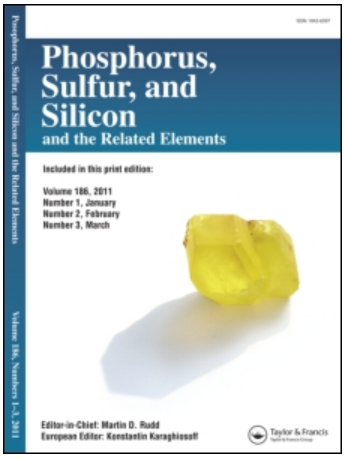

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EFFICIENT SYNTHESIS OF α-ENAMINOPHOSPHONATES IN THE SERIES OF PIPERIDINE AND MORPHOLINE. Examples of synthetic applications

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EFFICIENT SYNTHESIS OF α-ENAMINOPHOSPHONATES IN THE SERIES OF PIPERIDINE AND MORPHOLINE

Examples of Synthetic Applications

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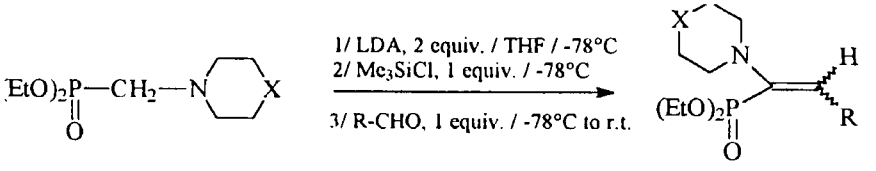
Various α-piperidino or α-morpholino alkenylphosphonates are conveniently prepared from the related α-hetero-substituted methylphosphonates, through a Peterson olefination process, which can be easily adapted for a direct homologation of aldehydes into carboxylic acids. An efficient synthesis of α-piperidino or α-morpholino alkylphosphonates and phosphonic acids is proposed.

Keywords: Peterson reaction; homologation of aldehydes into carboxylic acids; α-piperidino or α-morpholino alkenylphosphonates; α-piperidino or α-morpholino alkylphosphonates; α-piperidino or α-morpholino alkylphosphonic acids

INTRODUCTION

α-Phosphonylated enamines are useful intermediates in organic chemistry.[1,2] For example, their lithiated derivatives proved to be effective masqued homoenolate anions of carboxylic acids;[3,4] on the other hand, they have been employed as interesting precursors of α-amino alkylphosphonic acids.[5] Known since some decades ago, these attractive compounds generally require multi-step processes for their preparations, which were reviewed by Ahlbrecht and Farnung.[6]

*Corresponding author.



1a (X = CH_2) or **1b** (X = O) **2**

Pursuing our work on the synthetic applications of *in situ* generated α-phosphonylated α-silylated lithiated anions[7–9], we describe here an efficient and (*Z*)-stereoselective synthesis of 1-(diethylphosphono)enamines **2** from diethyl 1-piperidino or 1-morpholinomethylphosphonates **1a** or **1b**, by a one-pot process using a Peterson reaction as a key step (Scheme 1).

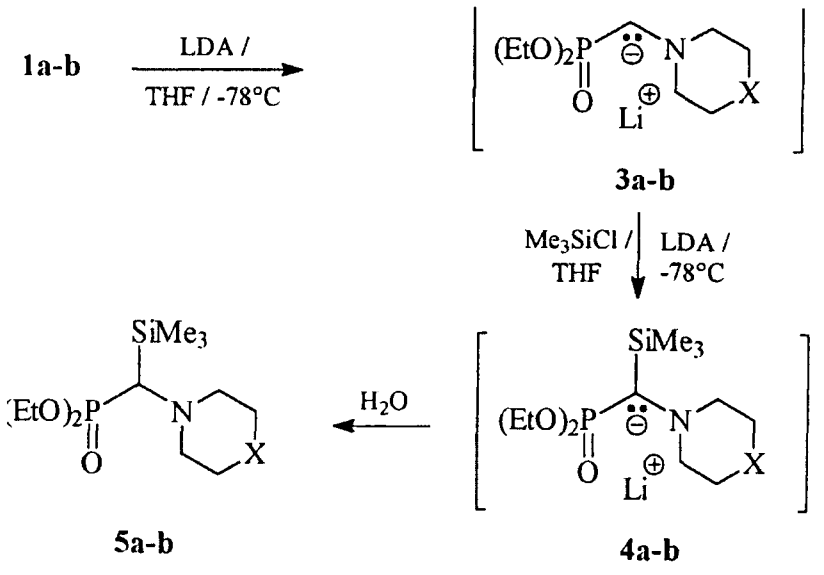
This strategy was then applied to a one-pot homologation reaction of aldehydes into carboxylic acids. Finally, phosphonoenamines **2** were used for preparing new α-amino phosphonic acids in the series of piperidine and morpholine.

RESULTS AND DISCUSSION

Synthesis of 1-(Diethylphosphono)enamines 2 from Phosphonates 1a or 1b

When treated at low temperature with an excess of lithium diisopropylamide (LDA), the readily available[10] phosphonates **1** were easily transformed into their lithiated derivatives **3**, as proved by ^{31}P NMR spectroscopy [δ (THF) = 48.2 and 47.8 for **3a** and **3b**, respectively]. Subsequent addition of trimethylchlorosilane at the same temperature led to the *in situ* formation of the α-silylated lithiated anions **4**, as proved by ^{31}P analysis [δ (THF) = 52.5 and 53.0 for **4a** and **4b**, respectively],[11] and by isolation and characterization (see Experimental Part) of the corresponding α-trimethylsilylated phosphonates **5** obtained from the lithiated intermediates **4**, upon hydrolysis at room temperature (Scheme 2).

