Three-component catalytic method for synthesis of α-amino phosphonates with the use of α-amino acids as amine component

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Interaction of aliphatic and aromatic aldehydes and ketones with optically active L-α-amino acids or their esters in the three-component catalytic one-pot synthesis of α-aminophosphonates was studied. The corresponding α-amino phosphonates are formed in high yields as mixtures of diastereomers.

Key words: α-amino phosphonates, the Kabachnick—Fields reaction, phthalocyanines, aluminum chloride, glycine, alanine, phenylalanine, α-amino acids, carbonyl compounds.

Isostructural to α-amino acids α-amino phosphonates are biologically active compounds.[1,2] In this respect, phosphorus-containing bioisosteric analogs of selective antagonists of metabotropic glutamatic receptors are of particular interest.[3]

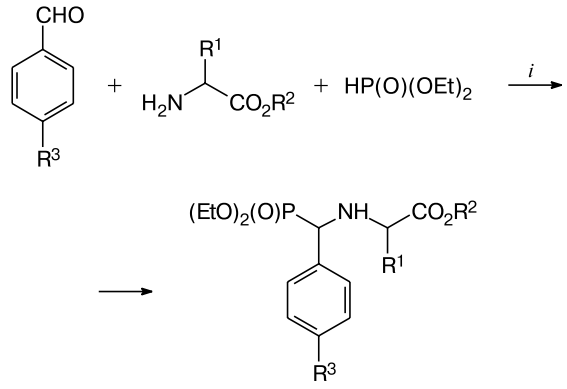
A few examples for synthesis of α-amino phosphonates based on several amino acids are known from the literature.[4,5] However, it was shown that the classic version of the Kabachnick—Fields reaction takes place with formaldehyde only and attempts to extend this reaction to aliphatic aldehydes and ketones failed. Earlier we have proposed the three-component catalytic one-pot synthesis of α-amino phosphonates (the Kabachnick—Fields reaction) with the use of metal-containing *tert*-butylphthalocyanines as catalysts.[6,7] The use of phthalocyanine catalysis enabled us to remarkably broaden the scope of this reaction including involvement of the spatially hindered ketones.[7]

The present work is in the course of our investigations dealing with the variations of amine component in this reaction. Earlier, on a model indan-1-one we have shown the principal possibility of utilization of α-amino acid esters in three-component catalytic reaction for the synthesis of α-amino phosphonates.[8]

We have found that benzaldehyde and 4-trifluoromethylbenzaldehyde react with glycine ethyl ester and diethyl phosphite under conditions of the three-component catalytic synthesis[6,7] to form the corresponding α-amino phosphonates **1** and **2** in ~85% yield (Scheme 1).

2,4-Diketopiperazine formed by the dimerization of two molecules of glycine ethyl ester was isolated as a by-product in this reaction (*cf.* data in Ref. 9). In order to avoid the side cyclodimerization of starting amino acid component, we further used the *tert*-butyl esters of L-amino acids, the sterical hindrance of which prevents such a process. In fact, reactions of benzaldehyde or 4-trifluoromethylbenzaldehyde with L-alanine or L-phenylalanine *tert*-butyl esters in dichloromethane at ~20 °C allows us to obtain amino phosphonates **3—6** in 85—98% yields (see Scheme 1, Table 1).

Scheme 1



1—6

i. Pc^{t}AlCl, mol. sieves 4 Å, CH_2Cl_2

Compound	R^1	R^2	R^3
1	H	Et	H
2	H	Et	CF_3
3	Me	Bu^t	H
4	Me	Bu^t	CF_3
5	CH_2Ph	Bu^t	H
6	CH_2Ph	Bu^t	CF_3

On a model octanal the principal possibility of utilization of aliphatic aldehydes was shown (Scheme 2). Octanal reacts with L-alanine *tert*-butyl ester and diethyl phosphite to furnish α-amino phosphonates **7** (85%) and **8** (10%),

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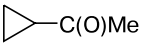
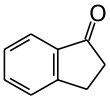
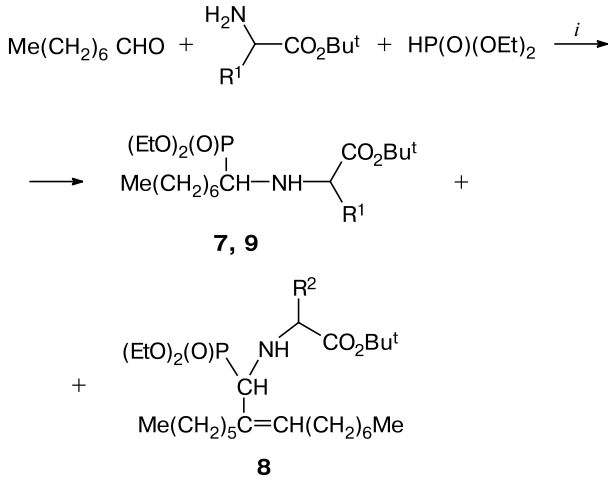
Table 1. Starting substrates (amino acids, esters, and carbonyl compounds) and the yields of α-amino phosphonates

Carbonyl compound	H_2N R^1 $COOR^2$		Reaction conditions: solvent, τ/h	Product	Yield (%)
	R^1	R^2			
PhCHO	H	Et	CH_2Cl_2, 24	**1**	85
4-$F_3CC_6H_4CHO$	H	Et	CH_2Cl_2, 24	**2**	85
PhCHO	Me	Bu^t	CH_2Cl_2, 24	**3**	95
4-$F_3CC_6H_4CHO$	Me	Bu^t	CH_2Cl_2, 24	**4**	98
PhCHO	CH_2Ph	Bu^t	CH_2Cl_2, 48	**5**	85
4-$F_3CC_6H_4CHO$	CH_2Ph	Bu^t	CH_2Cl_2, 48	**6**	85
$CH_3(CH_2)_6CHO$	Me	Bu^t	CH_2Cl_2, 24	**7**	85
				8	10
	CH_2Ph	Bu^t	CH_2Cl_2, 48	**9**	95
PhC(O)Me	Me	Bu^t	CH_2Cl_2, 24	**10**	95
	CH_2Ph	Bu^t	CH_2Cl_2, 48	**11**	80
	Me	Bu^t	CH_2Cl_2, 48	**12**	80
	CH_2Ph	Bu^t	CH_2Cl_2, 72	**13**	70
	Me	Bu^t	CH_2Cl_2, 72	**14**	80
	CH_2Ph	Bu^t	CH_2Cl_2, 72	**15**	65
4-$F_3CC_6H_4CHO$	H	H	MeOH, 72	**16**	20
				17	55
PhCHO	Me	H	CF_3CH_2OH, 120	**18**	70
PhCHO	CH_2Ph	H	CF_3CH_2OH, 120	**19**	45

α-amino phosphonate **8** being formed from the product of crotonic self-condensation of octanal. Reaction of L-phenylalanine under similar conditions takes place with the formation of the only product, α-amino phosphonate **9** in 95% yield.

Scheme 2



i. Pc^tAlCl, mol. sieves 4 Å, CH_2Cl_2

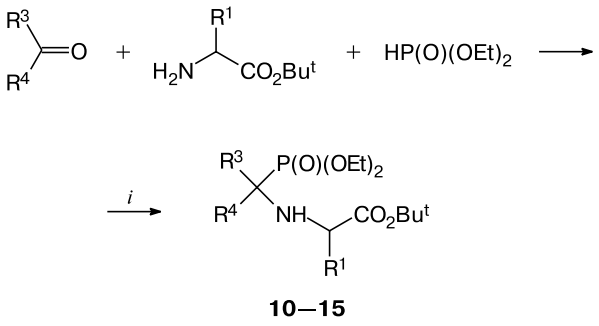
R^1 = Me (**7**, **8**), CH_2Ph (**9**)

To investigate the scope of the method, ketones such as acetophenone, cyclopropyl methyl ketone, and indan-1-one were involved into reaction with L-alanine and L-phenylalanine *tert*-butyl esters. The corresponding amino phosphonates **10—15** were obtained in 65—95% yields (Scheme 3, see Table 1).

Using aldehydes we showed that the very L-amino acids can be involved into this reaction giving rise to the corresponding carboxy-containing α-amino phosphonates in high yields (Scheme 4, see Table 1).

