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Phosphorylation of Alkyl-2-chloro-2,3-epoxyalkanoates with Trialkyl Phosphites: A Novel Approach to Alkyl 2-Diethoxyphosphoryloxy-2-alkenoates

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ABSTRACT: *Alkyl 2-chloro-2,3-epoxyalkanoates react with trialkyl phosphites to give mixtures of (E) and (Z) alkyl 2-diethoxyphosphoryloxy-2-alkenoates instead of the expected alkyl 2-oxo-3-dialkoxyphosphorylalkanoates. Thermal isomerization of the alkyl 2-chloro-2,3-epoxyalkanoates to alkyl 3-chloro-2-oxoalkanoates and subsequent Perkow reaction of the latter with trialkyl phosphites yields the same products but usually in different (E) to (Z) ratios. A likely mechanism for the unexpected reaction is discussed.*
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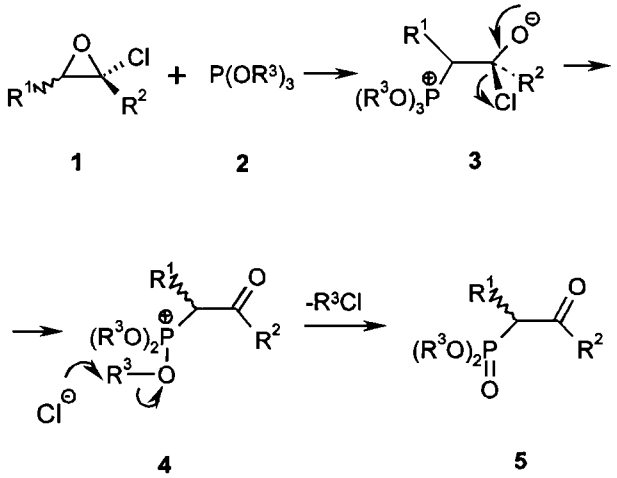
INTRODUCTION

1-Halooxiranes have proven to be particularly useful precursors of various α-functionalized alkyl ketones. The reactions sequence based on the ring opening of 1-chlorooxiranes with nucleophiles, such as amines, thiolates, alcoholates and organolithium compounds, followed by spontaneous elimination of the elements of hydrogen chloride from the resulting oxyanion, constitutes a simple and effective approach to α-aminoketones [1], α-thioalkylketones [2], α-alkoxyketones [2–4] and ketones with an elongated carbon chain [3,5,6] respectively. Similar transformation of 1-chlorooxiranes **1** with trialkyl phosphites **2**, completed by dealkylation of the phosphonium salt intermediates **4** with chloride anion, provides an attractive route to dialkyl-2-oxoalkylphosphonates **5** [7] (Scheme 1).

With the aim to evaluate the usefulness of this method for the preparation of alkyl 2-oxo-3-dialkoxyphosphorylalkanoates **8**, which are synthons of wide potential applicability [8], we attempted phosphorylation of the selected alkyl trans-2-chloro-2,3-epoxyalkanoates **6** with trialkyl phosphites **2** (Scheme 2). Unexpectedly, we found that the examined reactions occurred in a manner inconsistent



1 **2** **3** **4** **5**

SCHEME 1

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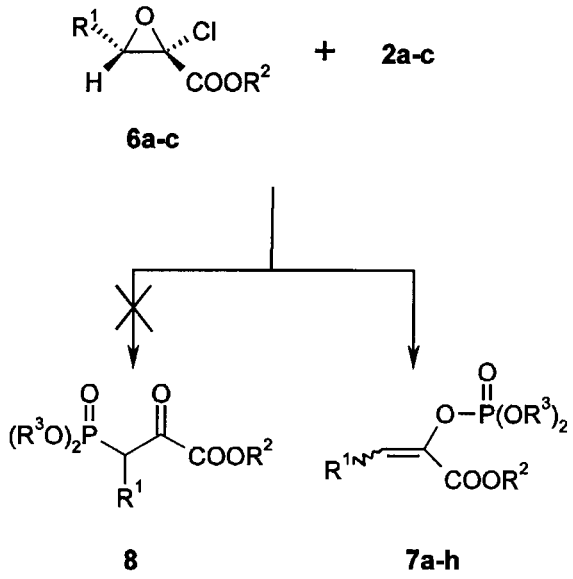
with the usual pattern, leading to the formation of the respective alkyl 2-diethoxyphosphoryloxy-2-alkenoates **7,** the compounds structurally related to PEP [9].

