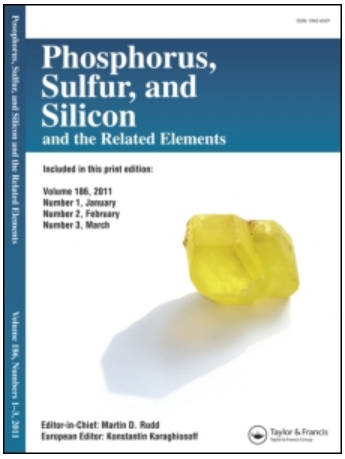


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# A CONVENIENT ROUTE TO 1-ALKOXYMETHYLVINYLPHOSPHONATES.A NOVEL REACTION OF DIETHYLPHOSPHONOACETIC ACID

Henryk Krawczyk[a]
[a] Institute of Organic Chemistry, Technical University (Politechnika), łódź, Zwirki 36, Poland

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# A CONVENIENT ROUTE TO 1-ALKOXYMETHYLVINYLPHOSPHONATES. A NOVEL REACTION OF DIETHYLPHOSPHONOACETIC ACID

HENRYK KRAWCZYK

*Institute of Organic Chemistry, Technical University (Politechnika), 90-924 Łódź, Żwirki 36, Poland*

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1-Alkoxymethylvinylphosphonates **3a–e** have been synthesized by piperidine catalyzed condensation of diethylphosphonoacetic acid **1** with paraformaldehyde in the presence of various primary and secondary alcohols. Similar reaction of the acid **1** with paraformaldehyde and sorbic alcohol **3f** afforded a mixture of three bicyclic compounds **7**, **9** and **11** in a ratio 2:1:1, respectively. The latter results strongly evidence the intermediacy of phosphonoacrylic acid **4** in the condensation. Under analogous conditions the olefin **14** was obtained from the acid (E,Z)-**13**.

*Key words:* Diethylphosphonoacetic acid, decarboxylative elimination, vinylphosphonates.

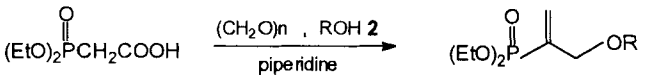


A great number of phosphonates has found widespread application in organic synthesis as well as in biochemistry, medicine and plant protection.[1] Consequently a significant effort has been directed towards development of methods for their simple and effective preparation. Most of the known approaches to the functionalized phosphonates are based on one of two strategies: i) preparations involving C—P bond formation, ii) syntheses consisting in structural modification of the carbon residue in simple phosphonates.[2] Extending the latter approach we have recently reported on the preparation of N-substituted 1-aminomethylvinylphosphonates based on the Mannich condensation of diethylphosphonoacetic acid **1**.[3,4]

In this paper we describe the results of our studies on a novel, piperidine catalyzed reaction of the acid **1** with paraformaldehyde and alcohols leading to 1-alkoxymethylvinylphosphonates **3**. We present some evidence that this condensation involves intermediacy of 2-phosphonoacrylic acid **4**. An optimalized procedure for the preparation of vinylphosphonates **3** is also described.

We found that heating of the acid **1** with excess of paraformaldehyde and a catalytic amount of piperidine in methanol gave 1-methoxymethylvinylphosphonate **3a** as a sole product in 78% yield (Scheme 1). In an attempt to prove that this is a general reaction we replaced methanol by other primary and secondary alcohols. The results presented in Table I show that facile conversion of the acid **1** into vinylphosphonates **3a–e** proceeded in all cases in high yields. The structure of compounds **3a–e** was unambiguously assigned on the basis of their $^{1}H$ NMR, $^{31}P$ NMR and IR data.