Reaction of glycine with 4-trifluoromethylbenzaldehyde and diethyl phosphite in methanol leads to a mixture of 20—30% of α-amino phosphonate **16** with a free carboxy group and 55—60% of its methyl ester **17** formed by esterification of the carboxy group. Apparently, in the course of this reaction L-amino acids give at first amino phosphonates with a free carboxy group, which further undergoes partial esterification by the solvent. The absence of diketopiperazine among the products of this reaction confirms the suggested sequence of the processes. Attempted reaction between benzaldehyde and alanine

Scheme 3

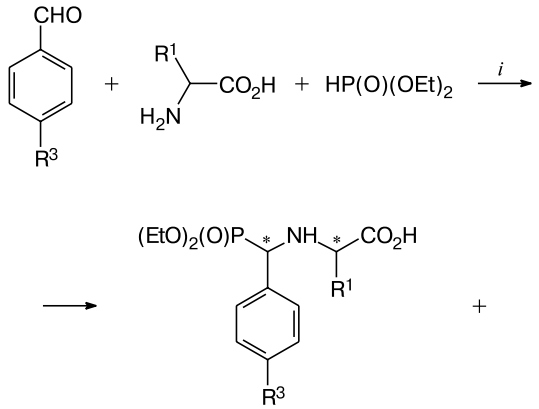


10—15

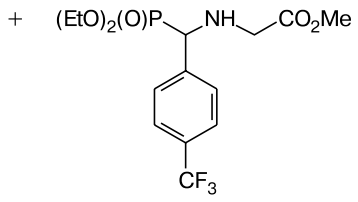
i. Pc^{t}AlCl, mol. sieves 4 Å, CH_2Cl_2

Compound	R^1	R^3	R^4 (R^3, R^4)
10	Me	Me	Ph
11	CH_2Ph	Me	Ph
12	Me	Me	*cyclo*-C_3H_5
13	CH_2Ph	Me	*cyclo*-C_3H_5
14	Me		
15	CH_2Ph		

Scheme 4



16, 18, 19



17

i. Pc^{t}AlCl, mol. sieves 4 Å, MeOH or CF_3CH_2OH

Compound	R^1	R^3
16	H	CF_3
17	H	CF_3
18	Me	H
19	CH_2Ph	H

(phenylalanine) in methanol gave no products due to the low solubility of the amino acids. To increase the solubility we used 2,2,2-trifluoroethanol and, as a result, α-amino phosphonates **18** and **19** based on alanine and phenylalanine with a free carboxy group were obtained in 70% and 45% yields. The absence of esterification products in these cases can be explained by the lower nucleophilicity of 2,2,2-trifluoroethanol.

Structures of α-amino phosphonates obtained were confirmed by IR, ^1H, ^{13}C, and ^{31}P NMR spectral data, as well as by analytical or mass-spectral data. Products **3—15** and **18—19** (see Table 1) were obtained as mixtures of diastereomers resulting in doubling of all the signals in ^{31}P, ^1H and ^{13}C NMR spectra of these compounds.

For α-amino phosphonates **14** and **18**, the diastereomeric ratios were 3 : 7 and 7 : 13 respectively. After additional chromatography the enriched diastereomeric mixtures of α-amino phosphonates **14a** and **14b** with diastereomeric excess of 16 : 1 and 8 : 1, as well as **18a** and **18b** with diastereomeric excess of 18 : 1 and 6 : 1 respectively were isolated.

In the ^{31}P NMR spectra a single signal in the 21.55—22.72 ppm region corresponds to each diastereomer of α-amino phosphonate. In the IR spectra the absorption bands of P=O group are present in the 1250—1260 cm^{-1} region, of NH group in the 3250—3500 cm^{-1} region, and characteristic of the ester carbonyl group bands in the 1730—1745 cm^{-1} region.

In the ^1H NMR spectra the signals of nonequivalent phosphonate ethoxy groups are observed for all the α-amino phosphonates obtained. A signal for the proton at α-carbon atom appears in the 3.90—4.26 ppm region as two doublets of the diastereomeric pair with the spin-spin coupling constants $^2J_{H,P}$ = 16.0—20.0 Hz. In case of products **1** and **2** based on glycine ethyl ester signals of the diastereotopic methylene protons appear as two doublets at 3.18 and 3.39 ppm (J_{AB} = 17.3 Hz). A broad signal in the 2.40—2.45 ppm region corresponds to amino group. Compounds **16**, **18** and **19** with a free carboxy group have the corresponding to betaine broad signal in the 6.2—7.5 ppm region.

In the ^{13}C NMR spectra of compounds **1—19** α-carbon atom adjacent to phosphorus atom resonates in the 52.72—69.14 ppm region with $^1J_{P,C}$ = 144.9—162.0 Hz. Signals of non-isochronic ethoxy groups at phosphorus atom are observed at 16 ppm ($^3J_{P,C}$ = 5.8 Hz) and in the 60.30—62.83 ppm region ($^2J_{P,C}$ = 6.7 Hz). Signals of the asymmetric carbon atom in the amino acid fragment appear as two (in case of the diastereomeric mixtures) doublets at 54—62 ppm with the spin-spin coupling constants $^3J_{P,C}$ = 13.9—19.0 Hz. Signal of CH_2 group of glycine occurs as a single doublet at 48.22 ppm ($^3J_{P,C}$ = 16.8 Hz). All the other signals in proton and carbon spectra of α-amino phosphonates correspond to the structure of car-

bon skeletons of starting carbonyl compound and amino acid ester.

In conclusion, we found that L-amino acids and their esters can be used as amine component in the three-component Kabachnick—Fields reaction in the presence of Pc^{t}AlCl. The reaction under study can serve as a convenient method for synthesis of phosphorus-containing α-amino acid derivatives based on aromatic and aliphatic aldehydes and ketones.

Experimental

NMR ^{1}H (400.13 MHz), ^{13}C (100.61 MHz), and ^{31}P (161.98 MHz) spectra were registered on a Bruker Avance 400 spectrometer in $CDCl_3$ with Me_4Si as internal standard (^{1}H, ^{13}C) and 85% aq. H_3PO_4 as external standard (^{31}P). IR spectra were recorded on a UR-20 spectrometer in CCl_4. Elemental analysis was carried out on a Vario-II CHN analyzer. Mass-spectra were registered on a Finnigan MAT Incos50 quadruple mass-spectrometer (EI, 70 eV, direct inlet of the sample). Specific rotation was measured on a EPO-1 AVNIEKIPRODMASh polarimeter at 23 °C, c = 1 in chloroform or methanol. Reaction progress and purity of the chromatographic isolation of substances were carried out by TLC on Silufol plates. The isolation was performed by column chromatography on silica gel 60 (Merck) (70—230 mesh ASTM).

Amino acid esters were obtained from the corresponding commercially available hydrochlorides by treatment with NaOH.

Synthesis of α-amino phosphonates 1 and 2. Carbonyl compound (2 mmol), molecular sieves 4 Å, and Pc^{t}AlCl (0.1 mmol) were added to a solution of ethyl glycinate (1.5 mmol) in dichloromethane (3 mL). The reaction mixture was stirred on a magnetic stirrer for 3 h, then another portion of ethyl glycinate (1.5 mmol) was added. The reaction mixture was stirred for another 3 h, after which diethyl phosphite (3 mmol) was added. The reaction progress was controlled by TLC (the reaction time is given in Table 1). Further work-up was carried out according to the general procedure.

Ethyl *N*-[(diethoxyphosphoryl)(phenyl)methyl]glycinate (1) was obtained from benzaldehyde and ethyl glycinate, the yield was 85%, R_f 0.54 ($CHCl_3$—MeOH, 10 : 1). Found (%): C, 54.21; H, 7.18; N, 4.21. $C_{15}H_{24}NO_5P$. Calculated (%): C, 54.71; H, 7.35; N, 4.25. ^{1}H NMR, δ: 1.17 (t, 3 H, Me, GlyOEt, J = 7.3 Hz); 1.19, 1.21 (both t, 3 H each, 2 Me, POEt, J = 7.0 Hz); 3.18 (H_A); 3.39 (H_B, AB-system, 2 H, CH_2, Gly, $^2J_{H,H}$ = 17.4 Hz); 3.97—4.04 (m, 4 H, 2POCH_2); 4.10 (q, 2 H, GlyOCH_2, J = 7.0 Hz); 4.26 (d, 1 H, C(1)H, $J_{H,P}$ = 19.2 Hz); 7.53—7.59 (m, 5 H, arom.). ^{31}P NMR, δ: 21.55. ^{13}C NMR, δ: 13.93 (s, Me, GlyOEt); 16.10, 16.16 (both d, Me, POEt, $^3J_{C,P}$ = 5.8 Hz); 48.22 (d, CH_2, Gly, J = 16.8 Hz); 59.61 (d, C(1), $^1J_{C,P}$ = 153 Hz); 60.79 (s, OCH_2, GlyOEt); 63.07 (d, POCH_2, $^2J_{C,P}$ = 6.6 Hz); 125.27, 127.21, 128.99, 139.04 ($C_{arom.}$); 171.31 (C=O, Gly). IR, ν/cm^{-1}: 1250 (P=O); 1745 (C=O); 3250, 3450 (NH).

