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α-Methylene β-amino phosphonic ester derivatives by amination of (1-trimethylsilanylmethyl-vinyl) phosphonic esters

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Abstract—(1-Trimethylsilanylmethyl-vinyl)-phosphonic esters are synthesised via Wittig–Horner reactions starting from methylenediphosphonic esters. The reactions of (1-trimethylsilanylmethyl-vinyl)-phosphonic esters with $NsONHCO_2Et$ and CaO, produce α-methylene *N*-(ethoxycarbonyl) β-amino phosphonic esters, isolated up to 60% yield, through addition of (ethoxycarbonyl) amine function on the double bond and silyl group elimination.

1. Introduction

Amino phosphonic acids and their derivatives have achieved an important role in many fields of chemistry.[1] They show a large variety of biological activity and applications in agriculture and medicine, and have been utilized as herbicides or pesticides,[2] antibacterial[3] or antiviral agents[4] and as enzyme inhibitors.[5]

A number of synthetic methods for the synthesis of α- or β-amino alkylphosphonates is reported.[6]

Recently we have focused our attention on the use of the ethyl *N*-{[(4-nitrobenzene)sulphonyl]oxy}carbamate ($NsONHCO_2Et$) **1** to aminate electron poor olefins as α,β-unsaturated esters[7] and nitro olefins[8] using an inorganic insoluble base such as CaO in CH_2Cl_2.

The reaction of γ-silylated α,β-unsaturated esters with **1** and CaO produced β,γ-unsaturated *N*-(ethoxycarbonyl) α-amino esters.[9]

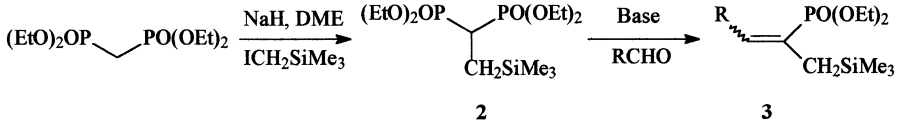
Recently starting from α,β-unsaturated phosphonic esters we obtained *N*-(ethoxycarbonyl)aziridine phosphonate, precursors of α or β-amino phosphonic acids.[10]

Our previous experience drove us to test the aziridination of (1-trimethylsilanylmethyl-vinyl) phosphonic esters with $NsONHCO_2Et$. The aziridine ring after elimination of the silyl group, would produce α-methylene β-amino phosphonic esters.

2. Results and discussion

We obtained substrates **3** by a Wittig–Horner reaction[11] (Scheme 1) starting from trimethylsilanylmethyl- tetraethylmethylenediphosphonates **2** and the corresponding aldehyde.

2 was obtained from tetraethylmethylenediphosphonate alkylated by iodomethyltrimethylsilane in the presence of NaH, according to the procedure used to alkylate the



2 **3**

Scheme 1. Synthesis of substrates **3**.

Keywords: amination; aziridines; phosphonic acids and derivatives; silicon and compounds.

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Table 1. Synthesis of substrate **3**: conditions and yields

Entry	R	Method	Reaction time (h)	**3** total yield (%)	*Z*/*E*
a	H	50% NaOH/CH_2Cl_2	6	84	–
b	CH_3	50% NaOH/CH_2Cl_2 TBAI	24	49	60/40
c	Ph	50% NaOH/CH_2Cl_2	6	53	30/70
d	$CH_3(CH_2)_4$	LDA/THF −78°C	2.5	69	58/42

triethylphosphonoacetate,[12] and purified by flash chromatography.

For **3a–c** the Wittig–Horner reaction was carried out in a two-phase system using 50% aqueous NaOH as base in CH_2Cl_2, for **3b** tetrabutylammonium iodide (TBAI) was necessary as a phase-transfer catalyst.

In the case of substrates **3d** we needed LDA in dry THF to obtain the desired product.[13] In all cases we obtained a mixture of *Z* and *E* isomers easily separated by flash-chromatography on silica gel with the reported ratio (Table 1).