The formation of the olefins **3** may be rationalized (Scheme 2) as being the result of Michael-like reaction of the corresponding alcohol with the initially formed 2-phosphonoacrylic acid **4** followed by addition of the resulting enolate **5** to formaldehyde or its immonium equivalent and subsequent decarboxylative elimination of




1 3

SCHEME 1

TABLE I

Vinylphosphonates **3a–e** prepared

| Product | R | Yield[a] (%) | $^{31}P$ NMR[b] |
|---|---|---|---|
| **3a** | $CH_3$ | 78 | 16.8 |
| **3b** | $(CH_3)_2CH$ | 78 | 16.7 |
| **3c** | $CH_2=CH-CH_2$ | 80 | 16.5 |
| **3d** | $C_6H_5-CH_2$ | 84 | 16.5 |
| **3e** | $HC\equiv C-CH_2$ | 74 | 17.0 |

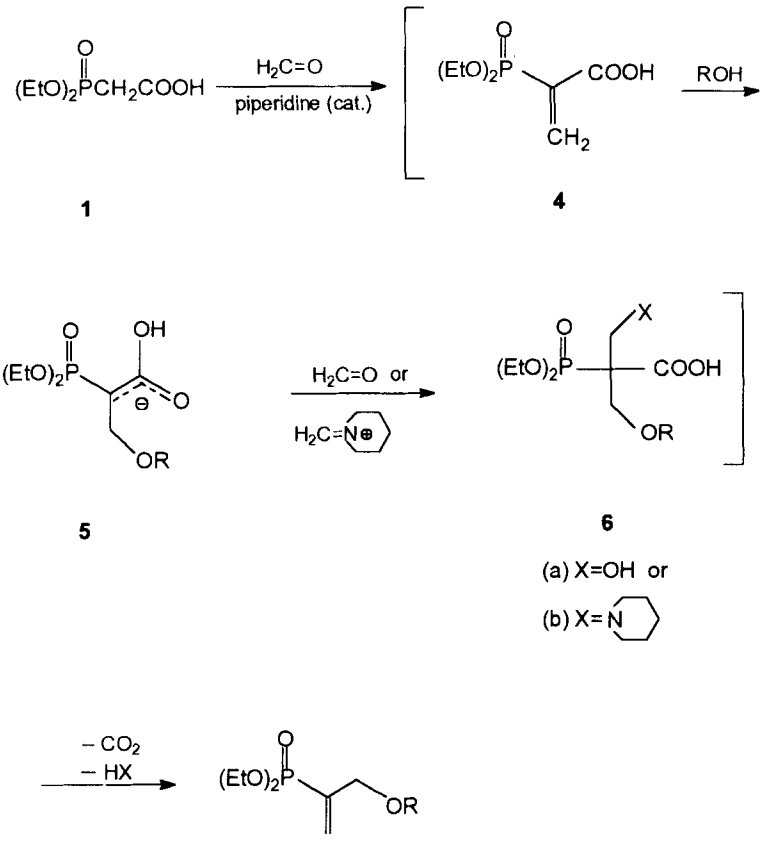
[a] isolated yield after distillation

[b] neat, relatively to 85% $H_3PO_4$



the adduct **6**. Since the structure of the intermediate **6** could not be experimentally confirmed we assumed that either alcohol **6a** or amine **6b** (Mannich base) undergo decarboxylative elimination. Both possibilities have been suggested in the literature.[5,6]

The hypothesis that the acid **4** is a precursor of the olefins **3** was confirmed by trapping experiment with sorbic alcohol **2f** (Scheme 3). This alcohol was expected to react with the acid **4** not only as a Michael donor but also as a 1,3-diene component of the Diels-Alder reaction to produce the triene **3f** and the adducts **8** and **10**, respectively. The standard condensation of the acid **1** with paraformaldehyde and sorbic alcohol at 100°C gave a mixture of three products **7**, **9** and **11** (in a 2:1:1 ratio) which could be readily separated by a column chromatography on silica gel. The compound **7** was characterised spectroscopically as an intramolecular Diels-Alder adduct of the expected triene **3f**. Although configuration of **7** could not be unequivocally assigned from the corresponding NMR spectra, cis geometry of its ring fusion was deduced on the basis of general rules concerning stereochemistry of intramolecular [4+2] cycloadditions. According to these rules thermally induced cycloadditions of 1,6,8-trienes substituted with a bulky electron-withdrawing group at C-2 carbon should proceed stereoselectively giving preferentially the corresponding cis-fused bicyclo [4.3.0] nonens.[7] The products **9** and **11** were identified as $\gamma$ and $\delta$ lactones, respectively. It might be assumed that they were formed by a consequent cyclization of the corresponding regioisomeric Diels-Alder adducts **8** and **10**. While the structure of the lactone **11** was fully confirmed by its IR and NMR spectra, the spectral data were insufficient to establish stereochemistry of a ring junction in the lactone **9**. However, assignment of cis geometry to this junction once