Piperazine-2,5-dione was isolated from a mixture of the products of this reaction, R_f 0.05 ($CHCl_3$—MeOH, 10 : 1), m.p. 310 °C (see Ref. 10). IR, ν/cm^{-1}: 1680 (C=O), 3300 (NH).

Ethyl *N*-{(diethoxyphosphoryl)[4-(trifluoromethyl)phenyl]-methyl}glycinate (2) obtained from 4-(trifluoromethyl)benzaldehyde and ethyl glycinate, the yield was 85%, R_f 0.53 ($CHCl_3$—MeOH, 10 : 1). Found (%): C, 48.03; H, 5.66; N, 3.43. $C_{16}H_{23}F_3NO_5P$. Calculated (%): C, 48.37; H, 5.83; N, 3.53. ^{1}H NMR, δ: 1.24 (t, 3 H, Me, GlyOEt, J = 7.3 Hz); 1.25, 1.28 (both t, 3 H each, 2 Me, POEt, J = 7.0 Hz); 2.62 (br.s, 1 H, NH); 3.22 (H_A); 3.41 (H_B, AB-system, 2 H, CH_2, Gly, $^2J_{H,H}$ = 17.3 Hz); 3.85—4.12 (m, 4 H, 2 POCH_2); 4.15 (q, 2 H, GlyOCH_2, J = 7.0 Hz); 4.26 (d, 1 H, C(1)H, $J_{H,P}$ = 19.1 Hz); 7.57, 7.62 (both d, 4 H each, arom.). ^{31}P NMR, δ: 21.76. ^{13}C NMR, δ: 14.18 (s, Me, GlyOEt); 16.26, 16.32 (both d, Me, POEt, $^3J_{C,P}$ = 6.1 Hz); 48.47 (d, CH_2, Gly, J = 16.8 Hz); 59.56 (d, C(1), $^1J_{C,P}$ = 152.2 Hz); 60.87 (s, OCH_2, GlyOEt); 63.08 (d, POCH_2, $^2J_{C,P}$ = 6.7 Hz); 125.36, 129.04, 139.35 ($C_{arom.}$); 171.53 (C=O, Gly). IR, ν/cm^{-1}: 1250 (P=O); 1745 (C=O); 3250 (NH).

Synthesis of α-amino phosphonates 3—14 (general procedure). Carbonyl compound (2 mmol), molecular sieves 4 Å, and Pc^{t}AlCl (0.1 mmol) (see Ref. 11) were added to a solution of the corresponding L-amino acid ester (3 mmol) in dichloromethane (3 mL). The reaction mixture was stirred on a magnetic stirrer for 3—4 h, then diethyl phosphite (3 mmol) was added. The reaction progress was controlled by TLC (the reaction time is given in Table 1). Molecular sieves were filtered off and washed with CH_2Cl_2—MeOH mixture (10 : 1, 3×2 mL). The filtrate was concentrated *in vacuo*, the residue was dissolved in minimum CH_2Cl_2—MeOH mixture (50 : 1) and chromatographed on a column with silica gel (length, 20 cm; diameter, 2.5 cm; eluent, CH_2Cl_2—MeOH, 50 : 1).

tert*-Butyl *N*-[(diethoxyphosphoryl)(phenyl)methyl]alaninate (3) was obtained from benzaldehyde and *tert*-butyl L-alaninate, the yield was 98%, R_f 0.60 ($CHCl_3$—MeOH, 10 : 1), $[\alpha]^{23}_D$ −30 ($CHCl_3$). Found (%): C, 58.02; H, 7.97; N, 3.63. $C_{18}H_{30}NO_5P$. Calculated (%): C, 58.17; H, 8.16; N, 3.77. ^{1}H NMR, δ: 1.10, 1.16, 1.20, 1.26 (all t, 6 H each, 2 Me, POEt, J = 7.1 Hz); 1.18, 1.19 (both d, 3 H each, Me, Ala, J = 7.0 Hz); 1.30, 1.39 (both s, 9 H each, 3 Me, Bu^t); 2.40 (br.s, 1 H, NH); 2.99, 3.27 (both q, 1 H each, Ala, J = 7.0 Hz); 3.74—4.10 (m, 4 H, 2 OCH_2); 3.99, 4.13 (both d, 1 H each, C(1)H, $^2J_{H,P}$ = 19.4 Hz, $^2J_{H,P}$ = 18.7 Hz); 7.21—7.30, 7.35—7.31 (both m, 5 H each, arom.). ^{31}P NMR, δ: 21.56, 21.68. ^{13}C NMR, δ: 16.10—16.30 (m, Me, POEt); 18.21, 19.25 (both s, Me, Ala); 27.72, 27.89 (both s, C$\underline{Me}_3$, Bu^t); 54.31, 55.31 (both d, CH, Ala, J = 18.9 Hz, J = 14.8 Hz); 59.13, 59.27 (both d, C(1), $^1J_{C,P}$ = 152.5 Hz, $^1J_{C,P}$ = 156.5 Hz); 62.60—62.83 (m, POCH_2); 80.73, 80.76 (both s, $\underline{C}Me_3$, Bu^t); 127.79, 128.20, 128.26, 128.45, 128.78, 134.84, 135.89 ($C_{arom.}$); 173.73, 174.03 (both s, C=O, Ala). IR, ν/cm^{-1}: 1260 (P=O); 1730 (C=O); 3340, 3450 (NH).

***tert*-Butyl *N*-{1-(diethoxyphosphoryl)[4-(trifluoromethyl)phenyl]methyl}alaninate (4)** was obtained from 4-(trifluoromethyl)benzaldehyde and *tert*-butyl L-alaninate, the yield was 95%, R_f 0.67 ($CHCl_3$—MeOH, 10 : 1). ^{1}H NMR, δ: 1.16, 1.23, 1.27, 1.34 (all t, 6 H each, 2 Me, POEt, J = 7.0 Hz); 1.22, 1.24 (both d, 3 H, Me, Ala, J = 7.0 Hz); 1.32, 1.42 (both s, 9 H each, 3 Me, Bu^t); 2.44 (br.s, 1 H, NH); 2.95, 3.26 (both q, 1 H each, Ala, J = 6.9 Hz); 3.90—4.12 (m, 4 H, 2 OCH_2); 4.20 (d, 1 H, C(1)H, $J_{H,P}$ = 19.4 Hz); 7.52—7.66 (m, 4 H, arom.). ^{31}P NMR, δ: 21.98, 22.12. ^{13}C NMR, δ: 16.22—16.40 (m, Me, POEt); 18.44, 19.37 (both s, Me, Ala); 27.78, 27.97 (both s, C$\underline{Me}_3$,

* For the most products the diastereomeric ratio cannot be determined by ^{1}H and ^{31}P NMR methods due to the overlap of the signals.

Bu^t); 54.63, 55.56 (both d, CH, Ala, J = 17.6 Hz, J = 13.9 Hz); 59.05, 59.18 (both d, C(1), $^1J_{C,P}$ = 150.8 Hz, $^1J_{C,P}$ = 156.6 Hz); 62.95—63.22 (m, $POCH_2$); 81.13, 81.17 (both s, $\underline{C}Me_3$); 125.25, 125.28, 128.93, 129.14, 139.52, 140.44 ($C_{arom.}$); 173.76, 173.95 (both s, C=O, Ala). IR, ν/cm^{-1}: 1260 (P=O); 1730 (C=O); 3340, 3440 (NH). MS, *m/z*: 439 [M]$^+$, 382 [M – Bu^t]$^+$, 338 [M – COOBu^t]$^+$, 302 [M – P(O)(OEt)$_2$]$^+$, 245 [M – P(O)(OEt)$_2$ – Bu^t]$^+$, 200 [M – P(O)(OEt)$_2$ – COOBu^t – H]$^+$, 138 [P(OH)(OEt)$_2$]$^+$, 57 [Bu^t]$^+$.