The amination reactions on substrates **3** were carried out by adding $NsONHCO_2Et$ and CaO portion wise reaching the molar ratio and the time reported in Table 2. The reaction produces the aziridine ring **4** detected in the crude reaction mixture by ^1H NMR and GC-MS spectral data (Scheme 2).

By treating the crude reaction mixture with AcOH for 26 h, the silyl group was eliminated and the α-methylene β-amino phosphonic esters **5** were obtained.

The products were isolated by flash-chromatography on silica gel. The two isomers *E* and *Z* gave the same product; the *Z* isomers have been shown to be more reactive. The reaction of the *Z* isomers with $NsONHCO_2Et$ needed only four equivalents of reagent for the disappearance of the starting material and gave the isolated products **5** in higher yields (Table 2).

The aziridination reactions using Et_3N in homogenous solution of CH_2Cl_2,[14] conditions of generation of the (ethoxycarbonyl)nitrene, gave only traces of aziridines.

In summary, in this paper we have reported the route to obtain (1-trimethylsilanylmethyl-vinyl) phosphonic esters; these are allylsilanes, versatile intermediates utilised in organic synthesis.[15] Furthermore we have found a new synthetic route employing $NsONHCO_2Et$ for the preparation of α-methylene β-(ethoxycarbonyl) amino alkylphosphonates; these are important building blocks for the synthesis of phosphonopeptides in which α-methylene β-amino phosphonic acids are present, such as the antibiotic A53868A.[16] They could also be converted into β-amino phosphonic acids having the α position, functionality derived from a C=C double bond.

3. Experimental

3.1. General

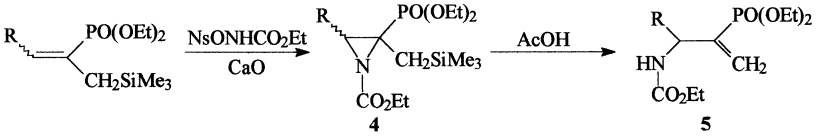
GC analyses were performed on a HP 5890 Series II gas chromatograph with a capillary column (methyl silicone, length 12.5 m, internal diameter 0.2 mm, film thickness 0.25 μm). GC-MS were done on a HP G1800A GCD system with a capillary column (phenyl methyl silicone, length 30 m, internal diameter 0.25 mm, film thickness 0.25 μm). Microanalyses were carried out on a CE Instruments EA1110. ^1H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ on a Gemini 200 spectrometer, with $CHCl_3$ as internal standard. ^{31}P NMR spectra were obtained in $CDCl_3$ on a Bruker AC 300 spectrometer, with H_3PO_4 as internal standard. IR spectra in CCl_4 were done by a Perkin–Elmer 1600 Series FTIR spectrometer.

3.2. Synthesis of [1-(diethoxy-phosphoryl)-2-trimethylsilanyl-ethyl]-phosphonic acid diethyl ester 2

To 60% NaH (0.88 g, 22 mmol; suspension in mineral oil) in dry DME (12 mL), tetraethylmethylenediphosphonate (5.8 g, 20 mmol) was added dropwise, under argon at 0°C.

Table 2. Synthesis of **5**: conditions and yields

Entry	R	Substrate: $NsONHCO_2Et$:CaO	Reaction time (h)	Substrate: AcOH	**5** total yield (%)
a	H	1:4:4	4	1:8	60
b (*Z*)	CH_3	1:4:4	5	1:8	51
b (*E*)	CH_3	1:8:8	24	1:10	42
c(*Z*)	Ph	1:10:10	30	1:10	35
c(*E*)	Ph	1:10:10	24	1:10	22
d(*Z*)	$CH_3(CH_2)_4$	1:4:4	5	1:8	61
d(*E*)	$CH_3(CH_2)_4$	1:8:8	24	1:10	41



Scheme 2. Synthesis of α-methylene β-amino phosphonic esters **5**.

