilyl chloride were removed in vacuo. Crude thiophosphate **3** formed was dissolved in THF (5 mL) and added by a syringe (30 min) to a stirred suspension of NaH (50 mg, 2.1 mmol) in THF (20 mL) at –10 °C under argon. After cooling to –70 °C, a solution of aldehyde (2 mmol) in THF (5 mL) was added by a syringe over a period of 10 min and the reaction mixture was stirred at this temperature for 1 h. Then it was warmed gradually to r.t. and was stirred for 1 h before quenching with NH_4Cl (5 mL). The mixture was poured into dilute HCl and extracted with Et_2O (3 ×). The organic extracts were combined and washed with brine, dried ($MgSO_4$), and the solvent evaporated in vacuo to give a crude product, which was purified by flash chromatography with petroleum ether–EtOAc (10:1 to 5:1, gradient elution).

(*Z*/*E*)-3-Ethylidenedihydrofuran-2-one (5a)
Yield: 69%; colorless oil; R_f 0.5 (1:1 hexane–EtOAc).

^{1}H NMR data are identical with that previously reported.[4n]

MS (EI): *m*/*z* (%) = 112 (M^+, 35), 67 (M^+ – COOH, 100), 54 (40), 41 (39).

(*Z*/*E*)-3-Propylidenedihydrofuran-2-one (5b)
Yield: 82%; colorless oil; R_f 0.52 (1:1 hexane–EtOAc).

^{1}H NMR and ^{13}C NMR data are identical with that previously reported.[6a]

MS (EI): *m*/*z* (%) = 126 (M^+, 80), 67 (M^+ – CH_2COOH, 100), 41 (54), 39 (50).

(*Z*/*E*)-3-Hexylidenedihydrofuran-2-one (5c)
Yield: 92%; colorless oil; R_f 0.55 (1:1 hexane–EtOAc).

^{1}H NMR data were identical with that previously reported.[4o]

MS (EI): *m*/*z* (%) = 168 (M^+, 43), 125 (100), 99 ([M^+ – C_5H_9], 20), 67 (C_5H_7, 38).

(*Z*)-3-Decylidenedihydrofuran-2-one (5d)
Yield: 30%; yellow oil; R_f 0.58 (1.2:1 hexane–EtOAc).

IR (film): 2954, 1757, 1671, 1466, 1129, 1029 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.86 (t, $J_{H,H}$ = 6.5 Hz, 3 H, CH_3), 1.20 (br s, 12 H, CH_2), 1.57–1.60 (m, 2 H, CH_2), 2.69 (dt, $J_{H,H}$ = 1.8, 7.3 Hz, 2H, CH_2), 2.89 (dt, $J_{H,H}$ = 2.0, 7.3 Hz, 2 H, C*H*$_2$CH$_2$O), 4.29 (t, $J_{H,H}$ = 7.4 Hz, 2 H, CH_2O), 6.22 (tt, $J_{H,H}$ = 2.3, 7.5 Hz, 1 H, C=CH).

^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_3), 22.6, 27.4, 28.1, 29.0, 29.2, 29.4, 29.5, 30.2, 31.8 (CH_2), 65.2 (*C*H$_2$O), 123.2 (*C*=CH), 144.4 (C=CH), 170.1 (C=O).

MS (EI): *m*/*z* (%) = 224 (M^+, 16), 125 ($C_9H_{17}^+$, 100), 99 ([M^+ – C_9H_{17}], 24.5), 86 ([M^+ – $C_{10}H_{18}$], 32).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.71; H, 10.93.

(*E*)-3-Decylidenedihydrofuran-2-one (5d)
Yield: 49%; yellow oil; R_f 0.55 (1.2:1 hexane–EtOAc).

IR (film): 2954, 1760, 1680, 1209, 1031 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.86 (t, $J_{H,H}$ = 6.0 Hz, 3 H, CH_3), 1.25 (br s, 12 H, CH_2), 1.46 (t, $J_{H,H}$ = 6.6 Hz, 2 H, CH_2), 2.17 (q, $J_{H,H}$ = 7.2 Hz, 2 H, CH_2), 2.84 (dt, $J_{H,H}$ = 2.4, 6.4 Hz, 2 H, C*H*$_2$CH$_2$O), 4.36 (t, $J_{H,H}$ = 7.5 Hz, 2 H, CH_2O), 6.73 (tt, $J_{H,H}$ = 2.9, 7.6 Hz, 1 H, C=CH).