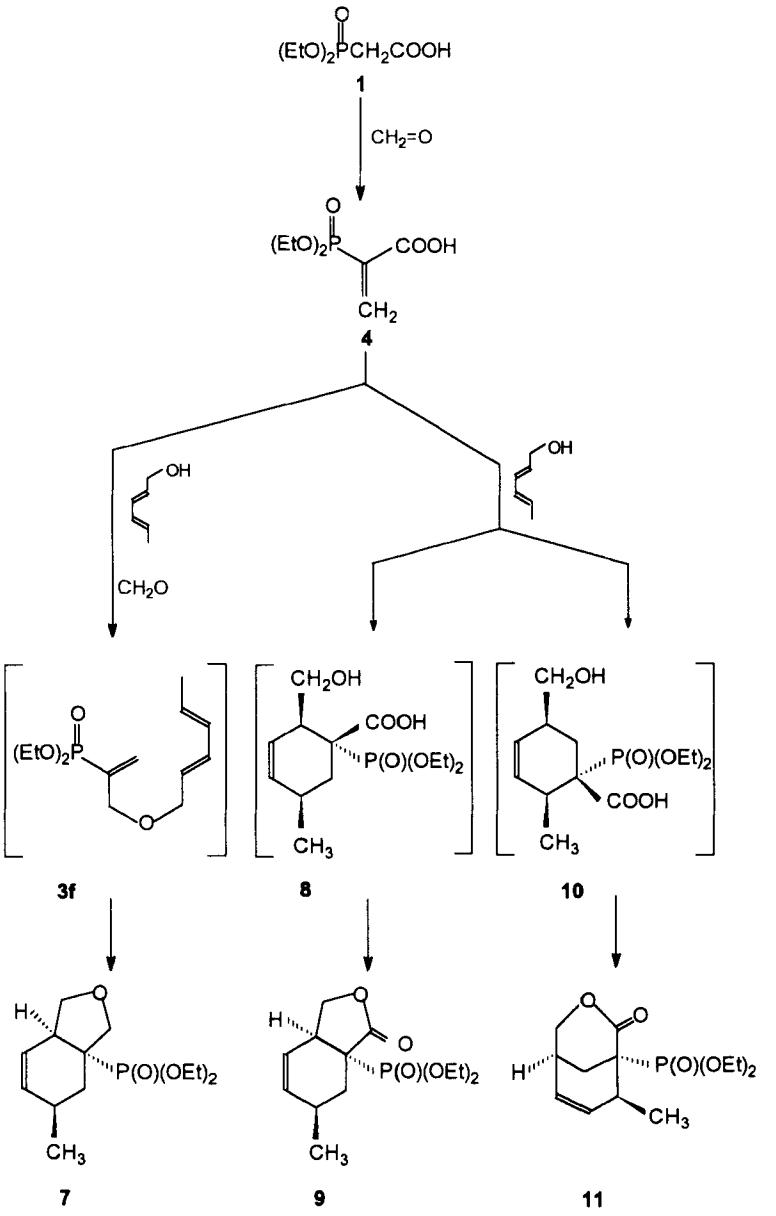



SCHEME 2



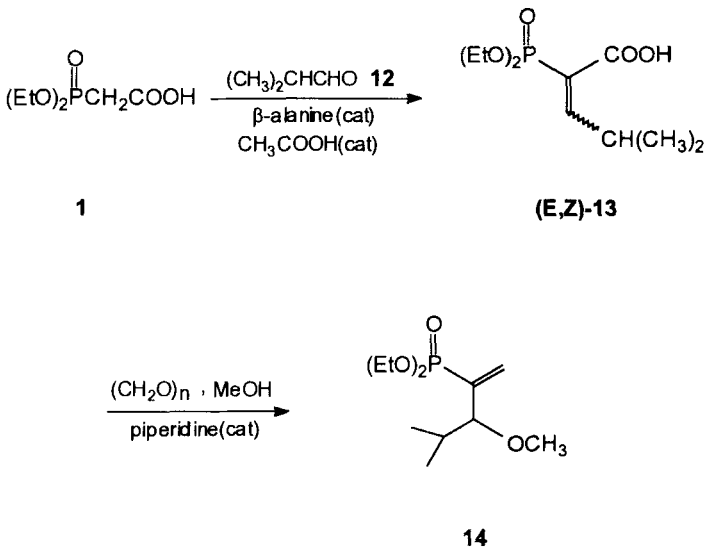
again could be based on general knowledge on [4+2] cycloadditions. In the light of the well known tendency of a carboxylic group to occupy endo position in the transition state of the Diels-Alder reactions involving acrylic acids derivatives as dienophiles[8] it was likely that the addition of the acid **4** to sorbic alcohol would occur stereoselectively providing mainly or exclusively regioisomeric cis $\beta$-hydroxy-carboxylic acids **8** and **10**. With this expectation in mind and taking into account that only the acids **8** and **10** having cis stereochemistry of hydroxymethyl and carboxyl groups can undergo lactonization it becomes evident that the formation of the lactones **9** and **11** confirms postulated intermediacy of the acid **4** in the discussed reactions. A similar pathway was proposed to explain the formation of bicyclic cis-lactones on reacting of $\alpha$-substituted acrylates with 1,6-bis(trimethylsilyloxy)-2,4-hexadiene.[9]

It should also be pointed out that the alternative route to the adducts **9** and **11** which would involve initial formation of sorbyl 2-diethylphosphonoacrylate followed by its intramolecular [4+2] cycloaddition may be excluded. Due to the steric reasons only 6-Z 1,6,8-trienes are able to undergo cyclization producing bridgehead structures like **11**.[10]




SCHEME 3

It was felt that the intermediacy of the acid **4** could be further confirmed by employing phosphonoacrylic acids synthesized from **1** and aldehydes other than formaldehyde. Thus, the Knoevenagel condensation of the acid **1** with isobutyraldehyde **12** performed in standard conditions afforded the acid (E,Z)-**13** in a ratio E: Z = 6:1 in nearly quantitative yield (Scheme 4). The reaction of the acid (E,Z)-**13** with paraformaldehyde, methanol and a catalytic amount of piperidine proved to be