After 0.5 h at room temperature, a solution of iodomethyltrimethylsilane (3.4 mL, 23 mmol) in DME (6 mL) was added and the resulting mixture was heated to 70°C. After being stirred for 3 h the mixture was poured into dilute aqueous ammonium chloride (60 mL) and the aqueous phase was extracted with diethyl ether. The combined organic phases were washed with brine and dried (Na_2SO_4). After evaporation of solvent the reaction mixture was purified by flash chromatography on silica gel (hexane: acetone=7:3) to obtain **2** as a yellowish oil (5g, 67% yield). GC-MS *m/z*: 374 (M^+ 0.3), 359(14), 237(100), 210(39), 165(64), 121(20), 109(20), 73(22); Anal. Calcd. for $C_{13}H_{32}O_6P_2Si$: C 41.70, H 8.61, Found: C 41.62, H 8.88; IR: $\nu_{P=O}$ 1250 cm^{-1}; ^1H NMR δ: 0.00 (s, 9 H, $SiCH_3$), 1.08 (td, 2 H, $SiCH_2$, J_{HH}=6.6 Hz, J_{HP}=18 Hz), 1.28 (t, 12 H, CH_2CH_3), 2.28 (tt, 1 H, CH, J_{HH}=6.6 Hz, J_{HP}=24.0 Hz), 4.02–4.22 (m, 8 H, OCH_2); ^{13}C NMR δ: −1.0 ($SiCH_3$), 11.2 (d, CH_2Si, J_{CCP}=6.1 Hz), 16.4 (d, CH_2CH_3, J_{CCOP}= 6.1 Hz), 32.0 (t, CH, J_{CP}=134.3 Hz), 62.4 (d, OCH_2, J_{COP}=6.1 Hz); ^{31}P NMR δ: 25.7.

3.3. Synthesis of 3a–c

To a stirred solution of the substrate **2** (5.35 mmol) in an heterogenous mixture of 50% aqueous sodium hydroxide (6 mL) and dichloromethane (6 mL), the aldehyde (5.50 mmol) was added dropwise. For **3a** a 30% formaldehyde aqueous solution was added. For **3b** the reaction was performed adding quaternary ammonium salt tetrabutylammonium iodide (TBAI) in catalytic amounts. The mixture was stirred for several hours, as reported in Table 1, then extracted with dichloromethane. The organic layer was dried (Na_2SO_4) and evaporated under vacuum. The mixture was purified by flash-chromatography on silica gel (hexane: ethylacetate=6:4) to yield the pure *Z* and *E* isomers in the ratio reported in Table 1.

3.3.1. (1-Trimethylsilanylmethyl-vinyl)-phosphonic acid diethyl ester 3a. Pale yellow oil, GC-MS *m/z*: 250 (M^+ 2), 235 (21), 207 (18), 193 (13), 182 (17), 179 (92), 177 (19), 167 (13), 165 (19), 155 (31), 153 (29), 139 (56), 138 (23), 137 (22), 123 (38), 122 (14), 120 (100), 75 (36), 73 (49), 45 (20); Anal. Calcd. for $C_{10}H_{23}O_3PSi$: C 47.98, H 9.26. Found: C 47.79, H 9.29. IR: $\nu_{P=O}$ 1251, $\nu_{C=C}$ 1556 cm^{-1}; ^1H NMR δ: 0.04 (s, 9 H, $SiCH_3$), 1.30 (t, 6 H, CH_2CH_3), 1.72 (d, 2 H, CH_2Si, J_{HP}=16.1 Hz), 4.05 (m, 4 H, OCH_2CH_3), 5.54 (d, 1 H, =CH, $J_{HP\ trans}$=49.8 Hz), 5.88 (d, 1 H, =CH, $J_{HP\ cis}$= 22.7 Hz); ^{13}C NMR δ: −1.3 ($SiCH_3$), 16.3 (d, CH_2CH_3, J_{CCOP}=6.3 Hz), 21.9 (d, CH_2Si, J_{CCP}=10.6 Hz), 61.6 (d, OCH_2CH_3, J_{COP}=6.0 Hz), 126.9 (d, $=CH_2$, J_{CCP}=10.0 Hz), 136.6 (d, =C, J_{CP}=171.5 Hz); ^{31}P NMR δ: 20.6.

