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### Stobbe-like condensation reactions of the anion of diethyl (2carboethoxy)benzylphosphonate with some aromatic and heterocyclic aldehydes

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#### ABSTRACT

Deprotonation of diethyl (2-carboethoxy)benzylphosphonate using sodium ethoxide followed by reaction of the carbanion with furfural or aryl aldehydes gives diethyl (*E*)-1-(2'-carboxyphenyl)-1phosphono-2-arylethenes that are formed via intramolecular Stobbe-like condensation reactions. © 2014 Elsevier Ltd. All rights reserved.

### 1. Introduction

The Horner-Emmons condensation reactions of phosphonate-stabilised anions with aldehydes and ketones find widespread use in the synthesis of alkenes.<sup>1</sup> In connection with other work we sought to synthesise the ester **1** via the apparently simple Horner-Emmons condensation of furfuraldehyde 2 with the carbanion derived from the benzylic phosphonate 3. Very poor yields of the desired ester 1 were obtained from this reaction, and we were led to investigate the alkaline aqueous phase that remained after extraction of the neutral ester from the reaction mixture. Here we found a novel product, formed by Stobbe-like reaction of the anion of the phosphonate **3** with the aldehyde **2**. In this paper, we provide evidence for the structure of this unexpected product, propose a mechanism for its formation and describe a number of analogous compounds that can be obtained by reaction of the anion of the phosphonate **3** with a range of different aldehydes.

### 2. Results and discussion

The phosphonate **3**, which was prepared in the conventional way from ethyl (2-bromomethyl)benzoate **4** and triethyl phosphite,

was deprotonated using ethanolic sodium ethoxide in dimethylformamide and then reacted with furfuraldehyde **2**. The usual work-up afforded ethyl (*E*)-2-[2-(2-furyl)ethenyl]benzoate **1** in only ~10% yield. However, acidification of the bright yellow aqueous washings gave a solid product (64% after recrystallisation) that was identified as being diethyl (*E*)-1-(2'-carboxyphenyl)-1phosphono-2-(2"-furyl)ethene **5**.







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The infrared spectrum of the vinylic phosphonate **5** shows  $\nu_{max}$  1712 (C=O) and 1197 (P–O) cm<sup>-1</sup>. The <sup>1</sup>H NMR spectrum confirms the presence of the phosphonate ester function and of the substituted aryl and furyl ring systems, and shows a 1H doublet at  $\delta_{\rm H}$  7.18 ppm that can be assigned to the vinylic proton  $\beta$  to the phosphonate group. The <sup>31</sup>P NMR spectrum of **5** exhibits a single resonance at  $\delta_{\rm P}$  17.8 ppm.

There are a number of literature reports<sup>2–6</sup> concerning the relationship between  $J_{H-P}$  and double bond geometry in vinyl phosphonates. For example, typical values that have been measured by Xu et al.<sup>3</sup> for  $J_{H-P}$  in a series of vinyl phosphonates that are geometrical isomers are 10–30 Hz for compounds where the vicinal vinylic proton is cis to the phosphonate group and 30–50 Hz where it is trans.

The doublet due to the vinylic proton of the phosphonate **5** has  $J_{H-P}$  23.6 Hz, falling clearly into the observed range for protons that are cis to the phosphorus atom, hence we are confident in concluding that the magnitude of this coupling constant is consistent with the assigned (*E*)-geometry.

We rationalise the formation of the vinylic phosphonate **5** on the basis of the mechanism outlined in Scheme 1. Here, condensation of the anion of the phosphonate **3** with furfuraldehyde **2** gives an intermediate **6** whose oxy-anion undergoes intramolecular reaction with the carboxylic rather than with the phosphonic ester function, to give the intermediate lactone **7**. In a final step, that is, reminiscent of the classical Stobbe condensation reaction,  $\beta$ -elimination of carboxylate ion from **7** yields the sodium salt **8** of the observed product **5**.



In principle, the intermediate **6** should possess the *erythro*configuration in order to deliver (*E*)-**8**. Bearing in mind that the initial carbon–carbon bond-forming step is reversible,<sup>7</sup> the oxyanion of the  $\beta$ -hydroxyphosphonate **6** (which is likely formed under kinetic control) would then have to very quickly undergo intramolecular cyclisation to lactone **7** since the thermodynamically more stable *threo*-configured  $\beta$ -hydroxyphosphonate oxyanion usually<sup>8</sup> prevails in Horner–Emmons reactions, leading to the formation of *trans*-alkenes. Alternatively, an E1<sub>CB</sub> pathway proceeding from either stereochemistry of the initial adduct **6** via a phosphonate anion derived from lactone **7** is plausible, although this then requires that the product **8** represents the thermodynamic outcome, as must the analogous products **9–12**.