^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_3), 22.6, 25.0, 28.1, 29.2, 29.24, 29.3, 29.4, 30.2, 31.8 (CH_2), 65.3 (CH_2O), 125.0 (*C*=CH), 141.0 (C=*C*H), 170.3 (C=O).

MS (EI): *m*/*z* (%) = 224 (M^+, 3.6), 125 ($C_9H_{17}^+$, 20.8), 99 ([M^+ – C_9H_{17}], 100), 86 ([M^+ – $C_{10}H_{18}$], 98).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.89; H, 10.81.

(*Z*/*E*)-3-Ethylidene-5-methyldihydrofuran-2-one (5e)
Yield: 72%; colorless oil; R_f 0.51 (1:1 hexane–EtOAc).

^{1}H NMR data were identical with that previously reported.[6b]

MS (EI): *m*/*z* (%) = 126 (M^+, 28), 82 (75), 81 (M^+ – COOH, 63), 53 (100), 41 (24).

(*Z*)-3-Decylidene-5-methyldihydrofuran-2-one (5f)
Yield: 45%; yellow oil; R_f 0.61 (1:1 hexane–EtOAc).

IR (film): 2938, 1748, 1655, 1480, 1170, 1090 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.87 (t, $J_{H,H}$ = 6.5 Hz, 3 H, CH_3), 1.25 (br s, 14 H, CH_2), 1.38 (d, $J_{H,H}$ = 6.2 Hz, 3 H, CH_3CHO), 2.41 (qd, $J_{H,H}$ = 1.9, 7.4 Hz, 1 H, C*H*$_2$CHO), 2.68 (tq, $J_{H,H}$ = 1.9, 7.3 Hz, 2 H, CH_2), 2.99 (ddq, $J_{H,H}$ = 1.8, 7.4, 15.7 Hz, 1 H, C*H*$_2$CHO), 4.58 (tq, $J_{H,H}$ = 6.3, 6.4 Hz, 1 H, CHO), 6.16 (tt, $J_{H,H}$ = 2.3, 7.7 Hz, 1 H, C=CH).

^{13}C NMR ($CDCl_3$): δ = 13.5 (CH_3), 20.7 (CH_3), 22.8, 24.7, 28.3, 29.0, 29.1, 29.2, 29.8, 31.2, 34.5 (CH_2), 75.4 (CHO), 124.5 (*C*=CH), 146.4 (C=*C*H), 168.1 (C=O).

MS (EI): *m*/*z* (%) = 238 (M^+, 16.7), 125 ($C_9H_{17}^+$, 100), 113 ([M^+ – C_9H_{17}], 40), 41 (25).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.21; H, 11.23.

(*E*)-3-Decylidene-5-methyldihydrofuran-2-one (5f)
Yield: 23%; yellow oil; R_f 0.57 (1:1 hexane–EtOAc).

IR (film): 2950, 1750, 1680, 1215, 1150 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.86 (t, $J_{H,H}$ = 6.2 Hz, 3 H, CH_3), 1.24 (br s, 14 H, CH_2), 1.38 (d, $J_{H,H}$ = 6.2 Hz, 3 H, C*H*$_3$CHO), 2.13 (tq, $J_{H,H}$ = 1.6, 7.3 Hz, 2 H, CH_2), 2.31–2.40 (m, 1 H, C*H*$_2$CHO), 2.97 (ddq, $J_{H,H}$ = 1.6, 7.7, 13.9 Hz, 1 H, C*H*$_2$CHO), 4.60 (tq, $J_{H,H}$ = 6.4, 6.5 Hz, 1 H, CHO), 6.69 (tt, $J_{H,H}$ = 2.9, 7.6 Hz, 1 H, C=CH).

^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_3), 21.2 (CH_3), 20.5, 25.0, 28.2, 29.1, 29.2, 29.4, 30.5, 32.4, 35.0 (CH_2), 75.9 (CHO), 125.0 (*C*=CH), 144.0 (C=*C*H), 169.4 (C=O).

MS (EI): *m*/*z* = 238 (M^+, 11.5), 125 ($C_9H_{17}^+$, 30), 113 ([M^+ – C_9H_{17}], 100), 41 (25).

HRMS: *m*/*z* calcd for $C_{15}H_{27}O_2$ [M + H]$^+$: 239.2011; found: 239.2010.

(*Z*)-3-Ethylidene-5-heptyldihydrofuran-2-one (5g)
Yield: 19%; yellow oil; R_f 0.62 (1:1 hexane–EtOAc).