3.3.2. (*Z*)-(1-Trimethylsilanylmethyl-propenyl)-phosphonic acid diethyl ester 3b. Pale yellow oil, GC-MS *m/z*: 264 (M^+, 3), 250 (13), 249 (84), 221 (30), 205 (16), 193 (96), 191(27), 187 (17), 155 (28),153 (15), 139 (46),138 (18), 137 (15), 135 (15), 123 (31), 121 (100), 83 (14), 77(13), 75 (47), 73 (76), 53 (16), 45 (29); Anal. Calcd. for $C_{11}H_{25}O_3PSi$: C 49.97, H 9.53. Found: C 49.85, H 9.52. IR: $\nu_{P=O}$ 1253, $\nu_{C=C}$ 1622 cm^{-1}; ^1H NMR δ: 0.00 (s, 9H, $SiCH_3$), 1.30 (t, 6H, CH_2CH_3, J_{HH}=7.3 Hz), 1.70 (d, 2 H, $SiCH_2$, J_{HP}=16.7 Hz), 2.00 (m, 3 H, $=CHCH_3$), 4.10 (m, 4 H, OCH_2), 6.08 (dq, 1 H, =CH, J_{HH}=7.3 Hz, $J_{HP\ trans}$= 54.0 Hz); ^{13}C NMR δ: −1.4 ($SiCH_3$), 16.2 (d, CH_2CH_3, J_{CCOP}=6.5 Hz), 16.3 (d, $=CHCH_3$, J_{CCCP}=7.6 Hz), 24.1 (d, CH_2Si, J_{CCP}=12.5 Hz), 60.4 (d, OCH_2, J_{COP}=6.0 Hz), 127.0 (d, =C, J_{CP}=171.1 Hz), 139.2 (d, =CH, J_{CCP}=11.5 Hz); ^{31}P NMR δ: 20.4.

3.3.3. (*E*)-(1-Trimethylsilanylmethyl-propenyl)-phosphonic acid diethyl ester 3b. Pale yellow oil, GC-MS *m/z*: 264 (M^+, 3), 250 (13), 248 (89), 221 (31), 205 (17), 193 (97), 191 (25), 187 (18), 177 (14), 165 (13), 154 (28), 153 (15), 139 (46), 138 (18), 137 (15), 123 (33), 121 (100), 83 (13), 77 (14), 75 (48), 73 (67), 53 (13), 45 (27); IR: $\nu_{P=O}$ 1250; $\nu_{C=C}$ 1622 cm^{-1}; Anal. Calcd. for $C_{11}H_{25}O_3PSi$: C 49.97, H 9.53. Found: C 49.88, H 9.46.^1H NMR: 0.05 (s, 9 H, $SiCH_3$), 1.35 (t, 6 H, CH_2CH_3, J_{HH}=7.3 Hz), 1.65–1.82 (m, 5 H, $CHCH_3$, $SiCH_2$), 3.98–4.20 (m, 4 H, OCH_2), 6.50 (dq, 1 H, =CH, J_{HH}=6.6 Hz, $J_{HP\ cis}$=27.0 Hz); ^{13}C NMR δ: −0.5 ($SiCH_3$), 14.9 (d, $=CHCH_3$, J_{CCCP}=20.8 Hz), 16.3 (d, CH_2CH_3, J_{CCOP}=6.4 Hz), 17.5 (d, $SiCH_2$, J_{CCP}=11.4 Hz) 61.3 (OCH_2, J_{COP}=6.0 Hz), 128.3 (d, =CP, J_{CP}= 178.7 Hz), 137.2 (d, =CH, J_{CCP}=11.4 Hz); ^{31}P NMR δ: 22.7.