The reaction appears to be fairly general for heteroaryl and aryl aldehydes, since we have obtained (Table 1) the analogous products

#### Table 1

Reactions of aldehydes with the anion of diethyl (2-carboethoxy)benzylphosphonate to yield vinylic phosphonates

Aldehyde	Vinyl phosphonate	% Yield <sup>a</sup>
Furan-2-carboxaldehyde	5	64
Thiophene-2-carboxaldehyde	9	70
Benzaldehyde	10	89
4-Methoxybenzaldehyde	11	79
4-Fluorobenzaldehyde	12	87
Cinnamaldehyde	15	53
2,2-Dimethylpropanal	_	0
Pyrrole-2-carboxaldehyde	_	0

<sup>a</sup> Yields of analytically pure materials after recrystallisation.

**9–12** by reacting the carbanion derived from the phosphonate **2** with, respectively, each of thiophene-2-carboxaldehyde, benzaldehyde, 4-methoxybenzaldehyde and 4-fluorobenzaldehyde. None of these reactions yielded detectable quantities of the 'normal' Horner–Emmons products.



The vinyl phosphonates **11** and **12** that were obtained from 4methoxybenzaldehyde and from 4-fluorobenzaldehyde were not at first obtained as solids, and were initially characterised by conversion into their methyl esters **13** and **14** using diazomethane. These esters were much more easily purified than the corresponding acids. However, after standing for several months each of the acids **11** and **12** solidified and could then be recrystallised. Cinnamaldehyde also reacted with the anion of the phosphonate **3**, yielding the (*E*,*E*)-dienyl phosphonate **15**, but pivalaldehyde failed to react, and neither did pyrrole-2-carboxaldehyde or cyclohexanone.



The formation of the thenyl-substituted vinylic phosphonate **9** is of interest. Murty et al.<sup>9</sup> have reported that when the benzylic phosphonate **16**, closely related to the phosphonate **3**, is reacted with thiophene-2-carboxaldehyde in THF in the presence of 2 equiv of potassium hydroxide, the 'normal' Horner–Emmons acid **17** is formed in 80% yield. In this instance the course of the reaction is dictated by the fact that the carboxylate ion already present in the deprotonated phosphonate **16** does not act as an internal electrophile towards the oxy-anion intermediate formed during the reaction.

### 3. Conclusions

Intramolecular trapping by a neighbouring carboethoxy group of the intermediate oxy-anion formed in the first stage of a Horner–Emmons reaction between an aldehyde and the anion of diethyl (2-carboethoxy)benzylphosphonate **3** diverts the reaction from its normal course, and leads to the formation of Stobbe-like products via the intervention of a presumed intermediate lactone.

### 4. Experimental

### 4.1. General

Unless otherwise stated, <sup>1</sup>H, <sup>13</sup>C, <sup>19</sup>F and <sup>31</sup>P NMR spectra were recorded for solutions in CDCl<sub>3</sub> using a Bruker Avance DPX 400 MHz spectrometer. Coupling constants are recorded in hertz. Assignments were verified where appropriate by  ${}^{1}H-{}^{1}H$  COSY,  ${}^{1}H-{}^{13}C$  COSY, HMBC and DEPT experiments. IR spectra were recorded for Nujol mulls (N) or liquid films (L) between sodium chloride plates using a Mattson FT-IR spectrometer. Mass spectra were obtained under electrospray conditions using a Micromass time-of-flight instrument. Melting points (uncorrected) were measured in unsealed capillary tubes using an Electrothermal IA9100 apparatus. Thin layer chromatography was carried out using Merck Kieselgel 60F<sub>254</sub> 0.2 mm silica gel plates. Column chromatography was carried out using Merck Kieselgel 60 (70–230 mesh) silica gel. All solvents were dried and distilled before use. Organic extracts of reaction products were dried over anhydrous magnesium sulfate. Combustion analyses were obtained from the Microanalytical Laboratory, University College, Dublin.