RESULTS AND DISCUSSION

All phosphorylations of trans-2-chloro-2,3-epoxyalkanoates **6a–c** with trialkyl phosphites **2a–c** were carried out in refluxing benzene. Standard workup and, in most cases, vacuum distillation of the crude reaction products gave the phosphoryloxyalkenoates **7a–h** as mixtures of (E) and (Z) isomers, with the former distinctly predominating (Table 1). Attempted separation of these mixtures with silica gel column chromatography appeared to be unsuccessful. Both the structure and the ratio of the isomeric products were unambiguously established by using ^{1}H and ^{31}P NMR spectroscopy. ^{1}H NMR data of (*E*) and (*Z*)-**7a** corresponded well to those previously reported [9]. Configurational assignments for (*E*) and (*Z*)-**7b–h** were made mainly on the basis of $^{4}J_{POCCH}$, which revealed characteristic larger values for (E) than for (Z) isomers [10]. The yield of particular reactions depended strongly on the spatial structure of the trialkyl phosphite used and decreased dramatically with increasing size of the alkoxy groups connected to the phosphorus atom; in contrast to satisfactorily occurring phosphorylations of **6a** and **6c** with trimethyl phosphite, analogous phosphorylations with triisopropyl phosphite were ineffective and were accompanied by competitive formation of side products, which were difficult to identify.



SCHEME 2

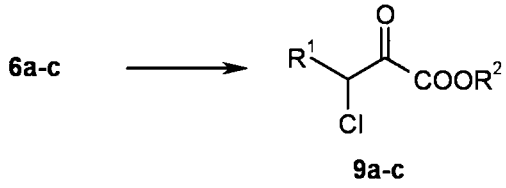
In search for a convincing mechanistic rationale for the experimental results, we anticipated that the starting 2-chloro-2,3-epoxyalkanoates **6a–c** might undergo preliminary thermal isomerization to the corresponding 3-chloro-2-oxoalkanoates **9a–c** (Scheme 3), which would subsequently be transformed into the final phosphoryloxyalkanoates **7a–h** by means of a standard Perkow reaction with trialkyl phosphites **2a–c.** Such isomerizations are generally known and well described [11,12].

To verify these hypotheses, the prepared 2-chloro-2,3-epoxyalkanoates **6a–c** were converted into the respective 3-chloro-2-oxoalkanoates **9a–c.** Heating **6a–c** in benzene under reflux for 2 hours gave starting material and only traces of 3-chloro-2-oxoalkanates **9a–c.** Rearrangement **6** → **9** took place, however, when benzene was replaced by xylene; for example, when **6a** was heated for 2 hours in refluxing xylene, a mixture of **6a** and **9a** in a 40:60 ratio

TABLE 1 Phosphoryloxyalkenoates **7a–h** Prepared from 2-Chloro-2,3-epoxyalkanoates **6a–c** and 3-Chloro-2-oxoalkanoates **9a–c**