IR (film): 2929, 1715, 1638, 1259, 1154, 1072 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, $J_{H,H}$ = 6.3 Hz, 3 H, CH_3), 1.25 (br s, 10 H, CH_2), 1.49–1.72 (m, 2 H, CH_2), 2.09 (td, $J_{H,H}$ = 1.6, 7.2 Hz, 3 H, =CHC*H*$_3$), 2.51–2.56 (m, 2 H, C*H*$_2$CHO), 4.07–4.34 (m, 1 H, CHO), 6.14 (tq, $J_{H,H}$ = 1.7, 7.2 Hz, 1 H, C=CH).

^{13}C NMR ($CDCl_3$): δ = 14.1 (2 CH_3), 22.5, 22.6, 25.2, 28.3, 29.1, 31.5, 35.3 (CH_2), 79.4 (CHO), 124.1 (*C*=CH), 142.3 (C=*C*H), 165.8 (C=O).

MS (CI): *m*/*z* = 211 (M^+ + H, 100).

HRMS: *m*/*z* calcd for $C_{13}H_{23}O_2$ [M + H]$^+$: 211.1698; found: 211.1695.

(*E*)-3-Ethylidene-5-heptyldihydrofuran-2-one (5g)
Yield: 48%; yellow oil; R_f 0.57 (1:1 hexane–EtOAc).

IR (film): 2930, 2858, 1730, 1645, 1260, 1199, 1093 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.85 (t, $J_{H,H}$ = 6.5 Hz, 3 H, CH_3), 1.25 (br s, 11 H, CH_2), 1.75 (ddd, $J_{H,H}$ = 1.2, 2.2, 7.2 Hz, 3 H, =CHCH_3), 1.91, 1.98 (2 quintet, $J_{H,H}$ = 2.8 Hz, 1 H, CH_2), 2.32–2.41 (m, 1 H, CH_2CHO), 2.54, 2.62 (2 br s, 1 H, CH_2CHO), 4.17 (ddt, $J_{H,H}$ = 2.3, 5.1, 7.3 Hz, 1 H, CHO), 7.08 (ddq, $J_{H,H}$ = 2.2, 7.2 Hz, 1 H, C=CH).

^{13}C NMR ($CDCl_3$): δ = 14.0 (2 CH_3), 22.5, 22.55, 24.8, 27.4, 29.0, 31.6, 35.3 (CH_2), 79.2 (CHO), 126.2 (*C*=CH), 140.6 (C=*C*H), 166.9 (C=O).

MS (CI): *m*/*z* = 211 (M^+ + H, 100%).

HRMS: *m*/*z* calcd for $C_{13}H_{23}O_2$ $[M + H]^+$: 211.1698; found: 211.1696.

(*Z*)-3-Decylidene-5-heptyldihydrofuran-2-one (5h)
Yield: 37%; yellow semisolid; R_f 0.68 (1.5:1 hexane–EtOAc).

IR (film): 2953-2855, 1722, 1634, 1465, 1146, 1115 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.86 (t, $J_{H,H}$ = 6.2 Hz, 6 H, CH_3), 1.25 (br s, 22 H, CH_2), 1.62 (br s, 3 H, CH_2), 1.89 (dt, $J_{H,H}$ = 2.9, 4.7 Hz, 0.5 H, CH_2), 1.95 (dt, $J_{H,H}$ = 2.8, 5.3 Hz, 0.5 H, CH_2), 2.40 (dt, $J_{H,H}$ = 1.8, 7.2 Hz, 2 H, CH_2), 2.55 (pseudo quintet, $J_{H,H}$ = 7.0 Hz, 2 H, CH_2CHO), 4.11–4.24 (m 1 H, CHO), 6.00 (dt, $J_{H,H}$ = 1.6, 7.1 Hz, 1 H, C=CH).

^{13}C NMR ($CDCl_3$): δ = 13.9 (2 CH_3), 21.9, 22.4, 22.5, 23.4, 24.8, 28.5, 29.1, 29.2, 29.24, 29.4, 29.8, 31.5, 31.7, 34.3, 35.3 (CH_2), 79.3 (CHO), 124.5 (*C*=CH), 147.2 (C=*C*H), 165.9 (C=O).

MS (CI): *m*/*z* = 323 (M^+ + H, 100).

HRMS: *m*/*z* calcd for $C_{21}H_{39}O_2$ $[M + H]^+$: 323.2950; found: 323.2940.