### 4.2. Ethyl (2-bromomethyl)benzoate 4

A mixture of ethyl *o*-toluate (15 g, 91.5 mmol), *N*-bromosuccinimide (19.6 g, 110 mmol) and AIBN (60 mg) was refluxed in CCl<sub>4</sub> (250 mL) for 2 h to give the bromo-ester **4** as a colourless oil, bp 92–94 °C/0.1 mmHg (lit.<sup>10</sup> bp 100–105 °C/1.0 mmHg),  $\nu_{max}$  (L) 1730 cm<sup>-1</sup>;  $\delta_{\rm H}$  1.44 (3H, t, *J* 7.3, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 4.43 (2H, q, *J* 7.3, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 4.98 (2H, s, CH<sub>2</sub>Br), 7.35–7.43 (1H, m, *H*-5), 7.44–7.53 (2H, m, *H*-3 and *H*-4) and 7.98 (1H, d, *J* 7.5, *H*-6) ppm.

### 4.3. Diethyl (2-carboethoxy)benzylphosphonate 3

Ethyl (2-bromomethyl)benzoate **4** (15 g; 62 mmol) and triethyl phosphite (11 g; 66 mmol) were heated together without solvent at 160 °C during 24 h. Distillation yielded diethyl (2-carboethoxy) benzylphosphonate **3** (13.6 g; 90%) as a colourless oil, bp 138–140 °C/0.1 mmHg (lit.<sup>11</sup> bp 170–174 °C/0.1 mmHg),  $\nu_{max}$  (L) 1718 and 1267 cm<sup>-1</sup>;  $\delta_{H}$  1.21 (6H, t, *J* 7.2, OCH<sub>2</sub>CH<sub>3</sub>), 1.40 (3H, t, *J* 7.3, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3.81 (2H, d, <sup>2</sup>*J*<sub>H–P</sub> 23.2, –PCH<sub>2</sub>), 3.93–4.05 (4H, m, OCH<sub>2</sub>CH<sub>3</sub>), 4.36 (2H, q, *J* 7.2, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 7.27–7.34 (1H, m, *H*-5), 7.35–7.48 (2H, m, *H*-3 and *H*-4) and 7.87 (1H, d, *J* 8.0, *H*-6) ppm.

# 4.4. General procedure for reactions between diethyl (2-carboethoxy)benzylphosphonate 3 and an aldehyde

Diethyl (2-carboethoxy)benzylphosphonate **3** (1.2 g; 4 mmol) in dry DMF (5 mL) was added to ethanolic sodium ethoxide (1 M; 12 mmol; 12 mL) at room temperature under nitrogen. After 5 min an aldehyde (4 mmol; neat or dissolved in a little DMF) was added and the mixture was stirred during 1 h. It was then diluted with water, and neutral products and residual starting materials were extracted using ether. The aqueous phase was then acidified to pH=1 using concentrated hydrochloric acid and extracted using ethyl acetate to give acidic products. Each of these organic extracts was washed with brine, dried and evaporated. The crude neutral fraction was analysed by means of <sup>1</sup>H NMR spectroscopy. The acidic product generally solidified and was then further purified by recrystallisation, except where noted below.

## **4.5.** Diethyl (*E*)-[1-o-carboxyphenyl-2-(2'-furyl)vinyl]phosphonate 5

Following the general procedure, 2-furaldehyde (0.38 g; 4 mmol) gave a crude acidic product that was recrystallised from acetone to afford the *title compound* **5** (0.89 g; 64%) as a solid, mp 208–210 °C; [Found C 58.20, H 5.51%. C<sub>17</sub>H<sub>19</sub>O<sub>6</sub>P requires C 58.27, H 5.47%];  $\nu_{max}$  (N) 1712, 1614, 1593, 1571, 1209, 1162, 1141, 1054, 1024 cm<sup>-1</sup>;  $\delta_{H}$  1.15 (3H, t, *J* 7.0, OCH<sub>2</sub>CH<sub>3</sub>), 1.19 (3H, t, *J* 7.0, OCH<sub>2</sub>CH<sub>3</sub>), 3.90–4.05 (4H, m, OCH<sub>2</sub>CH<sub>3</sub>), 5.86 (1H, d, *J* 3.5, *H*-3″ furyl), 6.40 (1H, dd, *J* 3.5 and 2.0, *H*-4″ furyl), 7.18 (1H, d, <sup>3</sup>J<sub>H-P</sub> 23.6, *H*-2), 7.18 (1H, d, *J* 7.5, *H*-3′), 7.50 (1H, t, *J* 7.5, *H*-5′), 7.55–7.67 (2H, m,