SCHEME 4

considerably slower than that of the acid **1**. However several days of refluxing (approx. 200 h) gave the olefin **14** in 70% yield.

In summary the presently described synthesis provides a novel approach to the preparation of 1-substituted vinylphosphonates.[11]



## EXPERIMENTAL

$^1$H NMR spectra were recorded on Tesla BS 547 A or Bruker MSL-300 spectrometers at 80 and 300 MHz respectively, using TMS as internal standard. $^{31}$P NMR spectra were taken on a Bruker HFX-72 spectrometer at 36.43 MHz with 85% $H_3PO_4$ as external standard. IR spectra were recorded with Specord M 80 (C. Zeiss) instrument. Column chromatography was performed on $SiO_2$. TLC chromatography was carried out by using Kieselgel 60 $F_{254}$ plates (Merck). Diethylphosphonoacetic acid **1** was prepared according to a literature method.[12]

*General Procedure for the Preparation of Vinylphosphonates* **3a–e**

To a solution of the acid **1** (3.92 g, 20 mmol) in alcohol **2a–e** (25 ml) were added paraformaldehyde (1.8 g, 60 mmol) and piperidine (0.1 g). The resulting suspension was then allowed to react at reflux (except **2d**, 80°C) for 25–30 h until $^{31}$P NMR spectroscopic analysis revealed that the acid **1** had reacted. The reaction mixture was concentrated under reduced pressure and the residue dissolved in chloroform (40 ml). The chloroform solution was washed with water (3 × 5 ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was distilled in vacuo to afford analytically pure vinylphosphonates **3a–e**.

*Diethyl 1-methoxymethylvinylphosphonate* (**3a**): B.p. 74–75°C/0.6 Torr; $^1$H NMR $\delta$ 1.33 (6H, t, $J$ = 7.0, $2CH_3$), 3.38 (3H, s, $OCH_3$), 4.10 (6H, m, $3CH_2$), 6.04 (1H, ddt, $^3J_{HP}$ = 49.0, $^2J_{HH}$ = $^4J_{HH}$ = 1.9, P—C = $CH_{trans}$), 6.15 (1H, ddt, $^3J_{HP}$ = 24.0, $^2J_{HH}$ = $^4J_{HH}$ = 1.9, P—C = $CH_{cis}$); IR (film) $\vartheta_{P=O}$ 1260 cm$^{-1}$.

