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Synthesis of *N,N*-Bis(dialkoxyphosphinoylmethyl)- and *N,N*-Bis(diphenylphosphinoylmethyl)-β- and γ-amino acid Derivatives by the Microwave-Assisted Double Kabachnik–Fields Reaction

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ABSTRACT: *The title compounds were synthesized by the microwave-assisted, mostly solvent-free bis Kabachnik–Fields condensation of β-alanine and γ-aminobutyric acid or their esters with formaldehyde and >P(O)H species, such as dialkyl phosphites and diphenylphosphine oxide.* © 2014 Wiley Periodicals, Inc. Heteroatom Chem. 00:1–10, 2014; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21221

INTRODUCTION

The Kabachnik–Fields reaction is an important tool for the synthesis of α–aminophosphonates and related derivatives [1–5] that are of real or potential biological activity [3,6–8]. With regard to the synthesis, a number of catalytic versions were described including microwave (MW)-assisted variations [9,10]. It was suggested that under solvent-free and MW-assisted conditions, there is no need for any catalyst [11]. α- and β-Amino acids may also be the starting materials for the Kabachnik–Fields reaction [12–14].

As a significant modification, the double Kabachnik–Fields reaction was also elaborated to make available bis(phosphonomethyl)amine derivatives [15–18]. The bis(phosphinoylmethyl)amines are valuable intermediates as they may be converted to bisphosphine ligands after double deoxygenation [16–18].

It is also possible to prepare bis(phosphinoylmethyl) derivatives from amino acids or their esters by the double Kabachnik–Fields reaction. A few studies appeared on the synthesis of bis derivatives from α-amino acids or esters [19–22]. The bis(Kabachnik–Fields) reaction was utilized in the synthesis of an *N,N*-bis(dimethoxyphosphinoylmethyl)-γ-aminobutyric acid applying the reagents in an excess, and using tetrahydrofuran as the solvent

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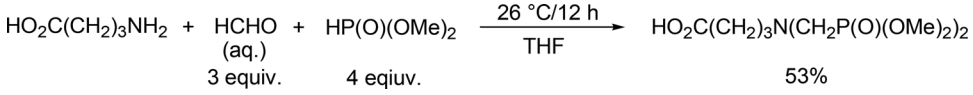
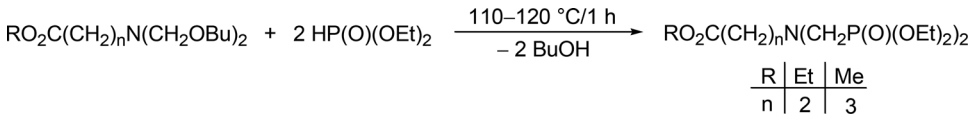


SCHEME 1 [23]



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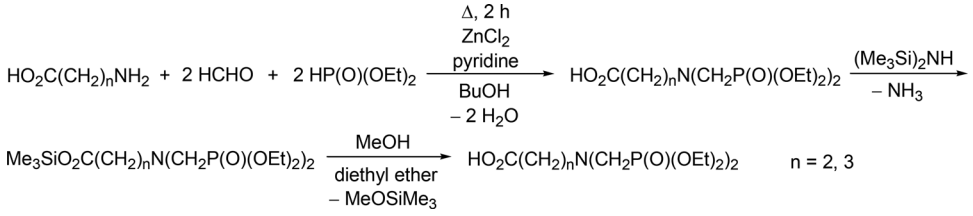

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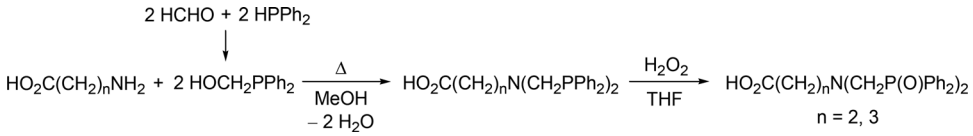


SCHEME 4 [25]

(Scheme 1) [23]. Other derivatives, such as *N,N*-bis-(diethoxyphosphinoylmethyl)-γ-aminobutyric acid or β-aminopropionic acid derivatives, were synthesized by somewhat related or different approaches suggested by Prishchenko (Schemes 2 and 3) [24]. Scheme 2 shows a method comprising a double nucleophilic substitution, whereas Scheme 3 involves a double Kabachnik–Fields reaction that is followed by the temporary derivatization of the bis-substituted aminobutyric and aminopropionic acids to obtain pure bis(diethoxyphosphinoylmethyl)-amino acids as the final products [24]. *N,N*–Bis-(diphenylphosphinoylmethyl)-γ-aminobutyric acid and the analogous β-aminopropionic acid were made available by a special method utilizing the diphenylphosphine formaldehyde adduct in the double *N*-alkylation of the amino acids (Scheme 4) [25].