*H*-4′ aryl and *H*-5″ furyl), 7.97 (1H, d, *J* 8.0, *H*-6′) and 12.70 (1H, s, exch D<sub>2</sub>O, CO<sub>2</sub>*H*) ppm;  $\delta_{\rm C}$  (100.6 MHz) 16.1 (d,  ${}^3J_{\rm C-P}$  6.8, OCH<sub>2</sub>CH<sub>3</sub>), 61.4 (d,  ${}^2J_{\rm C-P}$  5.8, OCH<sub>2</sub>CH<sub>3</sub>), 61.9 (d,  ${}^2J_{\rm C-P}$  5.8, OCH<sub>2</sub>CH<sub>3</sub>), 112.1 (C-4″), 113.6 (C-3″), 128.0 (d,  ${}^1J_{\rm C-P}$  187.6, C-1), 128.01 (C-5′), 128.3 (d,  ${}^2J_{\rm C-P}$  11.7, C-2), 130.3 (d,  ${}^3J_{\rm C-P}$  4.9, C-3′), 130.5 (C-6′), 131.0 (d,  ${}^3J_{\rm C-P}$  4.9, C-1′), 132.1 (C-4′), 136.6 (d,  ${}^2J_{\rm C-P}$  5.8, C-2′), 144.6 (C-5″), 150.6 (d,  ${}^3J_{\rm C-P}$  27.2, C-2″) and 167.4 (CO<sub>2</sub>H) ppm;  $\delta_{\rm P}$  (162 MHz) 17.8 ppm.

Ethyl (*E*)-2-[2-(2-furyl)ethenyl]benzoate<sup>12</sup> **1** (0.1 g; 10%) was obtained from the neutral extract as an oil,  $\nu_{max}$  (L) 1720 cm<sup>-1</sup>;  $\delta_{H}$  (300 MHz) 3.90 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 6.41 (2H, overlapping ms, *H*-3' and *H*-4'), 6.80 (1H, *J* 18.0, vinyl) and 7.21–7.90 (6H, ms, vinyl H, Ar*H* and *H*-5') ppm.

### 4.6. Diethyl (*E*)-[1-(*o*-carboxyphenyl)-2-(2'-thenyl)vinyl] phosphonate 9

From thiophene-2-carboxaldehyde (0.42 g; 4 mmol) there was obtained, after recrystallisation from acetone, the *title compound* **9** (1.02 g; 70%) as a solid, mp 197–200 °C; [Found C 55.54, H 5.33%. C<sub>17</sub>H<sub>19</sub>O<sub>5</sub>PS requires C 55.74, H 5.19%];  $\nu_{max}$  (N) 1713, 1605, 1570, 1203, 1161, 1138, 1058, 1027 cm<sup>-1</sup>;  $\delta_{\rm H}$  1.15 (3H, t, *J* 7.5, OCH<sub>2</sub>CH<sub>3</sub>), 1.19 (3H, t, *J* 7.5, OCH<sub>2</sub>CH<sub>3</sub>), 3.90–4.10 (4H, m, OCH<sub>2</sub>CH<sub>3</sub>), 6.99 (1H, apparent t, *J* 4.4, *H*-4″), 7.18 (1H, d, *J* 7.5, *H*-3′), 7.33 (1H, d, *J* 3.4, *H*-3″), 7.46 (1H, d, *J* 4.8, *H*-5″), 7.50–7.70 (3H, m, *H*-2, *H*-4′ and *H*-5′), 8.01 (1H, d, *J* 7.5, *H*-6′) and 12.65 (1H, s, exch D<sub>2</sub>O, CO<sub>2</sub>H) ppm;  $\delta_{\rm C}$  (100.6 MHz):  $\delta$  16.1 (d, <sup>3</sup>*J*<sub>C</sub>-P 5.8, OCH<sub>2</sub>CH<sub>3</sub>), 61.3 (d, <sup>2</sup>*J*<sub>C</sub>-P 4.9, OCH<sub>2</sub>CH<sub>3</sub>), 61.8 (d, <sup>2</sup>*J*<sub>C</sub>-P 5.8, OCH<sub>2</sub>CH<sub>3</sub>), 126.6 (*C*-4″), 127.8 (*C*-1, <sup>1</sup>*J*<sub>C</sub>-P 188), 128.7 (*C*-5′), 130.6 (*C*-5″), 131.0 (*C*-6′), 131.3 (d, <sup>3</sup>*J*<sub>C</sub>-P 4.9, *C*-3′), 131.7 (d, <sup>3</sup>*J*<sub>C</sub>-P 4.9, *C*-1′), 132.6 (*C*-4′), 132.8 (*C*-3″), 134.1 (d, <sup>2</sup>*J*<sub>C</sub>-P 12.6, *C*-2), 135.7 (d, <sup>2</sup>*J*<sub>C</sub>-P 6.8, *C*-2′), 138.4 (d, <sup>3</sup>*J*<sub>C</sub>-P 25.3, *C*-2″) and 167.2 (CO<sub>2</sub>H) ppm;  $\delta_{\rm P}$  (162 MHz) 18.1 ppm.