Anal. Calcd. for $C_8H_{17}O_4P$: C, 45.99; H, 8.20; P, 14.82.
Found: C, 46.22; H, 8.32; P, 14.64.

*Diethyl 1-isopropoxymethylvinylphosphonate* (**3b**): B.p. 75–77°C/0.4 Torr; $^1$H NMR $\delta$ 1.19 (6H, d, $J$ = 6.1, $2CH_3$), 1.33 (6H, t, $J$ = 7.0, $2CH_3$), 3.65 (1H, sept, $J$ = 6.1, CH), 4.10 (6H, m, $3CH_2$), 6.09 (1H, ddt, $^3J_{HP}$ = 47.2, $^2J_{HH}$ = $^4J_{HH}$ = 1.8, P—C = $CH_{trans}$), 6.11 (1H, ddt, $^3J_{HP}$ = 22.6, $^2J_{HH}$ = $^4J_{HH}$ = 1.8, P—C = $CH_{cis}$); IR (film) $\vartheta_{P=O}$ 1252 cm$^{-1}$.

Anal. Calcd. for $C_{10}H_{21}O_4P$: C, 50.83; H, 8.96; P, 13.10.
Found: C, 50.61; H, 8.77; P, 12.87.

*Diethyl-1-allyloxymethylvinylphosphonate* (**3c**): B.p. 95–97°C/0.4 Torr; $^1$H NMR $\delta$ 1.31 (6H, t, $J$ = 7.0, $2CH_3$), 4.01 (2H, dt, $^3J$ = 5.6, $^4J$ = 1.7, $OCH_2$), 4.05 (4H, m, $2CH_2$), 4.12 (2H, dt, $^3J_{HP}$ = 7.9, $^4J_{HP}$ = 1.7, P—C—$CH_2$), 5.18 (1H, ddt, $J_{cis}$ = 10.4, $^2J$ = $^4J$ = 1.7, $=CH_A$), 5.28 (1H, ddt, $J_{trans}$ = 17.2, $^2J$ = $^4J$ = 1.7, $=CH_B$), 5.90 (1H, ddt, $J_{trans}$ = 17.2, $J_{cis}$ = 10.4, $^3J$ = 5.6, $=CH$), 6.08 (1H, ddt, $^3J_{HP}$ = 46.7, $^2J_{HH}$ = $^4J_{HH}$ = 1.7, P—C = $CH_{trans}$), 6.14 (1H, ddt, $^3J_{HP}$ = 22.9, $^2J$ = $^4J$ = 1.7, P—C=$CH_{cis}$); IR (film) $\vartheta_{P=O}$ 1250 cm$^{-1}$.

Anal. Calcd. for $C_{10}H_{19}O_4P$: C, 51.27; H, 8.17; P, 13.22.
Found: C, 51.46; H, 8.31; P, 12.96.

*Diethyl 1-benzyloxymethylvinylphosphonate* (**3d**): B.p. 130–132°C/0.1 Torr; $^1$H NMR $\delta$ 1.30 (6H, t, $J$ = 7.0, $2CH_3$), 4.18 (4H, m, $2CH_2$), 4.23 (2H, dt, $^3J_{HP}$ = 8.5, $^2J_{HH}$ = $^4J_{HP}$ = 2.0), 4.55 (2H, s, $CH_2$), 6.10 (1H, ddt, $^3J_{HP}$ = 46.0, $^2J_{HH}$ = $^4J_{HH}$ = 2.0, P—C=$CH_{trans}$), 6.17 (1H, ddt, $^3J_{HP}$ = 22.4, $^2J_{HH}$ = $^4J_{HH}$ = 2.0, P—C=$CH_{cis}$), 7.3 (5H, m, Ar); IR (film) $\vartheta_{P=O}$ 1256 cm$^{-1}$.

Anal. Calcd. for $C_{14}H_{21}O_4P$: C, 59.14; H, 7.44; P, 10.89.
Found: C, 59.32; H, 7.72; P, 10.53.