(*E*)-3-Decylidene-5-heptyldihydrofuran-2-one (5h)
Yield: 17%; yellow semisolid; R_f 0.56 (1.5:1 hexane–EtOAc).

IR (film): 2924, 1735, 1656, 1378, 1161 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.87 (t, $J_{H,H}$ = 6.5 Hz, 6 H, CH_3), 1.25 (br s, 20 H, CH_2), 1.37–1.73 (m, 3 H, CH_2), 1.46 (t, $J_{H,H}$ = 6.6 Hz, 2 H, CH_2), 1.91, 1.98 (2 quintet, $J_{H,H}$ = 2.7, Hz, 1 H, CH_2), 2.12 (pseudo q, $J_{H,H}$ = 7.3 Hz, 2 H, CH_2), 2.27–2.43 (m, 1 H, CH_2CHO), 2.62 (br s, 1 H, CH_2CHO), 4.14–4.32 (m, 1 H, CHO), 7.02 (tt, $J_{H,H}$ = 2.1, 7.4 Hz, 1 H, C=CH).

^{13}C NMR ($CDCl_3$): δ = 13.9, 13.93 (CH_3), 22.4, 22.5, 22.7, 24.7, 27.4, 28.0, 28.2, 28.5, 28.9, 29.1, 29.2, 29.3, 31.5, 31.7, 35.3 (CH_2), 79.1 (CHO), 125.0 (*C*=CH), 146.0 (C=*C*H), 166.9 (C=O).

Anal. Calcd for $C_{21}H_{38}O_2$: C, 78.20; H, 11.87. Found: C, 77.89; H, 11.51.

(*Z*/*E*)-3-Ethylidenetetrahydropyran-2-one (5i)
Yield: 55%; colorless oil; R_f 0.51 (1:1 hexane–EtOAc).

^1H NMR data were identical with that previously reported.[15]

MS: *m*/*z* (%) = 126 (M^+, 50), 81 ([M^+ – COOH], 40), 83 (27.5), 53 (100).

(*Z*/*E*)-3-Propylidenetetrahydropyran-2-one (5j)
Yield: 80%; colorless oil; R_f 0.51 (1:1 hexane–EtOAc).

^1H NMR and ^{13}C NMR data were identical with that previously reported.[6a]

MS: *m*/*z* (%) = 140 (M^+, 40), 97 (24), 95 ([M^+ – COOH], 32), 81 (40), 67 (100).

(*Z*/*E*)-3-Decylidenetetrahydropyran-2-one (5k)
Yield: 48% of a nonseparable mixture of *Z*/*E* (2:1) isomers; yellow oil; R_f 0.61 (1:1 hexane–EtOAc).

IR (film): 2954, 1727, 1631, 1447, 1218, 1057 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.85 (t, $J_{H,H}$ = 6.1 Hz, 3 H, CH_3), 1.23 (br s, 12 H, CH_2), 1.60–2.09 (m, 4 H, CH_2), 2.33–2.40 (m, 2 H, CH_2), 2.42 (t, $J_{H,H}$ = 7.2 Hz, 2 H, CH_2), 4.21 (t, $J_{H,H}$ = 7.4 Hz, 2 H, CH_2O, major), 4.28 (t, $J_{H,H}$ = 7.5 Hz, 2 H, CH_2O, minor), 6.13 (tt, $J_{H H}$ = 1.8, 7.5 Hz, 1 H, C=CH, major), 7.12 (tt, $J_{H,H}$ = 2.5, 7.6 Hz, 1 H, C=CH, minor).

^{13}C NMR ($CDCl_3$): δ = 13.3 (CH_3), 21.8, 22.6, 25.4, 28.1, 29.1, 29.2, 29.3, 29.5, 30.6, 31.5 (CH_2), 67.9 (CH_2O, major and minor), 123.0 (*C*=CH, major), 125.3 (*C*=CH, minor), 143.4 (C=*C*H, minor), 145.0 (C=*C*H, major), 165.8 (C=O, major) 167.1 (C=O, minor).

MS (EI): *m*/*z* (%) = 238 (M^+, 15), 125 ($C_9H_{17}^+$, 100), 99 ([M^+ – $C_{10}H_{19}$], 80).

HRMS: *m*/*z* calcd for $C_{15}H_{27}O_2$ $[M + H]^+$: 239.2011; found: 239.2005.