					7	
Compound	*R*[1]	*R*[2]	*R*[3]	*Substrate* **6** *or* **9**	*Yield* (%)	*E/Z*[c]
7a	Me	Me	Me	**6a**	72[a]	25/75
				9a	75[a]	25/75
7b	Me	Me	Et	**6a**	40[a]	25/75
				9a	65[a]	40/60
7c	Me	Me	iPr	**6a**	20[b]	25/75
				9a	55[a]	40/60
7d	Me	iPr	Me	**6b**	60[a]	20/80
				9b	75[a]	30/70
7e	Me	iPr	Et	**6b**	40[a]	25/75
				9b	55[a]	40/60
7f	Et	Me	Me	**6c**	60[a]	30/70
				9c	91[a]	30/70
7g	Et	Me	Et	**6c**	30[a]	40/60
				9c	70[a]	40/60
7h	Et	Me	iPr	**6c**	15[b]	30/70
				9c	45[a]	40/60

[a]Yield of the isolated product based on **6** or **9** respectively.
[b]Yield of the product calculated from ^{31}P NMR spectrum of the crude product.
[c]Taken from ^{31}P NMR data of the crude product.



SCHEME 3

was obtained. Completion of the rearrangements required the reaction times given in Table 2. The progress of the reaction was monitored by ^{1}H NMR spectroscopy.

In further experiments, the 3-chloro-2-oxoalkanoates **9a–c** were converted into the phosphoryloxyalkenoates **7a–h** by the Perkow reaction with the phosphites **2a–c**. Heating the substrates in refluxing benzene gave the expected crude products. Vacuum distillation afforded pure **7a–h** as mixtures of (E) and (Z) isomers. Yields and isomer ratios are given in Table 1.

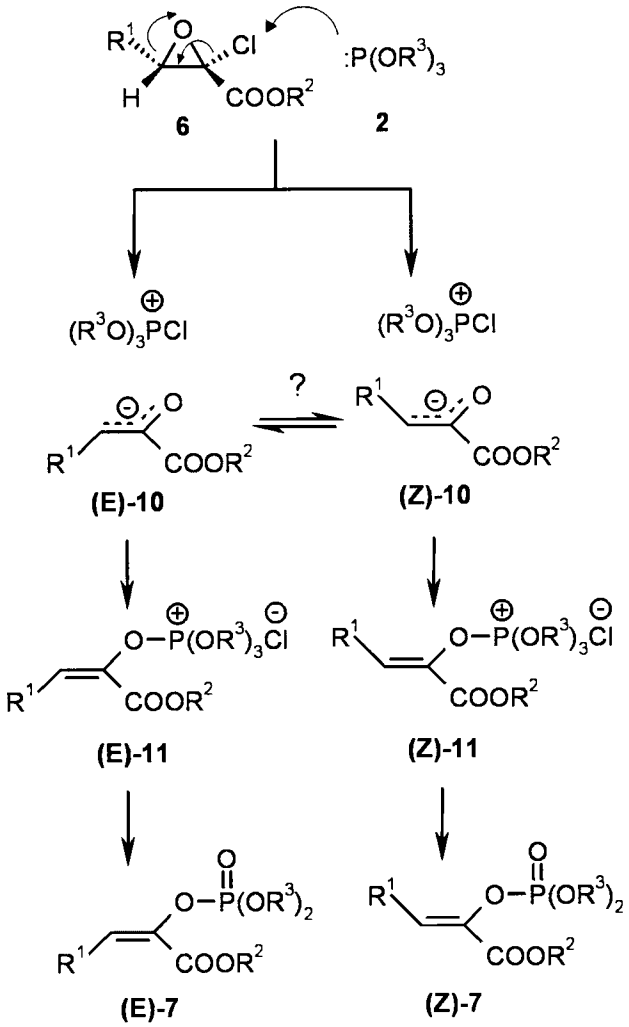
The obtained results show that the reactions of epoxyalkanoates **6a–c** with phosphites **2a–c** do not involve an initial rearrangement to the 2-oxoalkanoates **9a–c** but follow a diverse pathway. Both the different E/Z stereoselectivities observed in most cases of parallel phosphorylations of **6** and **9**, and the fact that the rearrangement **6** → **9** requires more vigorous conditions (refluxing xylene) than those employed in the reactions of **6** with phosphites (refluxing benzene) support such a conclusion.