Moreover, when an aldehyde was added slowly at $-78°C$ to α-silylated lithiated anions **4**, prepared as in Scheme 2, an exothermic reaction took place, leading to enamino phosphonates **2**, resulting from the Peterson olefination process. Phosphonates **2** were obtained in good isolated yield and with high (*Z*)-stereoselectivity (Table I). The stereochemistry of compounds **2** was assigned according to the $^3J_{H-C=C-P}$ coupling constant measurements in their ^1H NMR spectra:[12,13] $^3J_{HP}$ values vary from 45 to 37 Hz for (*Z*)-isomers and from 16 to 11 Hz for (*E*)-isomers (see Experimental Part). Moreover, in ^{31}P NMR spectra



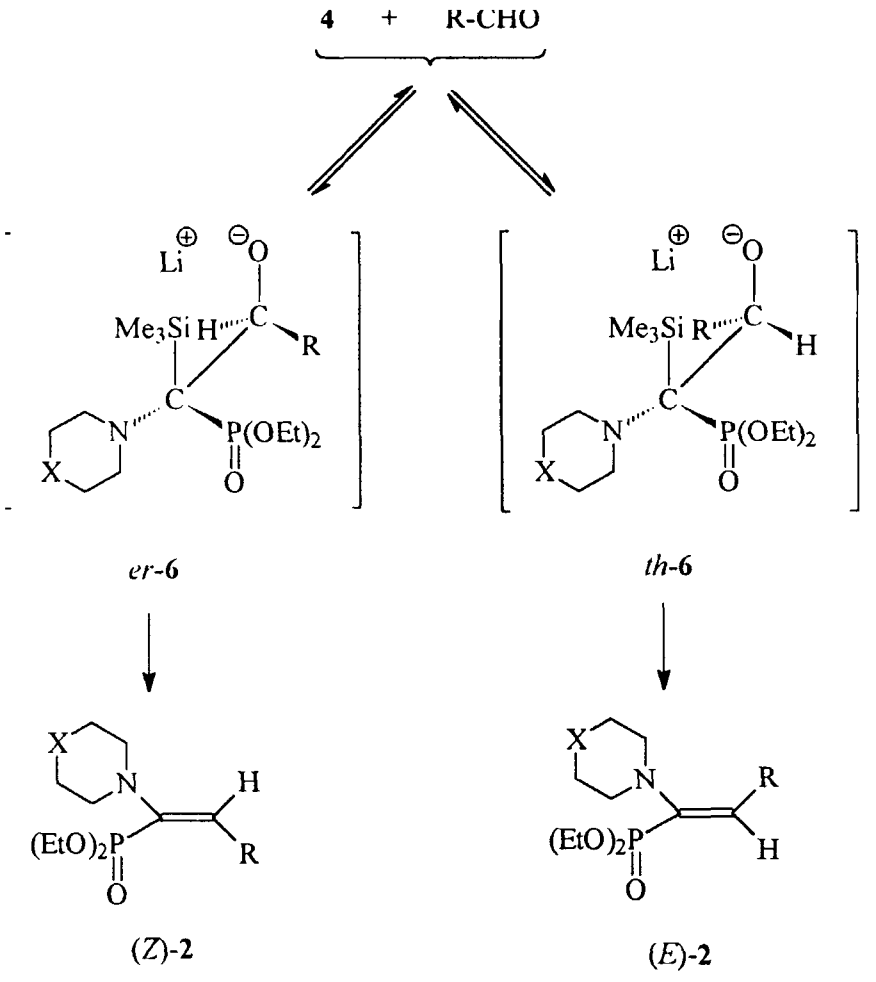
of compounds **2**, the signal of the (*Z*)-isomer appeared 1.6 to 4.1 ppm up field from the one of (*E*)-isomer (Table I).

The (*Z*)-stereoselectivity of this Peterson process might be explained by the fast decomposition of the hindered *erythro*-adduct *er*-**6**, leading to the enaminophosphonate (*Z*)-**2**, after *syn*-elimination of the oxophilic silylated moe-

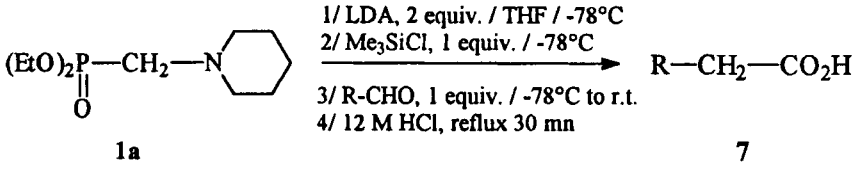
TABLE I Synthesis and ^{31}P NMR Data of Compounds **2**

Product	*X*	*R*	*Z:E*[a]	*^{31}P NMR ($CDCl_3$, δ_{ppm})*		*Yield %*[b]
				Z	*E*	
2a	CH_2	Ph	95:5	12.5	16.0	68
2b	CH_2	4-Me-C_6H_4	95:5	11.5	15.6	70
2c	CH_2	4-MeO-C_6H_4	94:6	12.5	16.1	66
2d	CH_2	2-Cl-C_6H_4	90:10	10.5	13.5	70
2e	CH_2	3,4-OCH_2O-C_6H_3	90:10	13.1	16.6	68
2f	CH_2	(*E*)-C_6H_5-CH=CH	80:20	13.5	15.5	60
2g	CH_2	i-Pr	80:20	13.8	15.7	62
2h	O	Ph	95:5	11.2[c]	14.7[c]	68
2i	O	4-MeO-C_6H_4	93:7	11.7	15.5	70
2j	O	i-Pr	85:15	13.5	15.1	60