3.3.4. (*Z*)-(2-Phenyl-1-trimethylsilanylmethyl-vinyl-)-phosphonic acid diethyl ester 3c. Pale yellow oil, GC-MS *m/z*: 326 (M^+, 13), 325 (20), 255 (13), 253 (14), 154 (15), 153 (12), 145 (48), 144 (16), 139 (21), 129 (18), 121 (45), 117 (13), 116 (31), 115 (100), 75 (32), 73 (54), 45(17); Anal. Calcd. for $C_{16}H_{27}O_3PSi$: C 58.87, H 8.34. Found: C 58.77, H 8.44. IR: $\nu_{P=O}$ 1239 cm^{-1}; ^1H NMR δ: 0.15 (s, 9 H, $SiCH_3$), 1.10 (t, 6 H, CH_2CH_3, J_{HH}=7.3 Hz), 1.95–2.10 (d, 2 H, J_{HP}=18 Hz, CH_2Si), 3.75–4.00 (m, 4 H, OCH_2CH_3), 7.00 (d, 1 H, =CH, $J_{HP\ trans}$=49 Hz), 7.22–7.55 (m, 5 H, Ph); ^{13}C NMR δ: −1.3 ($SiCH_3$), 15.9 (d, CH_2CH_3, J_{CCOP}=7.0 Hz), 26.4 (d, $SiCH_2$, J_{CCP}=12.4 Hz), 61.2 (d, OCH_2, J_{COP}= 7.0 Hz), 127.5 (CH arom), 128.9 (d, =CP, J_{CP}=172.1 Hz), 129.0 (CH arom.), 136.9 (d, C arom. J_{CCCP}=7.7 Hz), 140.6 (d, =CH, J_{CCP}=9.7 Hz); ^{31}P NMR δ: 18.7.

3.3.5. (*E*)-(2-Phenyl-1-trimethylsilanylmethyl-vinyl)-phosphonic acid diethyl ester 3c. Pale yellow oil, GC-MS *m/z*: 326 (M^+, 16), 325 (26), 311 (14), 255 (18), 253 (17), 154 (15), 145 (49), 144 (17), 138 (22), 129 (18), 121 (46), 117 (16), 116 (35), 115 (100), 75 (32), 73 (49), 45 (16), 43 (13); Anal. Calcd. for $C_{17}H_{27}O_3PSi$: C 58.87, H 8.34. Found: C 58.86, H 8.40. IR: $\nu_{P=O}$ 1237 cm^{-1}, $\nu_{C=C\ ring}$ 1596 cm^{-1}; ^1H NMR δ: 0.02 (s, 9 H, $SiCH_3$), 1.35 (t, 6 H, CH_2CH_3, J_{HH}=7.3 Hz), 2.04–2.18 (d, 2 H, $SiCH_2$, J_{HP}= 22.0 Hz), 4.04–4.22 (m, 4 H, OCH_2CH_3), 7.22–7.40 (m, 6 H, Ph and CH); ^{13}C NMR δ: −0,5 ($SiCH_3$), 16.3 (d, CH_2CH_3, J_{CCOP}=6.3 Hz), 18.2 (d, $SiCH_2$, J_{CCP}=9.7 Hz), 61.5 (d, OCH_2, J_{COP}=6.0 Hz), 127.8 (CH arom.), 128.2 (CH arom.), 129.3 (d, =CP, J_{CP}=175.4Hz), 136.3 (d, C arom. J_{CCCP}=24.4 Hz), 138.5 (d, =CH, J_{CCP}=12.2 Hz); ^{31}P NMR δ: 23.2.

3.4. Preparation of 3d

To a stirred solution of a 2M LDA (1.32 mL, 2.64 mmol) in dry THF (1.45 mL), 900 mg (2.4 mmol) of **2** in dry THF (0.80 mL) were added, under argon at −78°C. After 5 min the bath was heated to −20°C and exanal (0.32 mL, 2.6 mmol) in dry THF (0.80 mL) was added dropwise.

The mixture was stirred for 2.5 h at room temperature then treated with water (5 mL) and the aqueous phase was extracted with diethyl ether. The organic layer was dried (Na_2SO_4) and evaporated under vacuum. The mixture was purified by flash-chromatography on silica gel (hexane: ethylacetate=7:3) to yield the pure *Z* and *E* isomers in the ratio reported in Table 1.