# 4.7. Diethyl (*E*)-[1-o-carboxyphenyl-2-phenylvinyl]phosphonate 10

Following the general procedure, benzaldehyde (0.42 g; 4 mmol) gave a crude acidic product that was recrystallised from acetone to afford the title compound 10 (1.29 g; 89%) as a solid, mp 181-183 °C; [Found C 63.12, H 5.90%. C20H23O5P requires C 63.33, H 5.83%]; v<sub>max</sub> (N) 1716, 1615, 1593, 1570, 1201, 1162, 1139, 1061, 1031 cm<sup>-1</sup>;  $\delta_{\rm H}$  1.13–1.22 (6H, m, OCH<sub>2</sub>CH<sub>3</sub>), 3.90–4.05 (4H, m, OCH<sub>2</sub>CH<sub>3</sub>), 7.00-7.13 (3H, m, H-3', H-2" and H-6"), 7.15-7.25 (3H, m, H-3", H-4" and H-5"), 7.38 (1H, d,  ${}^{3}J_{H-P}$  24.6, H-2 vinyl), 7.48 (1H, t, J 7.5, H-5'), 7.54 (1H, t, J 7.5, H-4'), 7.95 (1H, d, J 7.5, H-6') and 12.80 (1H, s, exch D<sub>2</sub>O, CO<sub>2</sub>H) ppm;  $\delta_C$  (100.6 MHz) 16.1 (d,  ${}^{3}J_{C-P}$  5.8, OCH<sub>2</sub>CH<sub>3</sub>), 61.4 (d, <sup>2</sup>J<sub>C-P</sub> 5.8, OCH<sub>2</sub>CH<sub>3</sub>), 61.8 (d, <sup>2</sup>J<sub>C-P</sub> 5.8, OCH<sub>2</sub>CH<sub>3</sub>), 128.0 (C-5'), 128.3 (C-3" and C-5"), 128.8 (C-4"), 129.7 (C-2" and C-6"), 130.5 (C-3' and C-6'), 131.8 (d, <sup>3</sup>J<sub>C-P</sub> 3.9, C-1'), 131.83 (d, <sup>1</sup>J<sub>C-P</sub> 182.7, C-1), 132.3 (C-4'), 134.8 (d, <sup>3</sup>*J*<sub>C-P</sub> 22.4, C-1"), 136.5 (d, <sup>2</sup>*J*<sub>C-P</sub> 6.8, C-2'), 140.3 (d,  ${}^{2}J_{C-P}$  9.7, C-2) and 167.7 (CO<sub>2</sub>H) ppm;  $\delta_{P}$  (162 MHz) 17.9 ppm.

### **4.8.** Diethyl (*E*)-[1-(*o*-carboxyphenyl)-2-(4-methoxyphenyl) vinyl]phosphonate 11

From 4-methoxybenzaldehyde (0.54 g; 4 mmol) there was obtained the *title compound* **11** as a viscous oil (1.24 g; 79%) that very slowly solidified and that could then be recrystallised from EtOAc/ Et<sub>2</sub>O, mp 118–120 °C;  $\nu_{max}$  (N) 1711, 1616, 1605, 1571, 1178, 1128, 1052, 1024, 991 cm<sup>-1</sup>;  $\delta_{\rm H}$  1.16 (3H, t, *J* 7.0, OCH<sub>2</sub>CH<sub>3</sub>), 1.29 (3H, t, *J* 7.0, OCH<sub>2</sub>CH<sub>3</sub>), 3.69 (3H, s, –OCH<sub>3</sub>), 3.90–4.20 (4H, m, OCH<sub>2</sub>CH<sub>3</sub>), 6.75 (2H, d, *J* 8.8, *H*-3" and *H*-5"), 6.97 (2H, d, *J* 8.8, *H*-3" and *H*-5"), 7.09 (1H, d, *J* 8, *H*-3"), 7.31 (1H, d, <sup>3</sup>*J*<sub>P-H</sub> 24.6, *H*-2), 7.48 (1H, t, *J* 7.5, *H*-5'), 7.56 (1H, t, *J* 7.5, *H*-4'), 7.95 (1H, d, *J* 7, *H*-6') and 12.74 (1H, s, exch D<sub>2</sub>O, –CO<sub>2</sub>*H*) ppm;  $\delta_{\rm C}$  (100.6 MHz) 16.1 (d, <sup>3</sup>*J*<sub>P-C</sub> 5.8, CH<sub>3</sub>), 55.1 (OCH<sub>3</sub>), 61.2 (d, <sup>2</sup>*J*<sub>P-C</sub> 4.9, CH<sub>2</sub>), 61.7 (d, <sup>2</sup>*J*<sub>P-C</sub> 5.8, CH<sub>2</sub>), 113.8 (C-3") and C-5"), 127.3 (d,  ${}^{3}J_{P-C}$  23.3, C-1"), 128.0 (C-5'), 128.7 (d,  ${}^{1}J_{P-C}$  184.6, C-1), 130.5 (C-6'), 130.6 (d,  ${}^{3}J_{P-C}$  5.8, C-3'), 131.4 (C-2" and C-6"), 131.9 (d,  ${}^{3}J_{P-C}$  3.9, C-1'), 132.3 (C-4'), 136.8 (d,  ${}^{2}J_{P-C}$  6.8, C-2'), 140.1 (d,  ${}^{2}J_{P-C}$  10.7, C-2), 159.7 (C-4") and 167.7 (C=O) ppm;  $\delta_{P}$  (162 MHz) 18.6 ppm; HRMS (ESI): MH<sup>+</sup>, found 391.1314. C<sub>20</sub>H<sub>24</sub>O<sub>6</sub>P requires 391.1311.