***O*,*O*-Diethyl *S*-(2-Oxotetrahydrofuran-3-yl) Thiophosphate (3a); General Procedure**
O,*O*-Diethyl chlorothiophosphonate (**4**; 204 mg, 1 mmol) in CH_2Cl_2 (15 mL) was added dropwise with stirring to silyl enol ether **2a** (1.1 mmol) in CH_2Cl_2 (30 mL) at –70 °C. The mixture was stirred and allowed to warm slowly to r.t. Then the solvent and volatile products were removed in vacuo (0.1 mm Hg) to give crude, pure thiophosphate **3a** as a yellow oil in 92% yield. Analytically pure compound was obtained by flash chromatography (PE–EtOAc, 1:1).

IR (film): 2983–2943, 1756, 1239, 1016, 794, 575 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.38 (t, $J_{H,H}$ = 7.1 Hz, 6 H, CH_3CH$_2$OP), 2.40 (AB, $J_{H,H}$ = 8.6 Hz, 2 H, CH_2CH$_2$O), 2.81 (dddd, $J_{H,H}$ = 3.7, 6.7, 15.5 Hz, $^3J_{P,H}$ = 10.4 Hz, 1 H, CHSP), 4.07 (dt, $J_{H,H}$ = 8.9, 15.3 Hz, 1 H, CH_2O), 4.25 (dq, $J_{H,H}$ = 7.1 Hz, $^3J_{P,H}$ = 8.1 Hz, 2 H, CH$_3$CH_2OP), 4.26 (dq, $J_{H,H}$ = 7.2 Hz, $^3J_{P,H}$ = 8.1 Hz, 2 H, CH$_3$CH_2OP), 4.43 (dt, $J_{H,H}$ = 3.7, 9.2 Hz, 1 H, CH_2O).

^{13}C NMR ($CDCl_3$): δ = 15.3 (*C*H$_3$CH$_2$OP), 15.4 (*C*H$_3$CH$_2$OP), 31.3 ($^3J_{P,C}$ = 3.5 Hz, *C*H$_2$CH$_2$O), 40.9 ($^2J_{P,C}$ = 3.5 Hz, CHSP), 66.1 (CH_2O), 63.7 ($^2J_{P,C}$ = 3.7 Hz, CH_2OP), 63.8 ($^2J_{P,C}$ = 3.7 Hz, CH_2OP), 173.7 (C=O, $^3J_{P,C}$ = 7.8 Hz).

^{31}P NMR ($CDCl_3$): δ = 23.5.

HRMS: *m*/*z* calcd for $C_8H_{16}O_5PS$ $[M + H]^+$: 255.0456; found: 255.0455.

***O*,*O*-Diethyl *S*-(5-Methyl-2-oxotetrahydrofuran-3-yl) Thiophosphate (3b)**
Ratio of diastereomers 1:1.8; yield: 96%; white semisolid; mixture of isomers.

IR (film): 2982–2936, 1738, 1254, 1018, 974, 757, 559 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.36 (t, $J_{H,H}$ = 7.0 Hz, 3 H, CH_3CH$_2$OP), 1.37 (t, $J_{H,H}$ = 7.0 Hz, 3 H, CH_3CH$_2$OP), 1.40 (d, $J_{H,H}$ = 6.4 Hz, 3 H, CH_3), 1.45 (d, $J_{H,H}$ = 6.4 Hz, 3 H, CH_3), 2.00 (ddd, $J_{H,H}$ = 12, 12.7 Hz, $^3J_{P,H}$ = 10 Hz, 1 H, CHSP, major), 2.33–2.60 (m, 2 H, CH_2CH$_2$O), 2.90 (ddd, $J_{H,H}$ = 5.4, 12.9 Hz, $^3J_{P,H}$ = 8.7 Hz, 1 H, CHSP, minor), 4.22 (q, $J_{H,H}$ = 7.1 Hz, $^3J_{P,H}$ = 7.1 Hz, 2 H, CH$_3$CH_2OP), 4.24 (q, $J_{H,H}$ = 7.2 Hz, $^3J_{P,H}$ = 7.1 Hz, 2 H, CH$_3$CH_2OP), 4.53 (ddd, $J_{H,H}$ = 5.5, 6.1, 10.0 Hz, 1 H, CH$_3$C*H*O, minor), 4.77 (sextet, $J_{H,H}$ = 6.4, Hz, 1 H, CH$_3$C*H*O, major).