3.4.1. (*Z*)-(1-Trimethylsilanylmethyl-hept-1-enyl)phosphonic acid diethyl ester 3d. Pale yellow oil, GC-MS *m/z*: 320 (M^+, 3), 305 (26),291 (28), 278 (14), 277 (47), 264 (32), 263 (37), 250 (189), 249 (100); 247 (20), 235 (14), 221 (15), 210 (27), 204 (26), 191 (45), 183 (17), 182 (15), 154 (15), 139 (20), 122 (24), 120 (81), 109 (18), 81 (13), 75(38), 73(82), 67(19), 45(17); Anal. Calcd. for $C_{15}H_{33}O_3PSi$: C 56.22, H 10.38. Found: C 56.34, H 10.52. IR: $\nu_{P=O}$ 1246, $\nu_{C=C}$ 1618 cm^{-1}; ^1H NMR δ: −0.01 (s, 9 H, $SiCH_3$), 0.82 (t, 3 H, CH_2CH_3, J_{HH}=7.3 Hz), 1.20–1.42 (m, 12 H, 3 CH_2, 2 OCH_2CH_3), 1.65 (d, 2 H, CH_2Si, J_{HP}=16.1 Hz), 2.40 (m, 2 H, CH_2CH=), 4.00 (m, 4 H, OCH_2), 5.90 (dt, 1 H, =CH, J_{HH}=6.6 Hz, $J_{HP\ trans}$=51.3 Hz); ^{13}C NMR δ: −1.4 ($SiCH_3$), 13.9 (CH_2CH_3), 16.2 (d,OCH_2CH_3, J_{CCOP}=6.6 Hz), 22.4 (CH_2), 24.1 (d, CH_2Si, J_{CCP}=12.8 Hz), 29.3 (CH_2), 30.3 (d, CH_2CH=, J_{CCCP}=6.9 Hz), 31.4 (CH_2), 60.9 (d, OCH_2, J_{COP}=5.8 Hz), 128.6 (d, =C, J_{CP}=171.6 Hz), 145.6 (d, =CH, J_{CCP}=12.2 Hz).

3.4.2. (*E*)-(1-Trimethylsilanylmethyl-hept-1-enyl)phosphonic acid diethyl ester 3d. Pale yellow oil, GC-MS (*m/z*): 320 (M^+, 3); 305 (26); 291 (28); 278 (14); 277 (47); 264 (33); 263 (38); 250 (18); 249 (100); 235 (14); 221 (15); 210 (28); 204 (20); 191 (44); 183 (18); 182 (16); 154 (16); 139 (22); 122 (28); 120 (94); 109 (14); 81 (15); 77 (13); 75 (48); 73 (91); 67 (20); 53 (13); 45 (21); 41 (13); Anal. Calcd. for $C_{15}H_{33}O_3PSi$: C 56.22, H 10.38. Found: C 56.22, H 10.50. IR: $\nu_{P=O}$ 1251, $\nu_{C=C}$ 1612 cm^{-1}; ^1H NMR δ: 0.01 (s, 9 H, $SiCH_3$), 0.85 (t, 3 H, CH_2CH_3, J_{HH}=7.3 Hz), 1.18–1.46 (m, 12 H, 3 CH_2, 2 OCH_2CH_3), 1.68 (d, 2 H, CH_2Si, J_{HP}=20.5 Hz), 2.02 (m, 2 H, CH_2CH=), 4.00 (m, 4 H, OCH_2), 6.35 (dt, 1 H, =CH, J_{HH}=6.6 Hz, $J_{HP\ cis}$=23.4 Hz); ^{13}C NMR δ: −0.5 ($SiCH_3$), 13.9 (CH_2CH_3), 16.2 (d, OCH_2CH_3, J_{CCOP}=6.4 Hz), 17.7 (d, CH_2Si, J_{CCP}=11.5 Hz), 22.4 (CH_2), 28.2 (CH_2), 29.1 (d, CH_2CH=, J_{CCCP}=19.6 Hz), 31.5 (CH_2), 61.2 (d, OCH_2, J_{COP}=5.9 Hz), 126.8 (d, =C, J_{CP}=177.4 Hz), 143.0 (d, =CH, J_{CCP}=10.4 Hz).