# 4.9. Diethyl (*E*)-[1-(*o*-carbomethoxyphenyl)-2-(4-methoxyphenyl)vinyl]phosphonate 13

A portion of the acid 11 (1.0 g, 2.55 mmol) was dissolved in ethyl acetate and methylated using a slight excess of ethereal diazomethane. Column chromatography of the oily product afforded the *title compound* **13** as a colourless oil (0.36 g);  $v_{max}$  (L) 1726, 1604, 1572, 1180, 1130, 1051, 1026 cm<sup>-1</sup>;  $\delta_{\rm H}$  1.25 (6H, m, OCH<sub>2</sub>CH<sub>3</sub>), 3.74 (3H, s, OCH<sub>3</sub>), 3.77 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.08 (4H, m, OCH<sub>2</sub>CH<sub>3</sub>), 6.68 (2H, d, J 8.5, H-3" and H-5"), 6.98 (2H, d, J 8.5, H-2" and H-6"), 7.20 (1H, d, J 7.5, H-3'), 7.43 (1H, t, J 7.5, H-5') 7.47-7.60 (2H, m, H-2 and H-4') and 7.98 (1H, d, J 7.5, H-6') ppm;  $\delta_C$  (100.6 MHz):  $\delta$  15.8 (d,  ${}^{3}J_{C-P}$  6.8, OCH<sub>2</sub>CH<sub>3</sub>), 51.5 (CO<sub>2</sub>CH<sub>3</sub>), 54.7 (OCH<sub>3</sub>), 61.5 (d, <sup>2</sup>J<sub>C-P</sub> 5.8, OCH<sub>2</sub>CH<sub>3</sub>), 61.8 (d, <sup>2</sup>*J*<sub>C-P</sub> 6.8, OCH<sub>2</sub>CH<sub>3</sub>), 113.2 (*C*-3" and *C*-5), 127.1 (d, <sup>3</sup>*J*<sub>C-P</sub> 23.3, C-1"), 127.3 (d, <sup>1</sup>J<sub>C-P</sub> 186.6, C-1), 127.4 (C-5'), 130.3 (C-6'), 130.6 (d, <sup>4</sup>*J*<sub>C-P</sub> 5.8, C-3'), 131.0 (d, <sup>3</sup>*J*<sub>C-P</sub> 4.9, C-1'), 131.3 (C-2" and C-6"), 131.9 (C-4'), 136.4 (d, <sup>2</sup>J<sub>C-P</sub> 7.8, C-2'), 141.5 (d, <sup>2</sup>J<sub>C-P</sub> 10.7, C-2), 159.6 (C-4") and 167.1 (CO<sub>2</sub>CH<sub>3</sub>) ppm;  $\delta_P$  (162 MHz) 19.0 ppm; HRMS (ESI): MH<sup>+</sup>, found 405.1462. C<sub>21</sub>H<sub>26</sub>O<sub>6</sub>P requires 405.1468.