*Diethyl 1-propargyloxymethylvinylphosphonate* (**3e**): B.p. 120°C/0.4 Torr; $^1$H NMR $\delta$ 1.33 (6H, t, $J$ = 7.0, $2CH_3$), 2.48 (1H, t, $^4J$ = 2.4, H—C≡C), 4.2 (m, 8H, $4CH_2$), 6.09 (1H, ddt, $^3J_{HP}$ = 45.9, $^2J_{HH}$ = $^4J_{HH}$ = 1.7, P—C=$CH_{trans}$), 6.18 (1H, ddt, $^3J_{HP}$ = 24.3, $^2J_{HH}$ = $^4J_{HH}$ = 1.7, P—C=$CH_{cis}$); IR (film) $\vartheta_{P=O}$ 1255 cm$^{-1}$.

Anal. Calcd. for $C_{10}H_{17}O_4P$: C, 51.72; H, 7.38; P, 13.33.
Found: C, 51.97; H, 7.62; P, 13.05.

*Preparation of Phosphonates* **7**, **9**, *and* **11**

The reaction was carried out in the same manner as for vinylphosphonates **3a–e** using the acid **1** (1.96 g, 10 mmol), paraformaldehyde (0.9 g, 30 mmol) piperidine (0.1 g) and sorbic alcohol (15 ml). The reaction mixture was heated at 100°C for 30 h. The products were separated by column chromatography on silica gel using methylene chloride/methanol 100:1 as eluent.

*(3R*, 5R*, 7aR*)-3a-diethoxyphosphoryl-5-methyl-1,3,3,4,5,7a-hexahydrobenzo-[c]-furan* (**7**): Yield 0.71 g (25.9%); $^{31}$P NMR ($CHCl_3$) $\delta$ 32.3; $^1$H NMR ($CDCl_3$) $\delta$ 0.94 (3H, d, $J$ = 7.1), 1.20 (1H, m), 1.23 (3H, t, $J$ = 7.0), 1.24 (3H, t, $J$ = 7.0), 2.05 (1H, ddd, $J$ = 5.0, 11.0, 13.6), 2.48 (1H, m), 2.92 (1H, m), 3.45 (1H, t, $J$ = 7.8), 3.56 (1H, dd, $J$ = 6.1, 6.9), 4.10 (6H, m), 5.57 (2H, m); IR (film) 1234, 1142, 1058, 962, 734 cm$^{-1}$; Rf:0.21 ethyl acetate. Anal. Calcd. for $C_{13}H_{23}O_4P$: C, 56.92; H, 8.45; P, 12.29. Found: C, 56.57; H, 8.56; P, 11.87.

*(3aR*, 5S*, 7aS*)-3a-diethoxyphosphoryl-5-methyl-3a,4,5,7a-tetrahydro-(2H)-benzo[c]-furan-3-on* (**9**): Yield 0.35 g (12.0%). $^{31}$P NMR ($CHCl_3$) $\delta$ 23.5 $^1$H NMR ($CDCl_3$) $\delta$ 0.99 (3H, d, $J$ = 7.2), 1.28 (6H, t, $J$ = 7.1), 1.70 (1H, ddd, $J$ = 23.2, 13.8, 7.0), 2.23 (1H, ddd, $J$ = 13.8, 11.8, 5.7), 2.37 (1H, m), 3.36 (1H, m), 3.87 (1H, dd, $J$ = 8.6, 6.1), 4.10 (4H, m), 4.55 (1H, dd, $J$ = 8.4), 5.52 (1H, dddd, $J$ = 10.2, 3.5, 2.2, 1.0), 5.77 (1H, ddd, $J$ = 10.2, 3.3, 2.0); IR (film) 1768, 1244, 1180, 1022, 972, 734 cm$^{-1}$; Rf: 0.35 ethyl acetate. Anal. Calcd for $C_{13}H_{21}O_5P$: C, 53.78; H, 7.98; P, 10.66. Found: C, 54.02; H, 8.07; P, 10.37