This finding prompted us to postulate an alternative reaction mechanism. We believe that the new reaction is initiated by nucleophilic attack of the phosphite **2** on the "positive" chlorine atom of the 2-chloro-2,3-epoxyalkanoates **6**, which brings about the oxirane ring opening and the formation of the isomeric chlorophosphonium-enolates (*E*)-**10** and (*Z*)-**10**. Usual ligand exchange within the enolates **10** leads to the phosphonium salts (*E*)-**11** and (*Z*)-**11**. Finally, dealkylation of the salts **11** would give the phosphoryloxyalkenoates (*E*)-**7** and (*Z*)-**7** (Scheme 4).

It is an open question whether the enolates **10** might be generated in a one-step-electrocyclic process or in a two-step-reaction sequence with the chlorophosphonium salt **12** as the intermediate (Figure 1). Furthermore, it is unclear whether the observed ratio of the phosphoryloxyalkenoates (*E*)-**7** and (*Z*)-**7** reflects solely the nonstereospecific oxirane ring opening and how far the stereochemical outcome of the reaction might also be controlled by mutual interconversions of the chlorophosphonium salts (*E*)-**10** and (*Z*)-**10.**

There are literature data supporting this proposed mechanism. An attack of phosphorus (III) compounds on chlorine or bromine of α-halobenzyl phenyl sulfones or α-bromoacetophenones and the formation of anions stabilized by adjacent sulfonyl or carbonyl group have been reported [13,14]. Also, ring openings of epoxy anions of the type **12** leading to enolate anions have been observed [15,16].

In conclusion, we have demonstrated that the reaction of the epoxyalkanoates **6a–c** with trialkyl phosphites **2a–c** yields the phosphoryloxyalkenoates



SCHEME 4

TABLE 2 3-Chloro-2-oxoalkanoates **9a–c** Prepared

Compound	R^1	R^2	*Reaction Time (h)*	*Yield*[a] *(%)*
9a	Me	Me	5	81
9b	Me	iPr	8	65
9c	Et	Me	6	75

[a]Yield of isolated product based on **6**.

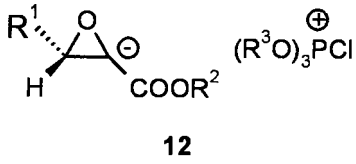


FIGURE 1

7a–h instead of the expected 2-oxo-3-dialkoxyphosphorylalkanoates **8.** Furthermore, an easy access to **6** makes this phosphorylation an interesting alternative to the known synthesis of PEP analogs [9]. Although the novel reaction does not occur effectively when sterically hindered phosphites are the starting materials, using trimethyl phosphite (**2a**) gives the final products **7a, d, f** in good yield. A plausible mechanistic explanation of the collected experimental data has also been proposed.

EXPERIMENTAL

^{1}H NMR (90 MHz or 250 MHz) and ^{31}P NMR (36.43 MHz or 101 MHz) spectra were recorded on Bruker HFX − 72 or Bruker DPX 250 spectrometers with tetramethylsilane (TMS) as an internal standard and 85% H_3PO_4 as an external standard, respectively. ^{31}P NMR spectra were recorded using broadband proton decoupling. All new compounds gave satisfactory microanalyses.

All reactions were carried out in an argon atmosphere using anhydrous reagents and solvents. *Trans*-2-chloro-2,3-epoxyalkanoates **6a–c** were synthesized from the corresponding alkyl dichloroacetates and aldehydes according to the published procedure [17,18].

Reaction of epoxyalkanoic esters **3a–c** *with trialkyl phosphites* **2a–c**

General procedure. A mixture of the ester **6** (0.02 mol) and phosphite **2** (0.026 mol) in benzene (20 mL) was heated under reflux for 2 hours. The resultant mixture was cooled to room temperature, and the solvent was evaporated to yield the crude vinyl phosphates **7a–h,** which were purified (except **7c** and **7h**) by vacuum distillation.