***tert*-Butyl *N*-[(diethoxyphosphoryl)(phenyl)methyl]phenylalaninate (5)** was obtained from benzaldehyde and *tert*-butyl L-phenylalaninate, the yield was 85%, R_f 0.63 ($CHCl_3$—MeOH, 10 : 1), $[\alpha]^{23}_D$ –71 ($CHCl_3$). Found (%): C, 64.49; H, 8.00; N, 3.23. $C_{24}H_{34}NO_5P$. Calculated (%): C, 64.38; H, 7.68; N, 3.13. ^{1}H NMR, δ: 1.10, 1.19, 1.23, 1.26 (all t, 6 H, 2 Me, POEt, J = 7.0 Hz); 1.22, 1.38 (both s, 9 H, 3 Me, Bu^t); 2.45 (br.s, 1 H, NH); 2.83—2.98, 3.68—3.75 ((both m, 2 H each, CH_2, Phe); 3.19, 3.55 (both t, 1 H each, Phe, J = 7.1 Hz, J = 6.7 Hz); 3.85—4.05 (m, 4 H, 2 OCH_2); 3.96, 4.15 (both d, 1 H each, C(1)H, $^2J_{H,P}$ = 18.0 Hz, $^2J_{H,P}$ = 18.7 Hz); 7.14—7.37 (m, 10 H, arom.). ^{31}P NMR, δ: 22.72. ^{13}C NMR, δ: 16.22—16.54 (m, Me, POEt); 27.74, 28.00 (both s, $C\underline{Me}_3$, Bu^t); 39.66, 39.77 (both s, CH_2, Phe); 59.20, 60.52 (both d, C(1), $^1J_{C,P}$ = 151.5 Hz, $^1J_{C,P}$ = 157.3 Hz); 60.30, 61.95 (both d, CH, Phe, $^3J_{C,P}$ = 17.6 Hz, $^3J_{C,P}$ = 14.6 Hz); 62.76—62.92 (m, OCH_2); 81.14, 81.21 (both s, $\underline{C}Me_3$); 126.48, 127.84, 127.94, 128.15, 128.24, 128.39, 128.68, 128.83, 129.55, 134.71, 136.26, 137.50, 137.78 ($C_{arom.}$); 172.86, 172.96 (both s, C=O, Phe). IR, ν/cm^{-1}: 1250 (P=O); 1730 (C=O); 3330, 3450 (NH).

***tert*-Butyl *N*-{(diethoxyphosphoryl)[4-(trifluoromethyl)phenyl]methyl}phenylalaninate (6)** was obtained from 4-(trifluoromethyl)benzaldehyde and *tert*-butyl L-phenylalaninate, the yield was 85%, R_f 0.64 ($CHCl_3$—MeOH, 10 : 1). ^{1}H NMR, δ: 1.16, 1.27, 1.31, 1.34 (all t, 6 H each, 2 Me, POEt, J = 7.0 Hz); 1.26, 1.41 (both s, 9 H each, 3 Me, Bu^t); 2.44 (br.s, 1 H, NH); 2.89—3.00 (m, 2 H, CH_2, Phe); 3.07, 3.10 (both t, 1 H each, Phe, J = 7.0 Hz, J = 6.7 Hz); 3.91—4.09 (m, 4 H, 2 OCH_2); 4.14, 4.16 (both d, 1 H each, C(1)H, $^2J_{H,P}$ = 16.4 Hz, $^2J_{H,P}$ = 16.0 Hz); 7.17—7.37 (m, 10 H, arom.). ^{31}P NMR, δ: 21.56, 21.58. ^{13}C NMR, δ: 16.23—16.55 (m, Me, POEt); 28.87, 29.00 (both s, $C\underline{Me}_3$); 39.87, 39.96 (both s, CH_2, Phe); 59.18, 60.47 (both d, C(1), $^1J_{C,P}$ = 152.2 Hz, $^1J_{C,P}$ = 157.3 Hz); 60.37, 62.03 (both d, CH, Phe, $^3J_{C,P}$ = 16.1 Hz, $^3J_{C,P}$ = 14.6 Hz); 62.93—63.21 (m, OCH_2); 81.17, 81.24 (both s, $\underline{C}Me_3$); 125.23, 127.09, 128.33, 128.67, 128.83, 129.75, 136.25, 139.61, 140.52 ($C_{arom.}$); 172.96, 173.03 (both s, C=O, Phe). IR, ν/cm^{-1}: 1260 (P=O); 1730 (C=O); 3330, 3440 (NH). MS, *m/z*: 515 [M]$^+$, 424 [M – $PhCH_2$]$^+$, 414 [M – COOBu^t]$^+$, 378 [M – P(O)(OEt)$_2$]$^+$, 370 [M – CF_3Ph]$^+$, 367 [M – $PhCH_2$ – Bu^t]$^+$, 321 [M – P(O)(OEt)$_2$ – Bu^t]$^+$, 310 [M – $CH(CH_2Ph)COOBu^t$]$^+$, 276 [M – P(O)(OEt)$_2$ – COOBu^t – H]$^+$, 204 [$PhCHCHCOOBu^t$]$^+$, 145 [CF_3Ph]$^+$, 138 [P(OH)(OEt)$_2$]$^+$, 91 [$PhCH_2$]$^+$, 57 [Bu^t]$^+$.

***tert*-Butyl *N*-{1-(diethoxyphosphoryl)octyl}alaninate (7)** was obtained from octanal and *tert*-butyl L-alaninate, the yield was 85%, R_f 0.44 ($CHCl_3$—MeOH, 10 : 1), R_f 0.48 (light petroleum—ethyl acetate, 1 : 1). Found (%): C, 57.97; H, 10.37; N, 3.55. $C_{19}H_{40}NO_5P$. Calculated (%): C, 57.99; H, 10.25; N, 3.56. ^{1}H NMR, δ: 0.85 (t, 3 H, $\underline{Me}(CH_2)_6$, J = 6.8 Hz); 1.21—1.33 (m, 19 H, Me, Ala, 2 Me, POEt; 5 CH_2, oct.); 1.40—1.56, 1.73—1.82 (both m, 2 H each, CH_2, oct.); 1.44 (s, 9 H, 3 Me, Bu^t); 1.92 (br.s, 1 H, NH); 2.73—2.86 (m, 1 H, CH, oct.); 3.53, 3.60 (both q, 1 H, Ala, J = 6.9 Hz); 4.09—4.17 (m, 4 H, 2 OCH_2). ^{31}P NMR, δ: 27.75, 28.38. ^{13}C NMR, δ: 14.00 (s, $\underline{Me}(CH_2)_6$); 16.38 (d, Me, POEt, $^3J_{C,P}$ = 5.1 Hz); 18.97, 19.67 (both s, Me, Ala); 22.55 (s, $Me\underline{CH_2}(CH_2)_5$); 26.05 (d, $Me(CH_2)_4\underline{CH_2}$, $^3J_{C,P}$ = 11.0 Hz); 26.30 (d, $Bu\underline{CH_2}(CH_2)_2$, $^4J_{C,P}$ = 9.8 Hz); 27.97 (s, $C\underline{Me}_3$, Bu^t); 28.21, 29.47 (both d, $Me(CH_2)_5\underline{CH_2}$, $^2J_{C,P}$ = 52.4 Hz, $^2J_{C,P}$ = 82.7 Hz); 30.57 (s, $Pr\underline{CH_2}(CH_2)_3$); 31.74 (s, $Et\underline{CH_2}(CH_2)_4$); 52.72, 55.44 (both d, C(1), $^1J_{C,P}$ = 148.6 Hz, $^1J_{C,P}$ = 161.7 Hz); 54.80, 56.47 (both d, CH, Ala, $^3J_{C,P}$ = 7.3 Hz, $^3J_{C,P}$ = 3.7 Hz); 61.91, 62.14 (both d, OCH_2, $^2J_{C,P}$ = 7.4 Hz, $^2J_{C,P}$ = 7.4 Hz); 80.78 (s, $\underline{C}Me_3$); 174.13, 175.18 (C=O, Ala). IR, ν/cm^{-1}: 1250 (P=O); 1730 (C=O); 3340, 3450 (NH).