### **4.10.** Diethyl (*E*)-[1-(o-carboxyphenyl)-2-(4-fluorophenyl)vinyl]phosphonate 12

4-Fluorobenzaldehyde (0.5 g; 4 mmol) gave the title compound 12 as a viscous oil (1.31 g; 87%), which very slowly became a solid that could be recrystallised from CH<sub>2</sub>Cl<sub>2</sub>, mp 176–178 °C;  $\nu_{max}$  (N) 1711, 1615, 1593, 1569, 1201, 1162, 1139, 1060 cm<sup>-1</sup>;  $\delta_{\rm H}$  1.17 (3H, t, J 7.2, OCH<sub>2</sub>CH<sub>3</sub>), 1.31 (3H, t, J 7.2, OCH<sub>2</sub>CH<sub>3</sub>), 3.98–4.12 (2H, m, OCH<sub>2</sub>CH<sub>3</sub>), 4.16 (2H, apparent quintet, J 7.2, OCH<sub>2</sub>CH<sub>3</sub>), 6.82 (2H, apparent t, J 8.5, H-3" and H-5"), 7.00 (2H, dd, J 8.9 and 5.5, H-2" and H-6"), 7.13 (1H, d, J 7.5, H-3'), 7.43–7.55 (3H, m, H-2, H-4' and H-5') and 8.08 (1H, d, J 7.5, H-6) ppm;  $\delta_{C}$  (100.6 MHz) 15.7 (d,  ${}^{3}J_{C-P}$  6.8, OCH<sub>2</sub>CH<sub>3</sub>), 15.8 (d, <sup>3</sup>J<sub>C-P</sub> 6.8, OCH<sub>2</sub>CH<sub>3</sub>), 62.3 (d, <sup>2</sup>J<sub>C-P</sub> 5.8, OCH<sub>2</sub>CH<sub>3</sub>), 62.7 (d, <sup>2</sup>*J*<sub>C-P</sub> 5.8, OCH<sub>2</sub>CH<sub>3</sub>), 114.9 (d, <sup>2</sup>*J*<sub>C-F</sub> 22.2, C-3" and C-5"), 127.9 (d, <sup>5</sup>*J*<sub>C-P</sub> 2.9, *C*-5′), 129.4 (d, <sup>1</sup>*J*<sub>C-P</sub> 187.6, *C*-1), 130.1 (d, <sup>3</sup>*J*<sub>C-P</sub> 4.9, C-3'), 130.3 (dd, <sup>3</sup>*J*<sub>C-P</sub> 22.8 and <sup>4</sup>*J*<sub>C-F</sub> 3.4, C-1"), 131.0 (s, C-6'), 131.5 (d,  ${}^{3}J_{C-F}$  8.7, C-2" and C-6": C-1' obscured by these signals), 132.2 (s, C-4'), 135.2 (d, <sup>2</sup>*J*<sub>C-P</sub> 6.8, C-2'), 140.6 (d, <sup>2</sup>*J*<sub>C-P</sub> 10.7, C-2), 162.3 (d, <sup>1</sup>*J*<sub>C-F</sub> 250.7, C-4") and 169.3 (C=O) ppm;  $\delta_{\rm P}$  (162 MHz) 18.2 ppm;  $\delta_{\rm F}$ (376.4 MHz) -111.4 ppm; HRMS (ESI): MH<sup>+</sup>, found 379.1108. C<sub>19</sub>H<sub>21</sub>FO<sub>5</sub>P requires 379.1111.