Methyl 2-(*dimethoxyphosphoryloxy*)*-2-butenoate* (**7a**). Oil; b.p. 80–84°C/0.8 mmHg (lit. [9] b.p. 85°C/1 mmHg). (*E*)-**7a:** ^{1}H NMR [19] ($CDCl_3$) δ 2.08 (dd, J = 7.5, 3.0 Hz, 3H), 3.82 (s, 3H), 3.88 (d, J = 11.5 Hz, 6H), 6.26 (dq, J = 3.0, 7.5 Hz, 1H); ^{31}P NMR [19] ($CDCl_3$) δ − 2.5. (*Z*)-**7a**: ^{1}H NMR [19] ($CDCl_3$) δ 1.88 (dd, J = 7.5, 3.0 Hz, 3H), 3.83(s, 3H), 3.90 (d, J = 11.5 Hz, 6H) 6.55 (dq, J = 2.0, 7.5 Hz, 1H); ^{31}P NMR [19] ($CDCl_3$) δ − 2.8.

Methyl 2-(*diethoxyphosphoryloxy*)*-2-butenoate* (**7b**). Oil; b.p. 103–110°C/0.7 mmHg, (*E*)-**7b:** ^{1}H NMR [19] ($CDCl_3$) δ 1.32 (t, J = 7.0 Hz, 6H), 2.09 (dd, J = 7.5, 3.0 Hz, 3H) 3.83 (s, 3H), 3.92–4.30 (m, 4H), 6.30 (dq, J = 3.0, 7.5 Hz, 1H); ^{31}P NMR [19] ($CDCl_3$) δ − 5.2. (*Z*)-**7b**: ^{1}H NMR [19] ($CDCl_3$) δ 1.30 (t, J = 7.0 Hz, 6H), 1.92 (dd, J = 7.5, 3.0 Hz, 3H), 3.80 (s, 3H), 3.92–4.30 (m, 4H), 6.60 (dq, J = 2.5, 7.5 Hz, 1H); ^{31}P NMR [19] ($CDCl_3$) δ − 5.6.

Methyl 2-(*diisopropoxyophosphoryloxy*)*-2-butenoate* (**7c**). (*E*)-**7c:** ^{31}P NMR [19] ($CDCl_3$) δ − 7.1, (*Z*)-**7c**: ^{31}P NMR [19] ($CDCl_3$) δ − 7.5.

Isopropyl 2-(*dimethoxyphosphoryloxy*)*-2-butenoate* (**7d**). Oil; b.p. 105–114°C/0.3 mmHg, (*E*)-**7d:** ^{1}H NMR [19] ($CDCl_3$) δ 1.30 (d, J = 7.0 Hz, 6H), 2.02 (dd, J = 7.5, 3.0 Hz, 3H) 3.75 (d, J = 11.0 Hz, 6H), 5.02 (heptet, J = 7.0Hz, 1H), 6.26 (dq, J = 3.0, 7.5 Hz, 1H); ^{31}P NMR [19] ($CDCl_3$) δ − 3.4. (*Z*)-**7d**: ^{1}H NMR [19] ($CDCl_3$) δ 1.26 (d, J = 7.0 Hz, 6H), 1.85 (dd, J = 7.5, 3.0 Hz, 3H), 3.83 (d, J = 11.0 Hz, 6H), 5.08 (heptet, J = 7.0 Hz, 1H), 6.51 (dq, J = 2.0, 7.5 Hz, 1H), ^{31}P NMR [19] ($CDCl_3$) δ − 3.7