***tert*-Butyl *N*-[1-(diethoxyphosphoryl)-2-hexyldec-2-en-1-yl]alaninate (8)** was obtained as a by-product in the synthesis of compound **7**, the yield was 10%, R_f 0.45 ($CHCl_3$—MeOH, 10 : 1), R_f 0.70 (light petroleum—ethyl acetate, 1 : 1). Found (%): C, 63.59; H, 10.83; N, 2.89. $C_{27}H_{54}NO_5P$. Calculated (%): C, 64.38; H, 10.81; N, 2.78. ^{1}H NMR, δ: 0.89 (t, 6 H, 2 $\underline{Me}(CH_2)_5$); 1.22—1.39 (m, 27 H, Me, Ala, 2 Me, POEt; 9 CH_2); 1.46 (s, 9 H, 3 Me, Bu^t); 1.99 (br.s, 1 H, NH); 2.04—2.13 (m, 2 H, $=CCH_2$); 2.18—2.32 (m, 2 H, $=CCH_2$); 3.21, 3.33 (both q, 1 H, Ala); 3.37, 3.53 (both d, 1 H, PCHN, $^2J_{H,P}$ = 19.8 Hz, $^2J_{H,P}$ = 20.7 Hz); 4.10—4.20 (m, 4 H, 2 OCH_2); 5.50, 5.63 (both q, 1 H each, =CH). ^{31}P NMR, δ: 24.15, 24.24. ^{13}C NMR, δ: 14.08 (s, 2 $\underline{Me}(CH_2)_5$); 16.39—16.66 (m, Me, POEt); 18.31, 19.50 (both s, Me, Ala); 22.65, 27.91, 28.42, 28.59, 29.19, 29.31, 29.66, 30.10, 31.71, 31.83 (CH_2 aliph.); 28.00, 28.04 (both s, $C\underline{Me}_3$); 53.97, 54.65 (both d, CH, Ala, J = 17.5 Hz, J = 13.9 Hz); 59.1, 59.15 (both d, C(1), $^1J_{C,P}$ = 150.0 Hz, $^1J_{C,P}$ = 157.4 Hz); 62.22, 62.45, 62.69, 62.97 (all d, OCH_2, $^2J_{C,P}$ = 7.3 Hz, $^2J_{C,P}$ = 7.3 Hz, $^2J_{C,P}$ = 7.3 Hz, $^2J_{C,P}$ = 6.6 Hz); 130.08, 130.36 (both d, =CH, $^2J_{C,P}$ = 11.0 Hz, $^2J_{C,P}$ = 10.7 Hz); 132.64, 134.46 (both d, =CH, $^3J_{C,P}$ = 8.0 Hz, $^3J_{C,P}$ = 3.7 Hz); 80.69, 80.93 (both s, $\underline{C}Me_3$); 174.17, 174.57 (C=O, Ala). IR, ν/cm^{-1}: 1260 (P=O); 1730 (C=O); 3350, 3450 (NH).

***tert*-Butyl *N*-[1-(diethoxyphosphoryl)octyl]phenylalaninate (9)** was obtained from octanal and *tert*-butyl L-phenylalaninate, the yield was 95%, R_f 0.47 ($CHCl_3$—MeOH, 10 : 1), R_f 0.50 (light petroleum—ethyl acetate, 1 : 1). Found (%): C, 63.62; H, 9.31; N, 2.99. $C_{25}H_{44}NO_5P$. Calculated (%): C, 63.88; H, 9.46; N, 2.98. ^{1}H NMR, δ: 0.86—0.90 (m, 3 H, $\underline{Me}(CH_2)_6$); 1.25—1.34 (m, 14 H, 2 Me, POEt, 4 CH_2 aliph.); 1.36, 1.37 (both s, 9 H, 3 Me, Bu^t); 1.44—1.56, 1.67—1.80 (оба м, 2 H, CH_2 aliph.); 1.85 (br.s, 1 H, NH); 2.74—2.83 (m, 1 H, CH, oct.); 2.86—2.92 (m, 2 H, Phe); 3.69, 3.91 (both t, 1 H each, Phe, J = 6.7 Hz, J = 7.2 Hz); 3.96—4.16 (m, 4 H, 2 OCH_2); 7.20—7.28 (m, 5 H, arom.). ^{31}P NMR, δ: 27.14, 28.00. ^{13}C NMR, δ: 13.82 (s, $\underline{Me}(CH_2)_6$, oct.); 16.25 (d, 2 Me, POEt, $^3J_{C,P}$ = 5.1 Hz); 22.36 (s, $Me\underline{CH_2}(CH_2)$); 25.86 (d, $Me(CH_2)\underline{CH_2}$, $^3J_{C,P}$ = 8.1 Hz); 28.77 (s, $Bu\underline{CH_2}(CH_2)_2$); 27.68 (s, $C\underline{Me}_3$); 28.21, 29.47 (both d, $Me(CH_2)_5\underline{CH_2}$, $^2J_{C,P}$ = 49.8 Hz, $^2J_{C,P}$ = 68 Hz); 30.39 (s, $Pr\underline{CH_2}(CH_2)_3$); 31.52 (s, $Et\underline{CH_2}(CH_2)_4$); 40.00, 40.12 (both s, CH_2, Phe); 53.41, 54.25 (both d, C(1), $^1J_{C,P}$ = 144.9 Hz, $^1J_{C,P}$ = 161.0 Hz); 60.92, 61.49 (both d, CH, Phe, $^3J_{C,P}$ = 7.3 Hz, $^3J_{C,P}$ = 7.3 Hz); 61.62—61.80, 62.04—62.10 (both m, OCH_2); 80.78 (s, $\underline{C}Me_3$); 126.17, 127.87, 129.25, 137.30, 137.54 ($C_{arom.}$); 172.85, 173.88 (C=O, Phe). IR, ν/cm^{-1}: 1250 (P=O); 1730 (C=O); 3330, 3450 (NH).

***tert*-Butyl *N*-[1-(diethoxyphosphoryl)-1-phenylethyl]alaninate (10)** was obtained from acetophenone and *tert*-butyl

L-alaninate, the yield was 95%, R_f 0.62 ($CHCl_3$—MeOH, 10 : 1), $[\alpha]^{23}_D$ −17 ($CHCl_3$). Found (%): C, 59.35; H, 8.40; N, 3.65. $C_{19}H_{32}NO_5P$. Calculated (%): C, 59.17; H, 8.39; N, 3.65. ^{1}H NMR, δ: 1.12, 1.17, 1.27, 1.37 (all t, 6 H each, 2 Me, POEt, J = 7.0 Hz); 1.21, 1.25 (both d, 3 H each, Me, Ala, J = 7.0 Hz); 1.31, 1.41 (both s, 9 H each, 3 CMe_3); 1.68, 1.74 (both d, 3 H each, Me, $^2J_{H,P}$ = 16.3 Hz, $^2J_{H,P}$ = 16.7 Hz); 2.90 (br.s, 1 H, NH); 2.97, 3.27 (both q, 1 H each, Ala, J = 6.9 Hz); 3.75—4.15 (m, 4 H, 2 OCH_2); 7.18—7.36, 7.54—7.61 (both m, 5 H each, arom.). ^{31}P NMR, δ: 25.72. ^{13}C NMR, δ: 16.18, 16.28 (both d, Me, POEt, $^3J_{C,P}$ = 5.4 Hz); 19.89, 20.86 (both s, Me, Ala); 21.29, 22.04 (both s, Me); 27.68, 27.75 (both s, C$\underline{Me}_3$); 51.51, 53.30 (both d, CH, Ala, J = 13.4 Hz, J = 13.4 Hz); 58.81, 59.99 (both d, C(1), $^1J_{C,P}$ = 150.4 Hz, $^1J_{C,P}$ = 155.8 Hz); 62.97—63.21 (m, OCH_2); 80.49, 80.53 (both s, $\underline{C}Me_3$); 127.13, 127.83, 128.27, 140.31 ($C_{arom.}$); 175.24, 175.35 (both s, C=O, Ala). IR, ν/cm^{-1}: 1250 (P=O); 1730 (C=O); 3340, 3450 (NH).