[a]Ratio determined on the crude product, by ^{31}P NMR integration measurements.
[b]Yield of isolated product, purified by column chromatography over neutral alumine (eluent:hexane/diethyl ether).
[c]Values of 14.9 (for the *Z*-isomer) and 16.5 (for the *E*-isomer) were reported.[17]



ity.[14,15] On the other hand, the predominant formation of the *erythro*-adduct *er*-**6** seems to be in agreement with the favoured approach of the carbanion **4** to the carbonyl compound,[16] namely with the smallest ligand on the carbanion (the amino moiety, in this case), pointing down between the two groups of the carbonyl, and with the trimethylsilyl group on the opposed side of the R group of the aldehyde; moreover, the small quantity of phosphonate (*E*)-**2** present in the mixture would result from the decomposition of the *threo*-adduct *th*-**6** (Scheme 3). To the best of our knowledge, very few examples of α-phosphonylated enamines in the piperidine or in the morpholine series were described in the chemical literature: in 1977, Ahlbrecht *et al*[6] prepared one compound **2** (R



1a **7**

= Me, X = CH_2) by thermal extrusion of methylsulfide from the corresponding diethyl 1-(methylthio)-1-piperidino-propylphosphonate; in 1981, Costisella *et al*[17] isolated **2h**, in 46% yield, as a product of Horner-Emmons reaction between morpholinomethane-*bis*-phosphonic acid tetraethylester and benzaldehyde. In both of above examples, mixtures of geometrical isomers were obtained, but corresponding (*E*):(*Z*) ratios were not given.

One-pot Homologation of Aldehydes into Carboxylic Acids

Homologation of carbonyl compounds by means of acyl anion equivalents is a very useful strategy in organic chemistry. Carbanions stabilized by a phosphorus group and bearing another α-heteroatom substituent represent an important class of such synthons.[18,19] In this way, carbanions of *N*-substituted aminomethylphosphonates, substituted at the α-position by a stabilizing aryl or heteroaryl group, were used in order to transform aromatic aldehydes into ketones of the desoxybenzoin series, *via* intermediate enamines resulting of the Horner-Emmons reaction.[20] Moreover, Costisella *et al*,[17] then Ahlbrecht *et al*[4] studied acidic hydrolysis of α-phosphonylated enamines in order to prepare the corresponding carboxylic acids. First authors showed that α-ketophosphonate was a reaction intermediate in the hydrolytic pathway using diluted aqueous HCl; the second ones described the direct transformation of phosphonoenamines into carboxylic acids using concentrated HCl or 48% HBr, under reflux.

In this work, we decided to examine the feasibility of an *in situ* hydrolysis of enamines **2** resulting of the Peterson reaction. Such a process offered the advantage of realizing the direct and one-pot transformation of an aldehyde into the carboxylic acid **7** containing one more carbon atom. We investigated this process in the piperidine series[21] (Scheme 4). Enamines **2**, prepared as described in Scheme 1, were not isolated from the reaction mixture, but they were subsequently hydrolyzed with concentrated HCl, under reflux for 30 mn. After usual work-up, carboxylic acids **7** were purified by acid-base double extraction and isolated in fair yields (Table II), similar to those reported by Gross *et al*, who achieved an analog homologation of aldehydes into carboxylic acids, but using a two-step process.[22]

TABLE II One-pot synthesis of carboxylic acids **7** from aldehydes R-CHO

Product	*R*	*Yield %*[a]
7a	Ph	55
7b	4-Me-C_6H_4	55
7c	4-MeO-C_6H_4	52
7d	2-Cl-C_6H_4	50
7e	3,4-OCH_2O-C_6H_3	58
7f	i-Pr	45

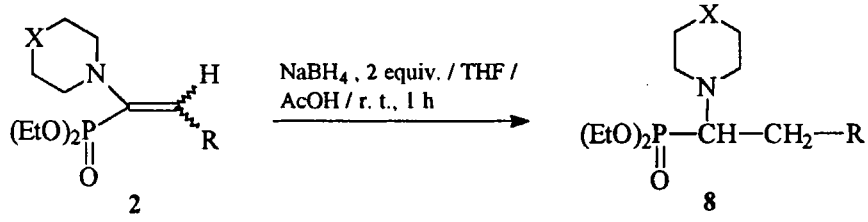
[a]Yield in purified product, whose physical data were in agreement with reported values (Aldrich catalogue).

Synthesis of α-Piperidino or α-Morpholino Alkylphosphonic Acids

Phosphonic acid analogs of α-amino carboxylic acids, α-amino alkylphosphonic acids and derivatives have found increasing interest due to their potential or established biological activity.[23] As in the carboxylic series, the most potent active compounds are concerned with amino acids having a primary, or more rarely a secondary amino group. Few examples of amino phosphonic acids bearing tertiary amino group are cited, but some of these compounds have shown fungicidal[24] or anti-viral[25] activities. Moreover, some alkylphosphonates substituted in the α-position by a piperidino,[26] a morpholino[27] or a 1,4-tetrahydrothiazino[28] group have found applications as sequestering agents or for their fungicidal activity. They have already been prepared in our laboratory from silylated phosphites and nitrogen derivatives of aldehydes.[29,30]