*(1R*, 5S*, 8R*)-1-diethoxyphosphoryl-8-methyl-3-oxabicyclo[3.3.1]non-6-en-2-on* (**11**): Yield 0.36 g (12.4%); $^{31}$P NMR ($CHCl_3$) $\delta$ 24.3, $^1$H NMR ($CDCl_3$) $\delta$ 1.16 (3H, dd, $J$ = 7.3, 0.6), 1.25 (3H, t, $J$ = 6.8), 1.28 (3H, t, $J$ = 7.0), 2.12 (1H, ddt, $J$ = 13.0, 3.9, 2.4), 2.35 (1H, dddd, $J$ = 13.0, 8.4, 2.5, 1.5), 2.51 (1H, m), 2.81 (1H, m), 4.10 (5H, m), 4.35 (1H, dd, $J$ = 10.8, 3.5), 5.59 (1H, dddd, $J$ = 9.8, 3.4, 2.0, 0.8), 5.70 (1H, m); IR (film) 1726, 1244, 1142, 1026, 966, 744 cm$^{-1}$; Rf:0.12 ethyl acetate. Anal. Calcd. for $C_{13}H_{21}O_5P$: C, 53.78; H, 7.98; P, 10.66. Found: C, 53.54; H, 7.74; P, 10.93.

*(E,Z)-2-Diethylphosphono-4-methyl-2-pentenoic acid* (**13**)

A mixture of the acid **1** (19.6 g, 0.1 m), isobutyraldehyde (7.9 g, 0.11 m), $\beta$-alanine (0.89 g, 0.01 m) and acetic acid (1.6 g, 0.02 m) in benzene (100 ml) was heated at reflux under a Dean-Stark water separator for 10 h. The reaction progress was occasionally monitored with $^{31}$P NMR. After **1** completely disappeared the benzene solution was washed with water (2 × 10 ml) and dried over $MgSO_4$. Removal of the solvent gave crude acid (E,Z)-**13** (23.0 g, 92%) which was used for further transformation without purification.

$^1$H NMR ($CDCl_3$) $\delta$ 1.07 (6H, d, $J$ = 6.6, $2CH_3$), 1.33 (6H, t, $J$ = 7.0, $2CH_3$), 3.2 (1H, m), 4.16 (4H, dq, $^3J_{HH}$ = 7.0, $^3J_{HP}$ = 7.3, $2CH_2$), 6.91 (1H, dd, $^3J_{HH}$ = 10.1, $^3J_{HP}$ = 23.5, P—C=CH, E-isomer), 7.90 (1H, dd, $^3J_{HH}$ = 11.6, $^3J_{HP}$ = 42.8, P—C=CH, Z-isomer), 10.85 (1H, bs); $^{31}$P NMR (neat) $\delta$ 15.2, 14.0 for E and Z isomers respectively, E:Z = 6:1.

*Diethyl 1-(1'-methoxy-2'-methyl)propylvinylphosphonate* (**14**)

The reaction was carried out in the same manner as for vinylphosphonates **3a–e**. A mixture of the acid (E,Z)-13 (5.0 g, 20 mmol), paraformaldehyde 2.4 g (80 mmol) and piperidine (0.2 g) in methanol (30 ml) was heated at reflux for approx. 200 h. Yield 3.5 g (70%), b.p. 75°C/0.4 Torr $^1$H NMR ($CDCl_3$) $\delta$ 0.86 (3H, d, $J$ = 6.6, $CH_3$), 0.96 (3H, d, $J$ = 7.5, $CH_3$), 1.34 (6H, t, $J$ = 7.0, $2CH_3$), 1.85 (1H, m), 3.26 (3H, s, $OCH_3$), 3.63 (1H, br.dd, $^3J_{HH}$ = 5.2, $^3J_{HP}$ = 10.6, CH), 5.96 (1H, dm, $^3J_{HP}$ = 47.4, P—C=$CH_{trans}$, 6.22 (1H, dm, $^3J_{HP}$ = 22.7, P—C=$CH_{cis}$); $^{31}$P NMR (neat) $\delta$ 17.1; IR (film) $\vartheta_{P=O}$ = 1248 $cm^{-1}$.

Anal. Calcd. for $C_{11}H_{23}O_4P$: C, 52.78; H, 9.26; P, 12.37.
Found: C, 52.64; H, 9.11; P, 12.63.

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