***tert*-Butyl *N*-[1-(diethoxyphosphoryl)-1-phenylethyl]phenylalaninate (11)** was obtained from acetophenone and *tert*-butyl L-phenylalaninate, the yield was 80%, R_f 0.68 ($CHCl_3$—MeOH, 10 : 1), $[\alpha]^{23}_D$ 1.5 ($CHCl_3$), $[\alpha]^{23}_D$ −4.0 (MeOH). Found (%): C, 65.22; H, 7.92; N, 3.21. $C_{25}H_{36}NO_5P$. Calculated (%): C, 65.03; H, 7.88; N, 3.03. ^{1}H NMR, δ: 1.08, 1.19, 1.23, 1.25 (all t, 6 H each, 2 Me, POEt, J = 7.0 Hz); 1.15, 1.31 (both s, 9 H each, 3 Me, Bu^t); 1.63, 1.70 (both d, 3 H each, Me, $^2J_{H,P}$ = 16.7 Hz, $^2J_{H,P}$ = 16.3 Hz); 2.80 (br.s, 1 H, NH); 2.82—2.94 (m, 2 H, Phe); 3.13, 3.53 (both t, 1 H each, Phe, J = 7.1 Hz, J = 6.9 Hz); 3.63—4.11 (all m, 4 H each, 2 OCH_2); 7.13—7.18, 7.20—7.33, 7.56—7.58 (all m, 5 H each, arom.). ^{31}P NMR, δ: 25.49, 25.64. ^{13}C NMR, δ: 16.22—16.48 (m, Me, POEt); 21.24 (s, Me); 27.63 (s, C$\underline{Me}_3$); 41.84, 42.06 (both s, CH_2, Phe); 57.45, 57.92 (both d, CH, Phe, $^3J_{C,P}$ = 13.2 Hz, $^3J_{C,P}$ = 16.1 Hz); 59.79, 60.81 (both d, C(1), $^1J_{C,P}$ = 156.7 Hz, $^1J_{C,P}$ = 152.2 Hz); 62.91—63.20 (m, OCH_2); 80.78, 80.84 (both s, $\underline{C}Me_3$); 126.46, 127.19, 127.31, 127.87, 128.01, 128.11, 128.42, 129.86, 137.57, 137.90, 138.67, 140.32 ($C_{arom.}$); 174.18, 175.36 (both s, C=O, Phe). IR, ν/cm^{-1}: 1250 (P=O); 1730 (C=O); 3330, 3450 (NH).

***tert*-Butyl *N*-[1-cyclopropyl-1-(diethoxyphosphoryl)ethyl]alaninate (12)** was obtained from cyclopropyl methyl ketone and *tert*-butyl L-alaninate, the yield was 80%, R_f 0.44 ($CHCl_3$—MeOH, 10 : 1). Found (%): C, 54.70; H, 9.20; N, 4.03. $C_{16}H_{32}NO_5P$. Calculated (%): C, 54.96; H, 9.25; N, 4.00. ^{1}H NMR, δ: 0.38—0.50 (m, 4 H, 2 CH_2, cycl.); 0.92, 0.98 (both d, 3 H each, Me, $^2J_{H,P}$ = 16.6 Hz, $^2J_{H,P}$ = 16.3 Hz); 1.05—1.16 (m, 1 H, cycl.); 1.20, 1.21 (both d, 3 H each, Me, Ala, J = 7.0 Hz); 1.29—1.33 (m, 6 H, Me, POEt); 1.42 (s, 9 H, 3 Me, Bu^t); 2.01 (br.s, 1 H, NH); 3.74, 3.79 (both q, 1 H each, Ala, J = 7.0 Hz); 4.09—4.22 (m, 4 H, 2 OCH_2). ^{31}P NMR, δ: 27.25, 27.46. ^{13}C NMR, δ: 0.03, 0.69 (both d, CH, cycl., $^2J_{C,P}$ = 9.40 Hz); 1.42, 1.66 (both s, 2 CH_2, cycl.); 14.49, 14.85 (both d, CH_3, $^2J_{C,P}$ = 2.7 Hz, $^2J_{C,P}$ = 2.7 Hz); 16.16—16.79 (m, Me, POEt); 21.41, 24.94 (both s, Me, Ala); 27.78, 27.80 (both s, C$\underline{Me}_3$); 51.04, 51.32 (both d, CH, Ala, $^3J_{C,P}$ = 6.7 Hz, $^3J_{C,P}$ = 5.4 Hz); 54.69 (d, C(1), $^1J_{C,P}$ = 158.2 Hz); 61.87, 62.00, 62.43, 62.61 (all d, OCH_2, $^2J_{C,P}$ = 6.72 Hz, $^2J_{C,P}$ = 8.06 Hz, $^2J_{C,P}$ = 8.06 Hz, $^2J_{C,P}$ = 6.72 Hz); 80.19, 80.29 (both s, $\underline{C}Me_3$); 176.31, 176.57 (both s, C=O, Ala). IR, ν/cm^{-1}: 1250 (P=O); 1730 (C=O); 3340, 3470 (NH).

***tert*-Butyl *N*-[1-cyclopropyl-1-(diethoxyphosphoryl)ethyl]-phenylalaninate (13)** was obtained from cyclopropyl methyl ketone and *tert*-butyl L-phenylalaninate, the yield was 70%, R_f 0.46 ($CHCl_3$—MeOH, 10 : 1). Found (%): C, 62.06; H, 8.72; N, 3.26. $C_{22}H_{36}NO_5P$. Calculated (%): C, 62.07; H, 8.55; N, 3.29. ^{1}H NMR, δ: 0.35—0.50 (m, 4 H, 2 CH_2, cycl.); 0.85, 0.88 (both d, 3 H each, Me, $^2J_{H,P}$ = 16.6 Hz, $^2J_{H,P}$ = 16.2 Hz); 0.92—0.96, 1.12—1.18 (both m, 1 H each, cycl.); 1.29, 1.30 (both t, 6 H, Me, 2 POEt, J = 7.0 Hz); 1.33, 1.34 (both s, 9 H, 3 Me, Bu^t); 2.07 (br.s, 1 H, NH); 2.78—2.87 (m, 2 H, Phe); 3.91, 3.97 (both t, 2 H, Phe, J = 7.1 Hz, J = 7.0 Hz); 4.05—4.14 (m, 4 H, 2 OCH_2); 7.19—7.27 (m, 5 H, arom.). ^{31}P NMR, δ: 27.17, 27.22. ^{13}C NMR, δ: 0.25, 0.85 (both d, CH, cycl., $^2J_{C,P}$ = 9.40 Hz); 1.17, 1.67 (both d, 2 CH_2, cycl., $^3J_{C,P}$ = 2.69 Hz); 14.76, 16.24 (both s, Me); 16.53, 16.58 (both d, Me, POEt, $^3J_{C,P}$ = 5.37 Hz); 27.79, 27.83 (both s, C$\underline{Me}_3$); 41.73, 42.21 (both s, CH_2, Phe); 55.19, 55.32 (both d, C(1), $^1J_{C,P}$ = 157.1 Hz, $^1J_{C,P}$ = 158.5 Hz); 57.07, 57.31 (both d, CH, Phe, $^3J_{C,P}$ = 9.4 Hz, $^3J_{C,P}$ = 6.7 Hz); 61.99, 62.26, 62.30, 62.53 (all d, OCH_2, $^2J_{C,P}$ = 8.06 Hz, $^2J_{C,P}$ = 6.72 Hz, $^2J_{C,P}$ = 8.06 Hz, $^2J_{C,P}$ = 6.72 Hz); 80.54, 80.66 (both s, $\underline{C}Me_3$); 126.29, 127.93, 129.69, 137.83, 138.07 ($C_{arom.}$); 175.10, 175.35 (both s, C=O, Phe). IR, ν/cm^{-1}: 1250 (P=O); 1730 (C=O); 3340, 3470 (NH).

***tert*-Butyl *N*-[1-(diethoxyphosphoryl)-2,3-dihydro-1*H*-inden-1-yl]alaninate (14)**[8] was obtained from indan-1-one and *tert*-butyl L-alaninate, the yield was 80%, R_f 0.50 ($CHCl_3$—MeOH, 10 : 1). Found (%): C, 60.44; H, 8.13; N, 3.45. $C_{20}H_{32}NO_5P$. Calculated (%): C, 60.44; H, 8.12; N, 3.52. IR, ν/cm^{-1}: 1250 (P=O); 1730 (C=O); 3320, 3470 (NH). The product was isolated as a mixture of diastereomers in a ratio of 3 : 7 (**14a** : **14b**). The mixture was subjected to further column chromatography on silica gel (length, 20 cm, diameter, 1.5 cm; eluent, chloroform—methanol (ratio 50 : 1)). The enriched with one of the diastereomeric products fractions were obtained: **14a** : **14b** = 16 : 1 and **14a** : **14b** = 8 : 1.