Enamines **2** appeared to be useful dehydro-precursors of α-piperidino or α-morpholino alkylphosphonic acids. Their reduction was easily achieved using two equivalents of sodium borohydride, in THF and in the presence of glacial acetic acid as protonating agent, leading to the expected diethyl α-piperidino or α-morpholino alkylphosphonates **8** in good yield (Scheme 5 and Table III). Results were not improved by using sodium cyanoborohydride in methanol as reducting system.[31]

Finally, phosphonates **8** were hydrolyzed with aqueous concentrated hydrochloric acid, by heating under reflux for 7 h. After usual work-up, the correspond-



2 **8**

TABLE III Synthesis and ^{31}P NMR Data of Compounds **8**

Product	*X*	*R*	*^{31}P NMR ($CDCl_3$, δ_{ppm})*	*Yield %*[a]
8a	CH_2	Ph	24.7	66
8b	CH_2	4-Me-C_6H_4	25.6	68
8c	CH_2	4-MeO-C_6H_4	25.6	70
8d	CH_2	2-Cl-C_6H_4	25.0	72
8e	CH_2	3,4-OCH_2O-C_6H_3	22.2	68
8f	CH_2	(*E*)-C_6H_5-CH=CH	25.3	64
8g	CH_2	i-Pr	27.0	78
8h	O	Ph	24.0	68
8i	O	4-MeO-C_6H_4	24.1	59
8j[b]	O	i-Pr	26.0	52

[a]Yield of isolated product, purified by acid-base double extraction. Purity controlled by ^{31}P, ^1H NMR spectroscopy and by C, H, N elemental microanalysis.
[b]Product **8j** has been prepared by reaction of diethyl phosphite with 2-methyl-1-morpholino-prop-1-ene, but not any data was given.[27]

ing α-piperidino or α-morpholino alkylphosphonic acids **9** were isolated in good yield (Scheme 6 and Table IV).

CONCLUSION

In summary, this paper describes a new and valuable synthesis of α-piperidino or α-morpholino alkenylphosphonates, based on the Peterson olefination strategy. This methodology has been conveniently adapted, first for an one-pot homologation of aldehydes into carboxylic acids, and secondly for the preparation of a new series of α-piperidino or α-morpholino substituted phosphonic acids.

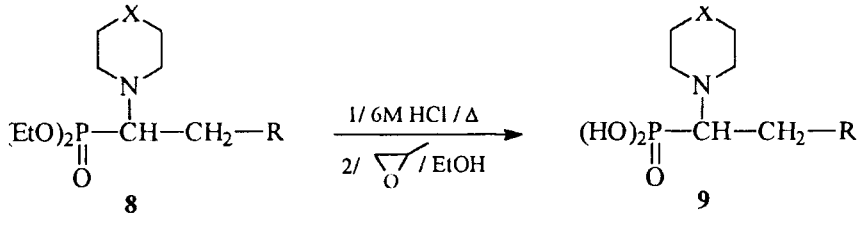


TABLE IV Synthesis, ^{31}P NMR and Physical Data of Compounds **9**

Product	*X*	*R*	*^{31}P NMR ($CDCl_3$, δ_{ppm})*	*Yield %*[a]	*Mp °C*
9a	CH_2	Ph	11.0	70	264
9b	CH_2	4-Me-C_6H_4	13.1	75	254
9c	CH_2	4-MeO-C_6H_4	13.1	80	250
9d	CH_2	2-Cl-C_6H_4	12.3	71	248
9e	CH_2	3,4-OCH_2O-C_6H_3	13.0	75	260
9f	CH_2	(*E*)-C_6H_5-CH=CH	12.7	70	>265
9g	CH_2	i-Pr	14.1	72	255
9h	O	Ph	11.5	60	228
9i	O	4-MeO-C_6H_4	11.8	62	238
9j	O	i-Pr	13.0	61	240

[a]Yield of isolated product, purified by crystallization from mixture ethanol/water (95/5). Purity controlled by ^{31}P, ^{1}H NMR spectroscopy and by C, H, N elemental microanalysis.

EXPERIMENTAL

Materials

Starting phosphonates **1a** and **1b** were prepared as previously reported.[10] Commercially available chemicals were obtained from Aldrich and used without further purification. Tetrahydrofuran (THF) was dried by distillation under N_2 from sodium benzophenone.

General Methods

NMR spectra were recorded on a Bruker AC 200 spectrometer at 200 MHz for ^{1}H, in reference to tetramethylsilane as an internal standard and at 81.01 MHz for ^{31}P, in reference to 85% H_3PO_4 as an external standard. All chemical shifts (δ) are expressed in ppm; the coupling constants (J) are given in Hz; conventional abreviations are used. Gas chromatography (GC) was performed on a Varian 3300 chromatograph equipped with a 15m OV-101 column. TLC was carried out using Merck 60 F-254 silica gel plates. Flash-chromatography was carried out over 230–400 mesh silica gel or over 50–200 mesh neutral alumina. Elemental microanalyses were performed on a Carlo Erba 1106 analyzer. Mass spectra were obtained with a GC-MS Hewlet Packard 5970 spectrometer; only significative peaks are reported, their relative abundance, in percent, is given in parentheses. All metallation reactions were carried out under dry inert gas.

Formation of α-silylated anions 4

To a 2.5 M solution of BuLi in hexanes (44 mL, 0.11 mol) and THF (40 mL) at −78°C, was added dropwise a solution of diisopropylamine (11.1 g, 0.11 mol) in THF (40 mL). After stirring for 15 mn, a solution of phosphonate **1** (0.05 mol) in THF (20 mL) was added dropwise at the same temperature. The mixture was stirred for about 30 mn until the complete formation of lithiated derivative **3**, then a solution of chlorotrimethylsilane (7 mL, 0.11 mol) in THF (5mL) was added at −78°C and stirring was continued for about 30 mn until the complete formation of lithiated derivative **4**. Formation of carbanions **3** and **4** was monitored by ^{31}P NMR spectroscopy.