^{13}C NMR ($CDCl_3$): δ = 15.4 (*C*H$_3$CH$_2$OP), 15.5 (*C*H$_3$CH$_2$OP), 21.3 (*C*H$_3$CH, major), 24.1 (*C*H$_3$CH, minor), 36.7 ($^3J_{P,C}$ = 3.5 Hz, *C*H$_2$CHO, major), 39.2 ($^3J_{P,C}$ = 3.5 Hz, *C*H$_2$CHO, minor), 41.5 ($^2J_{P,C}$ = 4.1 Hz, CHSP), 62.8 ($^2J_{P,C}$ = 6.9 Hz, CH_2OP), 63.1

($^2J_{P,C}$ = 3.7 Hz, CH_2OP), 74.3 (CH_3CHO, major), 75.2 (CH_3CHO, minor), 172.3 (C=O, $^3J_{P,C}$ = 7.8 Hz).

^{31}P NMR ($CDCl_3$): δ = 24.4 (35%), 23.8 (65%).

HRMS: *m/z* calcd for $C_9H_{18}O_5PS$ $[M + H]^+$: 269.0612; found: 269.0611.

_O_,_O_-Diethyl _S_-(5-Heptyl-2-oxotetrahydrofuran-3-yl) Thiophosphate (3c)

Ratio of diastereomers 1:2; yield: 78%; yellow semisolid; mixture of isomers.

IR (film): 2977–2863, 1737, 1247, 1009, 972, 793, 572 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.87 (t, $J_{H,H}$ = 6.5 Hz, 3 H, CH_3), 1.26 (br s, 8 H, CH_2), 1.37 (t, $J_{H,H}$ = 7.1 Hz, 3 H, CH_3CH_2OP), 1.374 (t, $J_{H,H}$ = 7.0 Hz, 3 H, CH_3CH_2OP), 1.42–1.92 (m, 4 H, CH_2), 1.97–2.08 (10 lines, $J_{H,H}$ = 2.1, 8.5, 11.0 Hz, 1 H, CHSP, major), 2.26–2.42 (m, 2 H, CH_2CHO, minor), 2.45–2.56 (8 lines, $J_{H,H}$ = 2.5, 7.9, Hz, 2 H, CH_2CHO, major), 2.87 (ddd, $J_{H,H}$ = 5.5, 13.0 Hz, $^3J_{P,H}$ = 8.8 Hz, 1 H, CHSP, minor), 4.08 (dd, $J_{H,H}$ = 7.1 Hz, $^3J_{P,H}$ = 7.8 Hz, 2 H, CH_3CH_2OP), 4.23 (q, $J_{H,H}$ = 7.2 Hz, $^3J_{P,H}$ = 7.1 Hz 2 H, CH_3CH_2OP), 4.44 (quintet, $J_{H,H}$ = 6.3, Hz, 1 H, CH_2CHO, major), 4.60 (quintet, $J_{H,H}$ = 6.5, Hz, 1 H, CH_2CHO, minor).

^{13}C NMR ($CDCl_3$): δ = 13.8 (CH_3), 15.7 (CH_3CH_2OP), 15.9 (CH_3CH_2OP), 22.3, 24.3, 24.5, 24.7, 25.1, 25.2, 28.3, 28.4, 28.8, 29.1, 29.2 (CH_2, major and minor), 31.4 (CH_2CHSP, major), 31.6 (CH_2CHSP, minor), 35.6 (CH_2CHO, minor), 35.9 (CH_2CHO, major), 47.4 ($^2J_{P,C}$ = 4.5 Hz, CHSP), 63.3 ($^2J_{P,C}$ = 5.9 Hz, CH_2OP), 63.9 (CH_2OP), 77.2 (CH_2CHO, major), 77.22 (CH_2CHO, minor) 170.1 (C=O, $^3J_{P,C}$ = 9.2 Hz).

^{31}P NMR ($CDCl_3$): δ = 24.4 (32.3%), 23.9 (67.7%).

MS (CI): *m/z* = 353 ($[M + H]^+$, 100%).

HRMS: *m/z* calcd for $C_{15}H_{30}O_5PS$ $[M + H]^+$: 353.1551; found: 353.1548.

_O_,_O_-Diethyl _S_-(2-Oxotetrahydropyran-3-yl) Thiophosphate (3d)

Yield: 75%; yellow oil.

IR (film): 2961–2848, 1748, 1260, 1016, 794, 596 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.34 (t, $J_{H,H}$ = 7.0 Hz, 6 H, CH_3CH_2OP), 1.60–1.68 (m, 2 H, CH_2), 1.85–2.22, (m, 2 H, CH_2), 2.42 (dt, $J_{H,H}$ = 7.2 Hz, $^3J_{P,H}$ = 7.4 Hz, 1 H, CHSP), 4.02–4.24 (m, 6 H, CH_3CH_2OP and CH_2O).