Diastereomer 14a, $[\alpha]^{23}_D$ −44 ($CHCl_3$). ^{1}H NMR, δ: 1.19, 1.27 (both t, 6 H each, 2 Me, POEt); 1.20 (d, 3 H, Me Ala, J = 7.0 Hz); 1.35 (s, 9 H, 3 Me, Bu^t); 1.94—2.07, 2.50—2.61 (both m, 2 H each, C(2)H_2, cycl.); 2.57 (br.s, 1 H, NH); 2.95—3.00 (m, 2 H, C(3)H_2, cycl.); 3.22 (q, 1 H, Ala, J = 7.0 Hz); 3.89—4.19 (m, 4 H, 2 OCH_2); 7.18—7.23, 7.46—7.48 (both m, 4 H, arom.). ^{31}P NMR, δ: 23.84. ^{13}C NMR, δ: 16.29, 16.40 (both d, Me, POEt, $^3J_{C,P}$ = 5.8 Hz); 21.75 (s, Me, Ala); 27.78 (s, C$\underline{Me}_3$); 30.23 (d, $^3CH_2$, cycl., $^3J_{C,P}$ = 3.7 Hz); 34.10 (d, C(2)H_2, cycl., $^2J_{C,P}$ = 2.2 Hz); 51.76 (d, CH, Ala, $^3J_{C,P}$ = 11.0 Hz); 62.84, 62.91 (both d, $POCH_2$, $^2J_{C,P}$ = 7.8 Hz); 68.87 (d, C(1), $^1J_{C,P}$ = 161.7 Hz); 80.53 (s, $\underline{C}Me_3$); 124.70, 125.86, 126.23, 128.31, 140.01, 145.06 ($C_{arom.}$); 175.98 (C=O, Ala).

Diastereomer 14b, $[\alpha]^{23}_D$ −19 ($CHCl_3$). ^{1}H NMR, δ: 1.17, 1.28 (both t, 6 H each, 2 Me, POEt, J = 7.0 Hz); 1.22 (d, 3 H, Me, Ala, J = 7.2 Hz); 1.36 (s, 9 H, 3 Me, Bu^t); 2.04—2.17, 2.60—2.72 (both m, 2 H each, C(2)H_2, cycl.); 2.43 (br.s, 1 H, NH); 2.95—3.01 (m, 2 H, C(3)H_2, cycl.); 3.44 (q, 1 H, Ala, J = 7.1 Hz); 3.88—4.19 (m, 4 H, 2 OCH_2); 7.16—7.24, 7.47, 7.49 (all m, 4 H each, arom.). ^{31}P NMR, δ: 24.07. ^{13}C NMR, δ: 16.25, 16.31 (both d, Me, POEt, $^3J_{C,P}$ = 5.8 Hz); 21.97 (s, Me, Ala); 27.75 (s, C$\underline{Me}_3$); 30.15 (d, C(3)H_2, cycl., $^3J_{C,P}$ = 3.7 Hz); 33.27 (d, C(2)H_2, cycl., $^2J_{C,P}$ = 2.9 Hz); 51.92 (d, CH, Ala, $^3J_{C,P}$ = 10.2 Hz); 62.48, 63.22 (both d, $POCH_2$, $^2J_{C,P}$ = 7.3 Hz); 68.74 (d, C(1), $^1J_{C,P}$ = 161.7 Hz); 80.46 (s, $\underline{C}Me_3$); 124.49, 125.73, 126.26, 128.20, 141.08, 144.54 ($C_{arom.}$); 175.80 (C=O, Ala).

Synthesis of α-amino phosphonates 15—17. L-Amino acid (2.2 mmol), molecular sieves 4 Å (500 mg), Pc^{t}AlCl (0.1 mmol),

and catalytic amount of triethylamine (0.2 mmol) were added to a solution of carbonyl compound (2 mmol) in MeOH or CF_3CH_2OH (4 mL). The reaction mixture was refluxed for 3 h, then diethyl phosphite (3 mmol) was added. The reaction progress was controlled by TLC (the reaction time is given in Table 1). Further work-up was carried out according to the general procedure.

***tert*-Butyl *N*-[1-(diethoxyphosphoryl)-2,3-dihydro-1*H*-inden-1-yl]phenylalaninate (15)** was obtained from indan-1-one and *tert*-butyl L-phenylalaninate, the yield was 65%, R_f 0.55 ($CHCl_3$—MeOH, 10 : 1). Found (%): C, 65.61; H, 7.82; N, 2.76. $C_{26}H_{36}NO_5P$. Calculated (%): C, 65.90; H, 7.68; N, 2.95. ^{1}H NMR, δ: 1.09, 1.17, 1.19, 1.25 (all t, 6 H each, 2 Me, POEt, J = 7.1 Hz); 1.21, 1.27 (both s, 9 H each, 3 Me, Bu^t); 1.75—2.02, 2.40—2.56 (both m, 2 H each, C(2)H_2, cycl.); 2.67 (br.s, 1 H, NH); 2.73—2.83 (m, 2 H, C(3)H_2, cycl.); 2.85—2.97 (m, 2 H, CH_2, Phe); 3.29, 3.56 (both t, 1 H each, Phe, J = 6.9 Hz, J = 6.9 Hz); 3.74—3.84, 3.88—4.19 (both m, 4 H, 2 OCH_2); 6.89—6.91, 7.00—7.04, 7.11—7.27, 7.46—7.49 (all m, 9 H each, arom.). ^{31}P NMR, δ: 23.68, 24.02. ^{13}C NMR, δ: 16.23—16.43 (m, Me, POEt); 27.71 (s, C$\underline{Me}_3$); 30.26 (s, C(3)H_2, cycl.); 33.06, 33.94 (both s, $^2CH_2$, cycl.); 41,81, 42.01, (both s, CH_2, Phe); 57.82, 57.91 (both d, CH, Phe, $^3J_{C,P}$ = 12.1 Hz, $^3J_{C,P}$ = 10.8 Hz); 62.56, 62.73, 62.94, 63.01 (all d, OCH_2, $^2J_{C,P}$ = 6.75 Hz, $^2J_{C,P}$ = 8.10 Hz, $^2J_{C,P}$ = 6.75 Hz, $^2J_{C,P}$ = 6.75 Hz); 68.61, 69.14 (both d, C(1), $^1J_{C,P}$ = 160.6 Hz, $^1J_{C,P}$ = 160.6 Hz); 80.72, 80.78 (both s, $\underline{C}Me_3$); 124.55, 125.98, 126.14, 126.28, 127.89, 127.93, 128.19, 128.24, 129.71, 129.86, 137.84, 139.64, 141.08, 144.58, 145.96 ($C_{arom.}$); 174.48, 174.87 (C=O, Phe). IR, ν/cm^{-1}: 1250 (P=O); 1730 (C=O); 3330, 3450 (NH).

***N*-{(Diethoxyphosphoryl)[4-(trifluoromethyl)phenyl]methyl}-glycine (16)** was obtained from 4-(trifluoromethyl)benzaldehyde and glycine, the yield was 20%, R_f 0.31 ($CHCl_3$—MeOH, 10 : 1). ^{1}H NMR, δ: 1.13, 1.16 (both m, 6 H each, 2 Me, POEt); 3.01, 3.17 (both s, 2 H each, CH_2, Gly); 3,72—4.11 (m, 4 H, 2 $POCH_2$); 4.10 (d, 1 H, C(1)H, $J_{H,P}$ = 15.7 Hz); 6.02 (br.m, 2 H, NH, OH); 7.36—7.60 (m, 4 H, arom.). ^{31}P NMR, δ: 21.38. ^{13}C NMR, δ: 16.07 (m, Me, POEt); 47.91 (d, CH_2, Gly, J = 19.0 Hz); 59.33 (d, C(1), $^1J_{C,P}$ = 152.2 Hz); 63.23, 63.47 (both d, $POCH_2$, $^2J_{C,P}$ = 7. Hz); 125.31, 128.83, 128.88, 138.68 ($C_{arom.}$); 173.32 (C=O, Gly). IR, ν/cm^{-1}: 1260 (P=O); 1730 (C=O); 3340, 3480 (NH). MS, *m/z*: 369 $[M]^+$, 324 $[M - COOH]^+$, 232 $[M - P(O)(OEt)_2]^+$, 186 $[M - P(O)(OEt)_2 - COOH - H]^+$, 145 $[CF_3Ph]^+$.