Syntheses of α-trimethylsilylated phosphonates 5

The solution of lithiated derivative **4** obtained as described above was treated with water (20 mL). The aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, then concentrated under reduced pressure giving a pale yellow oil. The crude product was purified by column chromatography over neutral alumina (eluent: diethyl ether).

Diethyl (1-piperidino)trimethylsilylmethylphosphonate **5a**: Pale yellow oil. Yield = 75%. ^{31}P NMR ($CDCl_3$): 28.5. ^1H NMR ($CDCl_3$): 0.2 (s, 9H); 1.3 (t, J = 7, 6H); 1.5 (m, 6H); 2.6 (m, 4H); 2.8 (d, J = 11, 1H); 4.2 (qi, J = 7, 4H). MS: 307 (M^+, 7), 278 (100), 170 (84), 96 (97).

Diethyl (4-morpholino)trimethylsilylmethylphosphonate **5b**: Pale yellow oil. Yield = 72%. ^{31}P NMR ($CDCl_3$): 27.6. ^1H NMR ($CDCl_3$): 0.2 (s, 9H); 1.4 (t, J = 7, 6H); 2.6 (m, 4H); 2.7 (d, J = 11, 1H); 4.2 (qi, J = 7, 4H); 3.7 (m, 4H).

Syntheses of enamino phosphonates 2

To the solution of lithiated derivative **4** obtained as described above, was added slowly, at −78°C, a solution of aldehyde (0.11 mol) in THF (5 mL), and stirring was continued at the same temperature for 30 mn. The resulting mixture was gradually warmed to room temperature, then treated with water (20 mL). After usual work-up, the crude product was purified by colum chromatography over neutral alumina (eluent: hexane/diethyl ether mixtures, in gradient) leading to pure enamino phosphonate **2**, isolated as pale yellow oily product.

Diethyl 2-phenyl-1-(1-piperidino)-ethenylphosphonate **2a**, as a 95/5 mixture of (*Z*)/(*E*) isomers. ^1H NMR ($CDCl_3$): 1.2 (*Z*) & 1.4 (*E*) (2t, J = 7, 6H); 1.5 to 1.7 (m, 6H); 2.6 to 3.1 (m, 4H); 4.2 (qi, J = 7, 4H); 6.4 (*Z*) & 6.7 (*E*) [2d,

J = 37 (*Z*) & 11 (*E*), 1H]; 7.4 (br. s, 5H). MS: 323 (M^+, 76), 186 (100), 84 (89).

Diethyl 2-(4-methylphenyl)-1-(1-piperidino)-ethenylphosphonate **2b**, as a 95/5 mixture of (*Z*)/(*E*) isomers. ^{1}H NMR ($CDCl_3$): 1.2 (*Z*) & 1.4 (*E*) (2t, J = 7, 6H); 1.5 to 1.7 (m, 6H); 2.3 (s, 3H); 2.8 to 3.1 (m, 4H); 3.8 (*Z*) & 3.9 (*E*) (2qi, J = 7, 4H); 6.4 (*Z*) & 6.8 (*E*) [2d, J = 37 (*Z*) & 11 (*E*), 1H]; 7.1 to 7.3 (m, 4H).

Diethyl 2-(4-methoxyphenyl)-1-(1-piperidino)-ethenylphosphonate **2c**, as a 94/6 mixture of (*Z*)/(*E*) isomers. ^{1}H NMR ($CDCl_3$): 1.1 (*Z*) & 1.2 (*E*) (2t, J = 7, 6H); 1.4 to 1.6 (m, 6H); 2.5 to 2.9 (m, 4H); 3.6 (*Z*) & 3.7 (*E*) (2s, 3H); 3.8 (*Z*) & 3.9 (*E*) (2qi, J = 7, 4H); 6.4 (*Z*) & 6.7 (*E*) [2d, J = 38 (*Z*) & 11 (*E*), 1H]; 6.7 to 7.6 (m, 4H). MS: 353 (M^+, 95), 216 (100), 190 (50), 132 (29), 84 (63).

Diethyl 2-(2-chlorophenyl)-1-(1-piperidino)-ethenylphosphonate **2d**, as a 90/10 mixture of (*Z*)/(*E*) isomers. ^{1}H NMR ($CDCl_3$): 1.2 (*Z*) & 1.4 (*E*) (2t, J = 7, 6H); 1.5 to 1.7 (m, 6H); 2.8 to 3.1 (m, 4H); 3.8 (*Z*) & 4.0 (*E*) (2qi, J = 7, 4H); 6.4 (*Z*) & 6.8 (*E*) [2d, J = 38 (*Z*) & 11 (*E*), 1H]; 7.1 to 7.6 (m, 4H).

Diethyl 2-(3,4-methylenedioxyphenyl)-1-(1-piperidino)-ethenylphosphonate **2e**, as a 90/10 mixture of (*Z*)/(*E*) isomers. ^{1}H NMR ($CDCl_3$): 1.2 (*Z*) & 1.4 (*E*) (2t, J = 7, 6H); 1.5 to 1.7 (m, 6H); 2.8 to 3.1 (m, 4H); 3.8 (*Z*) & 4.0 (*E*) (2qi, J = 7, 4H); 5.9 (s, 2H); 6.4 (*Z*) & 6.8 (*E*) [2d, J = 37 (*Z*) & 11 (*E*), 1H]; 6.8 to 7.0 (m, 3H).