Isopropyl 2-(*diethoxyphosphoryloxy*)*-2butenoate* (**7e**). Oil: b.p. 110–118°C/0.1 mmHg, (*E*)-**7e:** ^{1}H NMR [19] ($CDCl_3$) δ 1.34 (d, J = 7.0 Hz, 6H), 1.42 (t, J = 7.5 Hz, 6H) 2.09 (dd, J = 7.5, 3.0 Hz, 3H), 4.00–4.45 (m, 4H), 4.93–5.34 (m, 1H), 6.00 (dq, J = 3.0, 7.5 Hz, 1H); ^{31}P NMR [19] ($CDCl_3$), δ − 5.5. (*Z*)-**7e**: ^{1}H NMR [19] ($CDCl_3$), δ 1.34 (d, J = 7.0 Hz, 6H), 1.42 (t, J = 7.5 Hz, 6H), 1.87 (dd, J = 7.5, 3.0 Hz, 3H), 4.00–4.45 (m, 4H), 4.93–5.34 (m, 1H), 6.31 (dq, J = 2.5, 7.5 Hz, 1H); ^{31}P NMR [19] ($CDCl_3$) δ − 5.9.

Methyl 2-(*dimethoxyphosphoryloxy*)*-2-pentenoate* (**7f**). Oil; b.p. 95–101°C/0.4 mmHg. (*E*)-**7f:** ^{1}H NMR [19] ($CDCl_3$), δ 1.07 (t, J = 7.5 Hz, 3H), 2.46 (d quintet, J = 2.5, 7.5 Hz, 2H), 3.84 (s, 3H), 3.85 (d, J = 11.5 Hz, 6H), 6.19 (dq, J = 3.0, 7.5 Hz, 1H); ^{31}P NMR [19] ($CDCl_3$) δ − 3.2. (*Z*)-**7f**: ^{1}H NMR [19] ($CDCl_3$) δ 1.07 (t, J = 7.5 Hz, 3H), 2.34 (d quintet, J = 2.5, 7.5 Hz, 2H), 3.80 (s, 3H), 3.87 (d, J = 11.5 Hz, 6H), 6.50 (dq, 2.5, 7.5 Hz, 1H); ^{31}P NMR [19] ($CDCl_3$) δ − 3.6.

Methyl 2-(*diethoxyphosphoryloxy*)*-2-pentenoate* (**7g**). Oil; b.p. 115–123°C/0.2 mmHg, (*E*)-**7g;** ^{1}H NMR [19] ($CDCl_3$) δ 1.01 (t, J = 7.5 Hz, 3H), 1.30 (t, J = 7.0 Hz, 6H), 2.50 (d quintet, J = 2.5, 8.0 Hz, 2H), 3.78 (s, 3H), 3.92–4.40 (m, 4H), 6.07 (dt, J = 3.0 Hz, 8.0 Hz, 1H): ^{31}P NMR [19] ($CDCl_3$) δ − 5.6. (*Z*)-**7g**, ^{1}H NMR [19] ($CDCl_3$) δ 1.01 (t, J = 7.5 Hz, 3H), 1.29 (t, J = 7.0 Hz, 6H), 2.28 (d quintet, J = 2.5, 7.5 Hz, 2H), 3.81 (s, 3H), 3.92–4.40 (m, 4H), 6.38 (dt, J = 2.0, 7.5 Hz, 1H); ^{31}P NMR [19] ($CDCl_3$) δ − 5.9.

Methyl 2-(*diisopropoxyphosphoryloxy*)*-2-pentenoate* (**7h**). (*E*)-**7h**: ^{31}P NMR [19] ($CDCl_3$) δ − 7.3, (*Z*)-**7h**: ^{31}P NMR [19] ($CDCl_3$) δ − 7.6.

Rearrangement of 2-Chloro-2,3-epoxyalkanoates **6a–c** *to 3-Chloro-2-oxoalkanoates* **9a–c**

General procedure. Epoxyalkanoates **6a–c** (0.01 mol) were heated under reflux in xylene (15 mL) for the period of time given in Table 2. Evaporation of the solvent gave crude **9a–c**, which were purified by vacuum distillation.