Methyl *N*-{(diethoxyphosphoryl)[4-(trifluoromethyl)phenyl]methyl}glycinate (17) was obtained in the synthesis of compound **16**, the yield was 55%, R_f 0.49 ($CHCl_3$—MeOH, 10 : 1). ^{1}H NMR, δ: 1.24, 1.28 (both t, 6 H each, 2 Me, POEt, J = 7.0 Hz); 1.77 (br.s, 1 H, NH); 3.25 (H_A); 3.46 (H_B, AB-system, 2 H, CH_2, Gly, $^2J_{H,H}$ = 17.3 Hz); 3.69 (s, 3 H, Me, GlyOMe); 4.01—4.10 (m, 4 H, 2 $POCH_2$); 4.31 (d, 1 H, C(1)H, $J_{H,P}$ = 19.1 Hz); 7.57—7.71 (m, 4 H, arom.). ^{31}P NMR, δ: 21.51. ^{13}C NMR, δ: 16.24, 16.30 (both d, Me, POEt, $^3J_{C,P}$ = 5.9 Hz); 29.66 (s, Me, GlyOMe); 48.10 (d, CH_2, Gly, J = 17.1 Hz); 59.63 (d, C(1), $^1J_{C,P}$ = 153.0 Hz); 63.30 (d, $POCH_2$, $^2J_{C,P}$ = 8.1 Hz); 125.44, 129.05, 129.11, 130.28 ($C_{arom.}$); 171.83 (C=O, Gly). IR, ν/cm^{-1}: 1250 (P=O); 1730 (C=O); 3360, 3460 (NH). MS, *m/z*: 383 $[M]^+$, 246 $[M - P(O)(OEt)_2]^+$, 186 $[M - P(O)(OEt)_2 - COOMe - H]^+$, 145 $[CF_3Ph]^+$, 138 $[P(OH)(OEt)_2]^+$.

***N*-[(Diethoxyphosphoryl)(phenyl)methyl]alanine (18)** was obtained from benzaldehyde and L-alanine, the yield was 70%, R_f 0.31 ($CHCl_3$—MeOH, 10 : 1). Found (%): C, 53.05; H, 6.92; N, 4.60. $C_{14}H_{22}NO_5P$. Calculated (%): C, 53.33; H, 7.03; N, 4.44. IR, ν/cm^{-1}: 1260 (P=O); 1720 (C=O); 2300—3600 (OH); 3310, 3450 (NH). MS, *m/z*: 315 $[M]^+$. *N*-[(Diethoxyphosphoryl)(phenyl)methyl]alanine was isolated as a mixture of diastereomers in a ratio of 13 : 7 (**18a** : **18b**). The obtained mixture was subjected to further column chromatography on silica gel (length, 20 cm, diameter, 1.5 cm; eluent, chloroform—methanol (ratio 35 : 1)). The enriched with one of the diastereomeric products fractions were obtained: **18a** : **18b** = 18 : 1 and **18a** : **18b** = 6 : 1.

Diastereomer 18a, $[\alpha]^{23}_D$ −140 ($CHCl_3$). ^{1}H NMR, δ: 1.15, 1.29 (both t, 6 H each, 2 Me, POEt, J = 7.1 Hz); 1.33 (d, 3 H, Me, Ala, J = 7.3 Hz); 3.21 (q, 1 H, Ala, J = 7.1 Hz); 3.70—3.87, 3.95—4.10 (both m, 4 H each, 2 OCH_2); 4.11 (d, 1 H, C(1)H, $^2J_{H,P}$ = 18.2 Hz); 6.19 (br.m, 2 H, NH, OH); 7.31—7.42 (m, 5 H, arom.). ^{31}P NMR, δ: 22.52. ^{13}C NMR, δ: 16.18, 16.32 (both d, Me, POEt, $^3J_{C,P}$ = 5.9 Hz); 19.32 (s, Me, Ala); 54.59 (d, CH, Ala, J = 17.6 Hz); 59.43 (d, C(1), $^1J_{C,P}$ = 155.2 Hz); 63.13, 63.59 (both d, OCH_2, $^2J_{C,P}$ = 7.3 Hz, $^2J_{C,P}$ = 6.5 Hz); 128.51, 128.58, 128.72, 134.36 ($C_{arom.}$); 176.32 (s, C=O, Ala).

Diastereomer 18b, $[\alpha]^{23}_D$ −244 ($CHCl_3$). ^{1}H NMR, δ: 1.15, 1.30 (both t, 6 H, 2 Me, POEt, J = 7.1 Hz); 1.37 (d, 3 H, Me, Ala, J = 6.8 Hz); 3.48 (q, 1 H, Ala, J = 7.1 Hz); 3.75—3.83, 3.93—4.12 (both m, 4 H, 2 OCH_2); 4.12 (d, 1 H, C(1)H, $^2J_{H,P}$ = 19.4 Hz); 7.25 (br.m, 2 H, NH, OH); 7.32—7.42 (m, 5 H, arom.). ^{31}P NMR, δ: 23.06. ^{13}C NMR, δ: 16.20, 16.37 (both d, Me, POEt, $^3J_{C,P}$ = 5.9 Hz); 17.38 (s, Me, Ala); 54.26 (d, CH, Ala, J = 13.2 Hz); 58.73 (d, C(1), $^1J_{C,P}$ = 155.9 Hz); 63.28, 63.48 (both d, OCH_2, $^2J_{C,P}$ = 7.3 Hz); 128.41, 128.59, 128.70, 134.85 ($C_{arom.}$); 176.28 (s, C=O, Ala).

***N*-[(Diethoxyphosphoryl)(phenyl)methyl]phenylalanine (19)** was obtained from benzaldehyde and L-phenylalanine, the yield was 45%, R_f 0.38 ($CHCl_3$—MeOH, 10 : 1), $[\alpha]^{23}_D$ −300 ($CHCl_3$). ^{1}H NMR, δ: 1.13, 1.22 (both t, 6 H each, 2 Me, POEt, J = 7.0 Hz); 2.81 (dd, 1 H, Phe, J = 13.4 Hz, J = 9.6 Hz); 3.12 (dd, 1 H, Phe, J = 13.4 Hz, J = 4.3 Hz); 3.32 (dd, 1 H, Phe, J = 9.4 Hz, J = 4.6 Hz); 3.83—4.04 (m, 4 H, 2 OCH_2); 4.12, 4.13 (both d, 1 H, C(1)H, $^2J_{H,P}$ = 20.0 Hz); 6.40 (br.m, 2 H, NH, OH); 6.96, 7.12—7.31 (m, 10 H, arom.). ^{31}P NMR, δ: 22.74, 22.86. ^{13}C NMR, δ: 16.18, 16.23 (both d, Me, POEt, $^3J_{C,P}$ = 5.1 Hz); 38.5, 39.23 (both s, CH_2, Phe); 59.12 (d, C(1), $^1J_{C,P}$ = 152.96 Hz); 59.97 (d, CH, Phe, $^3J_{C,P}$ = 17.56 Hz); 63.09, 63.50 (both d, OCH_2, $^2J_{C,P}$ = 7.32 Hz, $^2J_{C,P}$ = 6.59 Hz); 126.71, 127.06, 127.98, 128.30, 128.38, 128.58, 128.73, 129.47, 129.58, 134.10, 137.25, 137.46 ($C_{arom.}$); 175.54, 175.57 (both s, C=O, Phe). IR, ν/cm^{-1}: 1260 (P=O); 1720 (C=O); 2400—3600 (OH), 3300, 3420 (NH). MS, *m/z*: 391 $[M]^+$, 346 $[M - COOH]^+$, 300 $[M - PhCH_2]^+$, 254 $[M - P(O)(OEt)_2]^+$, 208 $[M - P(O)(OEt)_2 - COOH - H]^+$, 138 $[P(OH)(OEt)_2]^+$, 91 $[PhCH_2]^+$.

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