Diethyl (E)-4-phenyl-1-(1-piperidino)-buta-1,3-dienylphosphonate **2f**, as a 80/20 mixture of *1-(Z)/1-(E)* isomers. ^{1}H NMR ($CDCl_3$): 1.2 (*Z*) & 1.3 (*E*) (2t, J = 7, 6H); 1.5 (m, 6H); 2.5 to 2.9 (m, 4H); 3.9 (*Z*) & 4.1 (*E*) (2qi, J = 7, 4H); 6.3 to 6.9 (m, 3H); 6.9 to 7.2 (m, 5H).

Diethyl 3-methyl-1-(1-piperidino)-but-1-enylphosphonate **2g**, as a 80/20 mixture of (*Z*)/(*E*) isomers. ^{1}H NMR ($CDCl_3$): 0.8 (d, J = 6, 6H); 1.1 (*Z*) & 1.2 (*E*) (2t, J = 7, 6H); 1.2 to 1.4 (m, 6H); 2.5 to 2.8 (m, 4H); 2.9 (m, 1H); 3.8 (*Z*) & 4.0 (*E*) (2qi, J = 7, 4H); 5.2 (*Z*) & 5.8 (*E*) [2dd, J = 43, J' = 11 (*Z*) & J = 13, J' = 11 (*E*), 1H]. ^{13}C NMR ($CDCl_3$): 15.7 (*Z*) & 16.0 (*E*) [2d, J = 7 (*Z*) & 6.2 (*E*)]; 21.6 (*E*) & 22.6 (*Z*) (2d, J = 2); 23.4 (*Z*) & 23.5 (*E*), 2s; 25.7 (*Z*) & 26.0 (*E*), 2s; 26.8 (d, J = 10); 52.3 (*Z*) & 53.7 (*E*) [2d, J = 5 (*Z*) & 3 (*E*)]; 60.6 (*E*) & 61.0 (*Z*) (2d, J = 6); 136.1 (*Z*) & 148.3 (*E*) [2d, J = 26 (*Z*) & 30 (*E*)]; 137.8 (*E*) & 139.6 (*Z*) [2d, J = 180 (*E*) & 208 (*Z*)]. MS: 289 (M^+, 44), 274 (77), 246 (87), 152 (97), 136 (100), 108 (54).

Diethyl 2-phenyl-1-(4-morpholino)-ethenylphosphonate **2h**, as a 95/5 mixture of (*Z*)/(*E*) isomers. ^{1}H NMR ($CDCl_3$): 1.1 (*Z*) & 1.2 (*E*) (2t, J = 7, 6H); 2.5 (m, 4H); 3.7 (m, 4H); 3.8 (qi, J = 7, 4H); 6.5 (*Z*) & 6.9 (*E*) [2d, J = 39 (*Z*) & 11 (*E*), 1H];[32] 7.3 (br. s, 5H).

Diethyl 2-(4-methoxyphenyl)-1-(4-morpholino)-ethenylphosphonate **2i**, as a 93/7 mixture of (*Z*)/(*E*) isomers. ^{1}H NMR ($CDCl_3$): 1.1 (*Z*) & 1.2 (*E*) (2t, J = 7, 6H); 2.5 (m, 4H); 3.7 (m, 4H); 3.8 (s, 3H); 3.85 (qi, J = 7, 4H); 6.5 (*Z*) & 6.9 (*E*) [2d, J = 40 (*Z*) & 12 (*E*), 1H]; 6.8 to 7.4 (m, 4H). ^{13}C NMR ($CDCl_3$): 15.8 (*Z*) & 16.3 (*E*) [2d, J = 6.8 (*Z*) & 6.2 (*E*)]; 51.5 (*Z*) & 51.8 (*E*), 2s; 55.0, s; 61.5 (*E*) & 61.8 (*Z*) [2d, J = 5.9 (*E*) & 6.4 (*Z*)]; 66.8 (*Z*) & 67.0 (*E*), 2s; 112.8 (*Z*) & 113.5 (*E*), 2s; 125.5 (*Z*) & 132.7 (*E*) [2d, J = 20 (*Z*) & 30 (*E*)]; 127.3 (*E*) & 127.9 (*Z*) [2d, J = 20 (*E*) & 5 (*Z*)]; 130.3 (*Z*) & 131.4 (*E*), 2s; 138 (*E*) & 140 (*Z*) [2d, J = 191 (*E*) & 207 (*Z*)]; 158.7 (*Z*) & 159.6 (*E*), 2s.

Diethyl 3-methyl-1-(4-morpholino)-but-1-enylphosphonate **2j**, as a 85/15 mixture of (*Z*)/(*E*) isomers. ^{1}H NMR ($CDCl_3$): 0.9 (d, J = 6, 6H); 1.3 (t, J = 7, 6H); 2.5 (m, 4H); 3.8 (m, 4H); 3.1 (m, 1H); 4.1 (qi, J = 7, 4H); 5.3 (*Z*) & 6.1 (*E*) [2dd, J = 44, J' = 9 (*Z*) & J = 15, J' = 9 (*E*), 1H].

One-pot Synthesis of Carboxylic Acids 7

The reaction mixture, resulting from the preparation of enamine **2** as described above, was concentrated in order to eliminate most of the solvent. A 12 M aqueous solution (12.5 mL) of hydrochloric acid was cautiously added. The resulting mixture was refluxed for about 30 mn, then cooled to room temperature, diluted with water (40 mL) and extracted with CH_2Cl_2 (2 × 40 mL) and ether (40 mL). The combined organic layers were concentrated under reduced pressure; the residue was dissolved in a saturated aqueous solution (40 mL) of sodium hydrogen carbonate, which was washed with CH_2Cl_2 (3 × 30 mL). The aqueous basic phase was acidified at pH ~ 1 with 4M HCl, then saturated with NaCl, and extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure leading to the corresponding carboxylic acid **7**, whose purity was controlled by GPC, ^{1}H NMR spectroscopy and microanalysis.