Methyl 3-chloro-2-oxobutanoate (**9a**). Oil; b.p. 65–68°C/14 mmHg, ^{1}H NMR ($CDCl_3$) δ 1.71 (d, J = 7.0 Hz, 3H), 3.93 (s, 3H), 5.06 (q, J = 7.0 Hz, 1H).

Isopropyl 3-chloro-2-oxabutanoate (**9b**). Oil; b.p. 80–83°C/14 mmHg (lit. [20] b.p. 78°C/11 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.31 (d, J = 6.0 Hz, 6H), 1.65 (d, J = 6.5 Hz, 3H), 5.02 (q, J = 6.5 Hz, 1H), 5.14 (heptet, J = 6.0 Hz, 1H).

Methyl 3-chloro-2-oxopentanoate (**9c**). Oil; b.p. 75–78°C/14 mmHg (lit. [17] b.p. 77–79°C/13 mmHg), ^{1}H NMR ($CDCl_3$) δ 1.01 (t, J = 7.0 Hz, 3H) 1.66–2.22 (m, 2H), 3.87 (s, 3H), 4.86 (dd, J = 6.0, 8.0 Hz, 1H).

Reactions of 3-Chloro-2-oxoalkanoates **9a–c** *with Trialkyl Phosphites* **2a–c**

General Procedure: A mixture of the oxoalkanoate **9** (0.02 mol) and phosphite **2** (0.026 mol) in benzene (20 mL) was heated under reflux for 2 hours. The resultant mixture was cooled to room temperature and the solvent was evaporated to yield the crude phosphoryloxyalkenoates **7a–h**, which were purified by vacuum distillation.

Phosphorylalkenoates **7a, 7b, 7d, 7e, 7**f, and **7**g had physical and spectral properties as described before.

Methyl 2-(*diisopropoxyphosphoryloxy*)*-2-butenoate* (**7c**). Oil; b.p. 111–118°C/0.1 mmHg (*E*)-**7c**: ^{1}H NMR [19] ($CDCl_3$) δ 1.07 (t, J = 7.5 Hz, 3H), 2.04 (dd, J = 7.5, 3.0 Hz, 3H), 3.80 (s, 3H), 4.82–5.35 (m, 2H), 6.31 (dq, J = 3.0, 7.5 Hz, 1H); ^{31}P NMR [19] ($CDCl_3$) δ − 7.1, (*Z*)-**7c**: ^{1}H NMR [19] ($CDCl_3$) δ 1.02 (t, J = 7.5 Hz, 3H), 1.95 (dd, J = 7.5, 3.0 Hz, 3H), 3.78 (s, 3H), 4.82–5.35 (m, 2H), 6.57 (dq, J = 2.0, 7.5 Hz, 1H); ^{31}P NMR [19] ($CDCl_3$) δ − 7.5.

Methyl 2-(*diisopropoxyphosphoryloxy*)*-2-pentenoate* (**7h**). Oil; b.p. 120–129°C/0.15 mmHg. (*E*)-**7h**: ^{1}H NMR [19] ($CDCl_3$) δ 1.04 (t, J = 7.5 Hz, 3H), 1.38 (d, J = 7.0 Hz, 6H), 2.51 (d quintet, J = 2.5, 7.5 Hz, 2H), 3.87 (s, 3H), 4.78–5.27 (m, 2H), 6.21 (dq, J = 3.0, 7.5 Hz, 1H); ^{31}P NMR [19] ($CDCl_3$) δ − 7.3, (*Z*)-**7h**: ^{1}H NMR [19] 1.04 (t, J = 7.5 Hz, 3H), 1.34 (d, J = 7.0 Hz, 6H), 2.39 (d quintet, J = 2.5, 7.5 Hz, 2H), 3.81 (s, 3H), 4.78–5.27 (m, 2H), 6.48 (dq, J = 2.5, 7.5 Hz, 1H); ^{31}P NMR [19] ($CDCl_3$) δ − 7.6.

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