# 4.11. Diethyl (*E*)-[1-(*o*-carbomethoxyphenyl)-2-(4-fluorophenyl)vinyl]phosphonate 14

A portion of **12** (0.74 g, 1.95 mmol) was dissolved in ethyl acetate and methylated using a slight excess of ethereal diazomethane. Column chromatography of the crude oily product afforded the *title compound* **14** as a colourless oil (0.45 g);  $v_{max}$  (L) 1726, 1622, 1601, 1570, 1192, 1161, 1132, 1051, 1024 cm<sup>-1</sup>;  $\delta_{\rm H}$  1.25 (6H, m, OCH<sub>2</sub>CH<sub>3</sub>), 3.78 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.08 (4H, m, OCH<sub>2</sub>CH<sub>3</sub>), 6.84 (2H, t, *J* 8.5, *H*-3" and *H*-5'), 7.03 (2H, dd, *J* 8.5 and 5.8, *H*-2" and *H*-6"), 7.18 (1H, d, *J* 7.5, *H*-3'), 7.40–7.70 (3H, m, *H*-2, *H*-4' and *H*-5') and 7.98 (1H, d, *J* 7.5, *H*-6') ppm;  $\delta_{\rm C}$  (100.6 MHz) 15.8 (d,  ${}^{3}J_{\rm C-P}$  5.8, OCH<sub>2</sub>CH<sub>3</sub>), 51.6 (s, CO<sub>2</sub>CH<sub>3</sub>), 61.6 (d,  ${}^{2}J_{\rm C-P}$  5.8, OCH<sub>2</sub>CH<sub>3</sub>), 61.9 (d,  ${}^{2}J_{\rm C-P}$  5.8, OCH<sub>2</sub>CH<sub>3</sub>), 114.9 (d,  ${}^{2}J_{\rm C-F}$  21.4, *C*-3" and *C*-5"), 127.6 (d,  ${}^{4}J_{\rm C-P}$  2.9, *C*-5'), 129.1 (part of d for C-1), 130.2–130.5 (m, C-3' and C-6'), 130.6–131 (m, C-1' and C-1"), 131.4 (d,  ${}^{3}J_{\rm C-F}$  8.7, *C*-2" and *C*-6") 131.9 (d,  ${}^{5}J_{\rm C-P}$  1.9, *C*-4'), 135.9 (d,  ${}^{2}J_{\rm C-P}$  6.8, *C*-2'), 140.5 (d,  ${}^{2}J_{\rm C-P}$  9.7, *C*-2), 162.2 (d,  ${}^{1}J_{\rm C-F}$  250.7, *C*-4") and 166.9 (CO<sub>2</sub>CH<sub>3</sub>) ppm;  $\delta_{\rm P}$  (162 MHz) 18.2 ppm;  $\delta_{\rm F}$  (376.4 MHz) –111.8 ppm; HRMS (ESI): MH<sup>+</sup>, found 393.1277. C<sub>20</sub>H<sub>23</sub>FO<sub>5</sub>P requires 393.1267.

### 4.12. Diethyl (*E*,*E*)-[1-*o*-carboxyphenyl-4-phenyl-buta-1,3-dienyl]phosphonate 15

From cinnamaldehyde (0.53 g; 4 mmol) there was obtained after recrystallisation from acetone the title compound 15 (0.82 g; 53%) as a solid, mp 184–186 °C; [Found C 64.19, H 6.11%. C<sub>20</sub>H<sub>23</sub>O<sub>5</sub>P requires C 64.17, H 6.15%]; v<sub>max</sub> (N) 1718, 1620, 1561, 1207, 1163, 1139, 1061, 1035 cm<sup>-1</sup>;  $\delta_{\rm H}$  1.15 (3H, t, J 7.0, OCH<sub>2</sub>CH<sub>3</sub>), 1.20 (3H, t, J 7.0, OCH<sub>2</sub>CH<sub>3</sub>), 3.90–4.05 (4H, m, OCH<sub>2</sub>CH<sub>3</sub>), 6.41 (1H, ddd, / 15.6, 11.0 and 2.5, H-3), 7.08 (1H, d, J 15.6, H-4), 7.12-7.24 (2H, m, H-2 and H-3'), 7.25-7.35 (5H, m, H-2", H-3", H-4", H-5" and H-6"), 7.50 (1H, dt, J 7.5, 7.5 and 1.0, H-5'), 7.61 (1H, t, J 7.5, H-4'), 7.91 (1H, d, J 7.5, H-6') and 12.78 (1H, s, exch D<sub>2</sub>O, CO<sub>2</sub>H) ppm;  $\delta_C$  (100.6 MHz) 16.1 (d,  ${}^{3}J_{C-P}$ 5.8, OCH<sub>2</sub>CH<sub>3</sub>), 61.3 (d, <sup>2</sup>J<sub>C-P</sub> 5.8, OCH<sub>2</sub>CH<sub>3</sub>), 61.7 (d, <sup>2</sup>J<sub>C-P</sub> 5.8, OCH<sub>2</sub>CH<sub>3</sub>), 123.8 (d, <sup>3</sup>*J*<sub>C-P</sub> 21.4, C-3), 126.9 (C-3" and C-5"), 128.0 (C-5'), 128.9 (C-2", C-4" and C-6"), 130.1 (C-6'), 131.0 (d, <sup>1</sup>J<sub>C-P</sub> 186.6, C-1), 131.1 (d, <sup>3</sup>*J*<sub>C-P</sub> 4.9, C-3'), 131.5 (C-4'), 132.2 (d, <sup>3</sup>*J*<sub>C-P</sub> 4.9, C-1'), 135.3 (d, <sup>2</sup>*J*<sub>C-P</sub> 7.8, C-2'), 135.9 (C-1"), 139.0 (C-4), 141.4 (d, <sup>2</sup>*J*<sub>C-P</sub> 9.7, C-2), 167.9 (CO<sub>2</sub>H) ppm; δ<sub>P</sub> (162 MHz) 17.9 ppm.

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