Synthesis of α-piperidino or α-morpholino Alkylphosphonates 8

To a solution of enamino phosphonate **2** (0.02 mol) in anhydrous THF (20 mL), was added sodium borohydride (1.52 g, 0.04 mol). The mixture was stirred for 10 mn, then glacial acetic acid (24 mL, 0.4 mol) was gradually added over 30 mn and stirring was continued for 1 h. The resulting mixture was made basic with 2.5 M NaOH, then extracted with CH_2Cl_2 (3 × 30 mL) and diethyl ether (30 mL). The combined organic layers were concentrated to give the crude product, which was dissolved in 4 M HCl (30 mL). The acid phase was washed

with CH_2Cl_2 (30 mL), then made basic with 2.5 M NaOH, and extracted with CH_2Cl_2 (3 × 30 mL) and diethyl ether (30 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure, leading to the purified phosphonate **8**.

Diethyl 2-phenyl-1-(1-piperidino)-ethylphosphonate **8a**: ^{1}H NMR ($CDCl_3$): 1.2 & 1.4 (2t, J = 7, 6H); 1.5 to 1.7 (m, 6H); 2.6 to 2.9 (m, 4H); 2.9 to 3.3 (m, 3H); 4.0 & 4.2 (2qi, J = 7, 4H); 7.5 (br. s, 5H).

Diethyl 2-(4-methylphenyl)-1-(1-piperidino)-ethylphosphonate **8b**: ^{1}H NMR ($CDCl_3$): 1.2 & 1.4 (2t, J = 7, 6H); 1.5 to 1.7 (m, 6H); 2.3 (s, 3H); 2.6 to 2.8 (m, 4H); 2.9 to 3.2 (m, 3H); 4.0 & 4.2 (2qi, J = 7, 4H); 7.1 to 7.3 (m, 4H).

Diethyl 2-(4-methoxyphenyl)-1-(1-piperidino)-ethylphosphonate **8c**: ^{1}H NMR ($CDCl_3$): 1.1 & 1.2 (2t, J = 7, 6H); 1.4 to 1.6 (m, 6H); 2.6 to 2.8 (m, 4H); 2.8 to 3.1 (m, 3H); 3.8 (s, 3H); 3.9 & 4.2 (2qi, J = 7, 4H); 6.7 to 7.2 (m, 4H). MS: 355 (M^+, 5), 234 (80), 217 (100), 202 (70).

Diethyl 2-(2-chlorophenyl)-1-(1-piperidino)-ethylphosphonate **8d**: ^{1}H NMR ($CDCl_3$): 1.2 & 1.4 (2t, J = 7, 6H); 1.5 to 1.7 (m, 6H); 2.6 to 2.9 (m, 4H); 3.0 to 3.4 (m, 3H); 3.9 & 4.2 (2qi, J = 7, 4H); 7.1 to 7.4 (m, 4H).

Diethyl 2-(3,4-methylenedioxyphenyl)-1-(1-piperidino)-ethylphosphonate **8e**: ^{1}H NMR ($CDCl_3$): 1.2 & 1.4 (2t, J = 7, 6H); 1.5 to 1.7 (m, 6H); 2.6 to 2.8 (m, 4H); 2.8 to 3.1 (m, 3H); 4.0 & 4.2 (2qi, J = 7, 4H); 5.9 (s, 2H); 6.6 to 6.8 (m, 3H).

Diethyl (E)-4-phenyl)-1-(1-piperidino)-but-3-enylphosphonate **8f**: ^{1}H NMR ($CDCl_3$): 1.2 & 1.3 (2t, J = 7, 6H); 1.5 (m, 6H); 3.1 (m, 7H); 4.0 & 4.3 (2qi, J = 7, 4H); 6.1 to 6.6 (m, 2H); 7.1 to 7.5 (m, 5H).

Diethyl 3-methyl-1-(1-piperidino)-butylphosphonate **8g**: ^{1}H NMR ($CDCl_3$): 0.8 & 0.9 (2d, J = 6, 6H); 1.1 & 1.2 (2t, J = 7, 6H); 1.2 to 1.4 (m, 6H); 1.6 to 1.8 (m, 2H); 2.4 to 2.9 (m, 6H); 3.8 & 4.1 (2qi, J = 7, 4H).

Diethyl 2-phenyl-1-(4-morpholino)-ethylphosphonate **8h**: ^{1}H NMR ($CDCl_3$): 1.1 & 1.2 (2t, J = 7, 6H); 2.6 to 2.9 (m, 4H); 3.0 to 3.2 (m, 3H); 3.6 (m, 4H); 4.0 & 4.2 (2qi, J = 7, 4H); 6.1 to 6.6 (m, 2H); 7.3 (br. s, 5H).

Diethyl 2-(4-methoxyphenyl)-1-(4-morpholino)-ethylphosphonate **8i**: ^{1}H NMR ($CDCl_3$): 1.2 & 1.4 (2t, J = 7, 6H); 2.5 to 2.8 (m, 4H); 2.8 to 3.2 (m, 3H); 3.5 (m, 4H); 3.7 (s, 3H); 3.9 & 4.2 (2qi, J = 7, 4H); 6.8 to 7.2 (m, 4H).