^{13}C NMR ($CDCl_3$): δ = 15.3 (CH_3CH_2OP), 15.4 (CH_3CH_2OP), 31.3 ($^3J_{P,C}$ = 3.5 Hz, CH_2CH_2O), 40.9 ($^2J_{P,C}$ = 3.5 Hz, CHSP), 66.1 (CH_2O), 63.7 ($^2J_{P,C}$ = 3.7 Hz, CH_2OP), 63.8 ($^2J_{P,C}$ = 3.7 Hz, CH_2OP), 173.7 (C=O, $^3J_{P,C}$ = 7.8 Hz).

^{31}P NMR ($CDCl_3$): δ = 25.0.

HRMS: *m/z* calcd for $C_9H_{18}O_5PS$ $[M + H]^+$: 269.0612; found: 269.0610.

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References

(1) (a) Edwards, O. E.; Ho, P.-T. *Can. J. Chem.* **1977**, *55*, 371. (b) Back, T. G.; Edwards, O. E.; Mac Alpine, G. A. *Tetrahedron Lett.* **1977**, 2651. (c) Hoye, T. R.; Caruso, A. J. *Tetrahedron Lett.* **1978**, 4611. (d) Rao, Y. S. *Can. J. Chem.* **1976**, *76*, 625. (e) Piers, E.; Wai, J. S. M. *J. Chem. Soc, Chem. Commun.* **1988**, 1245. (f) Niwa, M.; Iguchi, M.; Yamamura, S. *Tetrahedron Lett.* **1975**, 1539. (g) Niwa, M.; Iguchi, M.; Yamamura, S. *Tetrahedron Lett.* **1975**, 4395. (h) Niwa, M.; Iguchi, M.; Yamamura, S. *Chem. Lett.* **1975**, 655. (i) Amos, R. A.; Katzenellenbogen, J. A. *J. Org. Chem.* **1978**, *43*, 560. (j) Larson, G. L.; Betancourt de Perez, R. M. *J. Org. Chem.* **1985**, *50*, 5257. (k) Cromwell, M. E. M.; Gebhard, R.; Li, X.-Y.; Batenburg, E. S.; Hopman, J. C. P.; Lugtenburg, J.; Mathies, R. A. *J. Am. Chem. Soc.* **1992**, *114*, 10860. (l) Hanessian, S.; Cooke, N. G.; De Hoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276. (m) Lorimer, S. D.; Mawson, S. D.; Perry, N. B.; Weavers, R. T. *Tetrahedron* **1995**, *51*, 7287. (n) Hanessian, S.; Grillo, T.-A.; Smith, G.-M. *Tetrahedron* **1997**, *53*, 6281. (o) Farrant, E.; Mann, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1083. (p) Sai, H.; Ohmizu, H. *Tetrahedron Lett.* **1999**, *40*, 5019. (q) Gasperi, T.; Loreto, M. A.; Tardella, P. A.; Veri, E. *Tetrahedron Lett.* **2003**, *44*, 4953.

(2) (a) White, J. D.; Amedio, J. C. Jr.; Gut, S.; Jayasinghe, L. R. *J. Org. Chem.* **1989**, *54*, 4268. (b) White, J. D.; Amedio, J. C. Jr.; Gut, S.; Ohira, S.; Jayasinghe, L. R. *J. Org. Chem.* **1992**, *57*, 2270. (c) Narasaka, K.; Sakakura, T.; Uchimaru, T.; Guendin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954.

(3) (a) Takeda, K.; Sakurawi, K.; Ishii, H. *Tetrahedron* **1972**, *21*, 3757. (b) Wollenberg, R. H. *Tetrahedron Lett.* **1980**, *21*, 3139. (c) Chen, S.-Y.; Joullie, M. M. *Tetrahedron Lett.* **1983**, *24*, 5027.