3.5. Reaction of 3 with $NsONHCO_2Et$

To a stirred solution of the substrate **3** (5.0 mmol) in CH_2Cl_2 (2.5 mL), $NsONHCO_2Et$ (5.0 mmol, 1 equiv.) and CaO (5.0 mmol, 1 equiv.), were added, every 30 min, reaching the molar ratio substrate: reagent reported in Table 2. During the addition the flask was cooled in water bath to avoid overheating, as the reaction is exothermic. After stirring (4–24 h, Table 2), 100 mL of a pentane–CH_2Cl_2 mixture (2:1) was added. After filtration, the organic phase was concentrated in vacuo and treated with AcOH (8–10 equiv., Table 2) for 26 h. The mixture was washed with aqueous sodium bicarbonate, then extracted with CH_2Cl_2 and dried (Na_2SO_4). The solvent was evaporated under vacuum and the products **5** were isolated by flash-chromatography on silica gel (hexane: acetone=7:3) in the yield reported in Table 2.

3.5.1. [1-(Ethoxycarbonylamino-methyl)-vinyl]-phosphonic acid diethyl ester 5a. Colorless oil, GC-MS *m/z*: 265 (M^+, 14), 220 (26), 192 (65), 177 (28), 164 (84), 156 (38), 149 (20), 148 (18), 146 (20), 137 (32), 136 (100), 135 (13), 129 (14), 128 (31), 121 (42), 120 (31), 118 (54), 109 (44), 107 (18), 100 (16), 91 (13), 84 (20), 82 (33), 81 (39), 65 (27), 57 (28), 56 (40), 55 (22), 54 (21); Anal. Calcd. for $C_{10}H_{20}NO_5P$: C 45.28, H 7.60, N 5.28. Found: C 45.01, H 7.72, N 5.15; IR: ν_{NH} 3446, $\nu_{C=O}$ 1727, $\nu_{P=O}$ 1254 cm^{-1}; ^1H NMR δ: 1.13–1.34 (2 t, 9 H, CH_3), 3.82–4.20 (m, 8 H, OCH_2, NCH_2), 5.34 (br, 1 H, NH), 5.90 (d, 1 H, =CH_2, $J_{HP\ trans}$=46.9 Hz), 6.05 (d, 1 H, =CH_2, $J_{HP\ cis}$=22.0 Hz); ^{13}C NMR δ: 14.4 (CH_2CH_3), 16.1 (d, CH_2CH_3, J_{CCOP}=6.3 Hz), 42.2 (d, NCH_2, J_{CCP}=15.2 Hz), 60.8 (OCH_2), 62.0 (d, OCH_2, J_{COP}=5.7 Hz), 129.7 (d, =CH_2, J_{CCP}=7.7 Hz), 136.3 (d, =C, J_{CP}=172.6 Hz), 156.3 (C=O); ^{31}P NMR δ: 18.0.

3.5.2. (2-Ethoxycarbonylamino-1-methylene-propyl)-phosphonic acid diethyl ester 5b. Colorless oil, GC-MS *m/z*: 279 (M^+, 2), 264 (100), 218 (13), 206 (38), 192 (22), 164 (24), 137 (30), 136 (48), 135 (33), 120 (17), 117 (22), 109 (23), 82 (14), 81 (15), 53 (16), 44 (18); Anal. Calcd. for $C_{11}H_{22}NO_5P$: C 47.31, H 7.94, N 5.02. Found: C 47.25, H 7.96, N 4.91; IR: ν_{NH} 3440, $\nu_{C=O}$ 1722, $\nu_{P=O}$ 1250 cm^{-1}; ^1H NMR δ: 1.20–1.48 (m, 12 H, CH_3), 4.00–4.20 (m, 6H, OCH_2), 4.40–4.70 (m, 1 H, CH), 5.32 (br, 1 H, NH), 5.82–6.14 (t, 2 H, =CH_2, $J_{HP\ trans}$=45.4 Hz, $J_{HP\ cis}$=21.2 Hz); ^{13}C NMR δ: 14.6 ($CHCH_3$), 16.2 (d, CH_2CH_3, J_{CCOP}=6.1 Hz), 21.3 (CH_2CH_3), 50.0 (d, CH, J_{CCP}=12.9 Hz), 60.7 (OCH_2), 62.0 (d, OCH_2, J_{COP}=6.0 Hz), 129.7 (=CH_2), 136.8 (d, =C, J_{CP}=170.0 Hz), 156.1 (CO); ^{31}P NMR δ: 18.0.