Diethyl 3-methyl-1-(4-morpholino)-butylphosphonate **8j**: ^{1}H NMR ($CDCl_3$): 0.8 & 0.9 (2d, J = 6, 6H); 1.1 & 1.3 (2t, J = 7, 6H); 1.5 to 1.8 (m, 2H); 2.6 to 2.9 (m, 4H); 3.5 (m, 4H); 3.9 & 4.1 (2qi, J = 7, 4H).

Synthesis of α-piperidino or α-morpholino alkylphosphonic acids 9

An aqueous solution (85 mL) of 6M HCl was added to α-amino phosphonate **8** (0.02 mol) and the mixture was refluxed overnight. The cooled mixture was evaporated under reduced pressure, the residue was dissolved in water (50 mL)

and evaporated again; this operation was repeated 3 times. The resulting oil was dissolved in ethanol (50 mL) and propylene oxide was added to the solution until complete precipitation of the amino acid, which was collected by filtration, washed with acetone and dried under reduced pressure, giving pure amino phosphonic acid **9**, as a white solid.

2-Phenyl-1-(1-piperidino)-ethylphosphonic acid **9a**: ^{1}H NMR (DCl/D_2O): 1.5 to 1.7 (m, 6H); 2.6 to 3.6 (m, 7H); 7.1 (br. s, 5H). Anal. for $C_{13}H_{20}NO_3P$, calc.: C 57.99, H 7.43, N 5.20; found: C 57.4, H 7.1, N 5.1.

2-(4-Methylphenyl)-1-(1-piperidino)-ethylphosphonic acid **9b**: ^{1}H NMR (DCl/D_2O): 1.5 to 1.7 (m, 6H); 2.0 (s, 3H); 2.6 to 3.6 (m, 7H); 7.0 (m, 4H). Anal. for $C_{14}H_{22}NO_3P$, calc.: C 59.36, H 7.77, N 4.95; found: C 58.9, H 7.5, N 4.7.

2-(4-Methoxyphenyl)-1-(1-piperidino)-ethylphosphonic acid **9c**: ^{1}H NMR (DCl/D_2O): 1.4 to 1.6 (m, 6H); 2.6 to 3.1 (m, 7H); 3.8 (s, 3H); 6.7 to 7.2 (m, 4H). Anal. for $C_{14}H_{22}NO_4P$, calc.: C 56.19, H 7.35, N 4.68; found: C 56.1, H 7.6, N 4.5.

2-(2-Chlorophenyl)-1-(1-piperidino)-ethylphosphonic acid **9d**: ^{1}H NMR (DCl/D_2O): 1.5 to 1.7 (m, 6H); 2.6 to 3.4 (m, 7H); 7.1 to 7.4 (m, 4H). Anal. for $C_{13}H_{19}ClNO_3P$, calc.: C 51.40, H 6.26, N 4.61; found: C 51.8, H 6.4, N 4.4.

2-(3,4-Methylenedioxyphenyl)-1-(1-piperidino)-ethylphosphonic acid **9e**: ^{1}H NMR (DCl/D_2O): 1.5 to 1.7 (m, 6H); 2.6 to 3.1 (m, 7H); 5.9 (s, 2H); 6.6 to 6.8 (m, 3H). Anal. for $C_{14}H_{20}NO_5P$, calc.: C 51.40, H 6.26, N 4.61; found: C 51.8, H 6.4, N 4.4.

(E)-4-Phenyl)-1-(1-piperidino)-but-3-enylphosphonic acid **9f**: ^{1}H NMR (DCl/D_2O): 1.5 to 1.7 (m, 6H); 2.5 to 3.1 (m, 7H); 6.1 to 6.6 (m, 2H); 7.1 to 7.5 (m, 5H). Anal. for $C_{15}H_{22}NO_3P$, calc.: C 61.01, H 7.46, N 4.74; found: C 61.3, H 7.6, N 4.7.

3-Methyl-1-(1-piperidino)-butylphosphonic acid **9g**: ^{1}H NMR (DCl/D_2O): 1.1 (d, J = 6, 6H); 1.8 to 2.2 (m, 8H); 3.4 to 3.8 (m, 6H). Anal. for $C_{10}H_{22}NO_3P$, calc.: C 51.06, H 9.36, N 5.95; found: C 51.2, H 9.1, N 5.8.

2-Phenyl-1-(4-morpholino)-ethylphosphonic acid **9h**: ^{1}H NMR (DCl/D_2O): 3.4 to 4.0 (m, 7H); 4.0 to 4.4 (m, 4H); 7.3 (br. s, 5H). Anal. for $C_{12}H_{18}NO_4P$, calc.: C 53.13, H 6.64, N 5.17; found: C 52.9, H 6.9, N 5.4.

2-(4-Methoxyphenyl)-1-(4-morpholino)-ethylphosphonic acid **9i**: ^{1}H NMR (DCl/D_2O): 3.4 to 4.6 (m, 14H); 7.0 to 7.6 (m, 4H). Anal. for $C_{13}H_{20}NO_5P$, calc.: C 51.83, H 6.64, N 4.65; found: C 52.0, H 6.9, N 4.6.

3-Methyl-1-(4-morpholino)-butylphosphonate **9j**: ^{1}H NMR (DCl/D_2O): 1.1 (d, J = 6, 6H); 1.8 to 2.2 (m, 3H); 3.6 to 4.4 (m, 9H). Anal. for $C_9H_{20}NO_4P$, calc.: C 45.57, H 8.44, N 5.91; found: C 45.6, H 8.8, N 6.0.

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