(4) (a) Zimmer, H.; Rothe, J. *J. Org. Chem.* **1959**, *24*, 28. (b) Taniguchi, M.; Koga, K.; Yamada, S. *Tetrahedron* **1974**, *30*, 3547. (c) Takano, S.; Goto, E.; Hirama, M.; Ogasawara, K. *Heterocycles* **1981**, *16*, 381. (d) Takano, S.; Goto, E.; Hirama, M.; Ogasawara, K. *Heterocycles* **1981**, *16*, 951. (e) Minami, T.; Niki, I.; Agawa, T. *J. Org. Chem.* **1974**, *39*, 3236. (f) Falsone, G.; Wingen, U. *Tetrahedron Lett.* **1989**, *30*, 675. (g) Lee, K.; Jackson, J. A.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 5967. (h) Lankin, D. C.; Scalise, M. R.; Schmidt, J. C.; Zimmer, H. *J. Org. Chem.* **1974**, *2*, 95. (i) Grieco, P. A.; Pogonowski, C. S. *J. Org. Chem.* **1974**, *39*, 1958. (j) Grieco, P. A.; Wang, C.-L. J.; Burke, S. D. *J. Chem. Soc., Chem. Commun.* **1975**, 537. (k) Yamamoto, K.; Tomo, Y. *Chem. Lett.* **1983**, 531. (l) Paterson, I.; Fleming, I. *Tetrahedron Lett.* **1979**, *20*, 2179. (m) Paterson, I. *Tetrahedron Lett.* **1988**, *44*, 4207. (n) Tanaka, K.; Uneme, H.; Yamagishi, N.; Tanikaga, R.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2920. (o) Matsui, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1853.

(5) (a) Tamaru, Y.; Hojo, M.; Yoshida, Z.-I. *J. Org. Chem.* **1991**, *56*, 1099. (b) Ma, S.; Lu, X. *J. Org. Chem.* **1991**, *56*, 5120. (c) Liu, T.-L.; Carlson, R. M. *Synth. Commun.* **1993**, *23*, 1437. (d) Belline, F.; Carpita, A.; De Santis, M.; Rosi, R. *Tetrahedron* **1994**, *50*, 12029. (e) Zhu, G.; Lu, X. *Tetrahedron: Asymmetry* **1995**, *6*, 345. (f) Zhu, G.; Lu, X. *Tetrahedron: Asymmetry* **1995**, *6*, 1657. (g) Zhu, G.; Lu, X. *J. Organomet. Chem.* **1996**, *508*, 83. (h) Mincheva, Z. P.; Gao, Y.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 7947.

(6) (a) Murray, A. W.; Reid, R. G. *Synthesis* **1985**, 35. (b) Datta, A.; Ila, H.; Junjappa, H. *Tetrahedron* **1987**, *43*, 5367. (c) Haaima, G.; Mawson, S. D.; Routledge, A.; Weavers, R. T. *Tetrahedron* **1994**, *50*, 3557. (d) Corey, E. J.; Letavič, M. *J. Am. Chem. Soc.* **1995**, *117*, 9616. (e) Sai, H.; Ohmizu, H. *Tetrahedron Lett.* **1999**, *40*, 5019. (f) Častulik, J.; Mazal, C. *Tetrahedron Lett.* **2000**, *41*, 2741.

(7) (a) Dybowski, P.; Skowrońska, A. *Tetrahedron Lett.* **1991**, *32*, 4380. (b) Maciągiewicz, I.; Dybowski, P.; Skowrońska, A. *Synthesis* **2003**, 723; and references cited therein.

(8) (a) Krawczyk, E.; Skowrońska, A. *Heteroat. Chem.* **2000**, *11*, 353. (b) Krawczyk, E.; Owsianik, K.; Skowrońska, A.; Wieczorek, M.; Majzner, W. *New J. Chem.* **2002**, *26*, 1703; and references cited therein.
(9) Dybowski, P.; Skowrońska, A. *Synthesis* **1990**, 609.
(10) Rubottom, G. M.; Gruber, J. M.; Marrero, R.; Juve, H. D. Jr.; Kim, W.-H. *J. Org. Chem.* **1983**, *48*, 4940.
(11) Skowrońska, A.; Dembiński, R.; Gwara, J.; Michalski, J. *Phosphorus Sulfur Relat. Elem.* **1988**, *39*, 119; and references cited therein.
(12) Evans, D. A.; Nelson, J. V.; Taber, T. R. In *Topics in Stereochemistry*, Vol. 13; Allinger, N. L.; Eliel, E. L.; Wilen, S. H., Eds.; Wiley: New York, **1982**, 1–115.
(13) Heathcock, C. H.; Pirrung, M. C.; Young, S. D.; Hagen, J. P.; Jarvi, E. T.; Badertscher, U.; Marki, H.-P.; Montgomery, S. H. *J. Am. Chem. Soc.* **1984**, *106*, 8161.
(14) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.
(15) Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T. *Synthesis* **1990**, 1123.