3.5.3. [1-(Ethoxycarbonylamino-phenyl-methyl)-vinyl]-phosphonic acid diethyl ester 5c. Colorless oil, GC-MS *m/z*: 341 (M^+, 26); 295 (22); 294 (21); 269 (13); 268 (100); 240 (15); 238 (13); 212 (13); 204 (14); 196 (19); 193 (22); 179 (15); 178 (47); 158 (14); 156 (18); 137 (32); 136 (30); 132 (25); 131 (19); 130 (31); 116 (25); 109 (35); 107 (16); 106 (30); 104 (14); 103 (24); 91 (19), 82 (20), 80 (24), 79 (18), 77 (36), 45 (16), 44 (85); Anal. Calcd. for $C_{16}H_{24}NO_5P$: C 56.30, H 7.09, N 4.10. Found: C 56.52, H 7.31, N 4.08; IR: ν_{NH} 3358, $\nu_{C=O}$ 1733, $\nu_{P=O}$ 1254 cm^{-1}, ^1H NMR δ: 1.05 (t, 3 H, CH_2CH_3), 1.20–1.38 (m, 6 H, CH_2CH_3), 3.60–4.20 (m, 6 H, OCH_2), 5.60 (dd, 1 H, CH, J_{HH}=8.0 Hz, J_{HP}=17.6 Hz), 5.90 (br, 1 H, NH), 6.08 (d, 1 H, =CH_2, $J_{HP\ trans}$=44.7 Hz), 6.18 (d, 1 H, =CH_2, $J_{HP\ cis}$=21.2 Hz), 7.20–7.42 (m, 5 H, Ph); ^{13}C NMR δ: 15.5 (CH_3), 16.1 (d, CH_3, J_{CCOP}=5.8 Hz), 57.6 (d, CH, J_{CCP}=13.4 Hz), 61,1 (OCH_2), 61.9 (d, OCH_2, J_{COP}=6.1 Hz), 126.9 (CH arom.), 127.7 (CH arom.), 128.5 (CH arom.), 129.5 (d, =C, J_{CP}=170.9 Hz), 139.2 (=CH_2), 155.6 (C=O); ^{31}P NMR δ: 17.2.

3.5.4. (2-Ethoxycarbonylamino-1-methylene-heptyl)-phosphonic acid diethyl ester 5d. Colorless oil, GC-MS *m/z*: 335 (M^+, 0.08), 264 (100), 218 (13), 192 (20), 164 (18), 145 (12), 136 (26), 117 (25), 109 (14); Anal. Calcd. for $C_{15}H_{30}NO_5P$: C 53.72, H 9.02, N 4.18. Found: C 53.73, H

8.94, N 4.14; IR: ν_{NH} 3444, $\nu_{C=O}$1722, $\nu_{P=O}$1248 cm^{-1}; ^1H NMR δ: 0.88 (t, 3 H, CH_3), 1.15–1.42 (m, 15 H, 3 CH_2, 3 CH_3), 1.55–1.80 (m, 2 H, CH_2), 3.85–4.49 (m, 7 H, 3 OCH_2, CH), 5.42 (br, 1 H, NH), 5.91 (d, 1 H, $=CH_2$, $J_{HP\ trans}$= 46.1 Hz), 6.00 (d, 1 H, $=CH_2$, $J_{HP\ cis}$=21.2 Hz); ^{13}C NMR δ: 14.0 (CH_3), 15.5 (CH_3), 16.1 (d, CH_3, J_{CCOP}=6.6 Hz), 22.4 (CH_2), 25.7 (CH_2), 31.3 (CH_2), 34.6 (CH_2), 55.0 (d, CH, J_{CCP}=11.6 Hz), 60.6 (OCH_2), 62.0 (d, OCH_2, J_{COP}=6.0 HZ), 130.2 (d, $=CH_2$, J_{CCP}=9.4 Hz), 139.9 (d, =C, J_{CP}= 169.6 Hz); 155.8 (C=O).

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