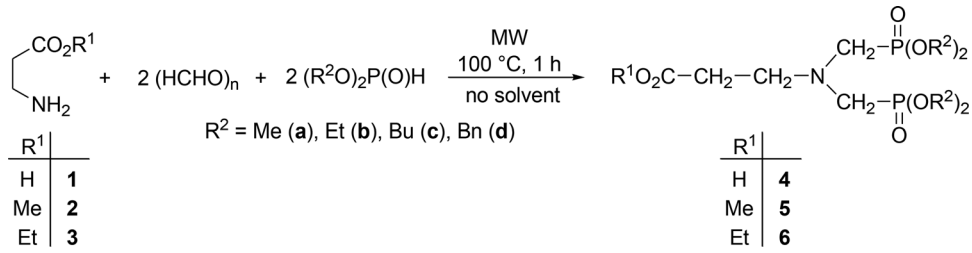
In this article, we describe the synthesis of the bis(phosphinoyl) derivatives of β-alanine and γ–aminobutyric acid and their esters by the double Kabachnik–Fields condensation.

RESULTS AND DISCUSSION

MW-Assisted Synthesis of β- and γ-Amino Acid Derivatives

First, the double Kabachnik–Fields reaction of β-alanine (**1**) and its methyl and ethyl esters (**2** and **3**) with 2 equiv of paraformaldehyde and 2 equiv of dialkyl phosphites, such as dimethyl phosphite, diethyl phosphite, dibutyl phosphite, and dibenzyl phosphite, was investigated under MW conditions. The methyl and ethyl esters of β-alanine (**2** and **3**) were liberated from the corresponding hydrochloride salts prior to the reaction. The condensations were performed at 100°C for 1 h in the absence of any solvents, and the expected *N,N*-bis(dialkoxyphosphinoylmethyl)-β-alanine derivatives (**4a–d**, **5a–d**, and **6a–d**) were obtained in yields of 70–99% after column chromatography (Scheme 5 and Table 1). Using diphenylphosphine oxide as the P reagent, the reactions were carried out in acetonitrile to overcome the heterogeneity of the reaction mixture. After a 1 h irradiation at 100°C, flash chromatography afforded the bis(diphenylphosphinoylmethyl) derivatives **7**, **8**, and **9** in yields of 61–89% (Scheme 6 and Table 1).

In the next round, γ-aminobutyric acid (**10**) and its methyl and ethyl esters (**11** and **12**) were reacted with 2 equiv of paraformaldehyde and the same amount of dialkyl phosphites. After an irradiation of 1 h at 100°C, the corresponding products **13a–d**, **14a–d**, and **15a–d** were obtained in yields of 60–97% (Scheme 7 and Table 2). The similar reaction of diphenylphosphine oxide afforded the



SCHEME 5 Double Kabachnik–Fields reaction of β-alanine derivatives, paraformaldehyde, and dialkyl phosphites.

TABLE 1 Yields of the Bis(>P(O)CH_2)-β-alanine Derivatives

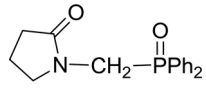
Entry	*Compound*	*Yield (%)*	*Compound*	*Yield (%)*	*Compound*	*Yield (%)*
1	**4a**	70	**5a**	73	**6a**	76
2	**4b**	85	**5b**	95	**6b**	87
3	**4c**	77	**5c**	90	**6c**	77
4	**4d**	96	**5d**	99	**6d**	91
5	**7**	61	**8**	89	**9**	85

TABLE 2 Yields of the Bis(>P(O)CH_2)-γ-aminobutyric Acid Derivatives

Entry	*Compound*	*Yield (%)*	*Compound*	*Yield (%)*	*Compound*	*Yield (%)*
1	**13a**	79	**14a**	86	**15a**	74
2	**13b**	76	**14b**	89	**15b**	96
3	**13c**	77	**14c**	93	**15c**	79
4	**13d**	81	**14d**	88	**15d**	97
5	**16**	60	**17**	94	**18**	80

bis(diphenylphosphinoylmethyl) derivatives **16**, **17**, and **18** in 60, 89, and 80% yields, respectively. These reactions had to be also carried out in acetonitrile due to the heterogeneity (Scheme 8 and Table 2).

It was found that in the reaction of γ-aminobutyric acid (**10**) or its ethyl ester (**12**), paraformaldehyde, and diphenyl phosphine oxide, a ring by-product, *N*–diphenylphosphinoylmethyl)-2-pyrrolidinone (**19**), was formed that was isolated in 18% and 35%, respectively.



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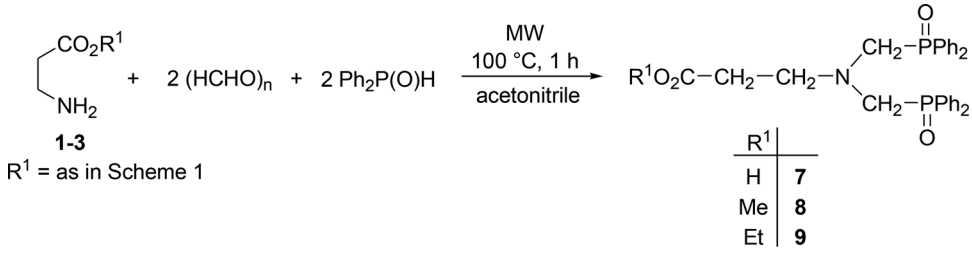
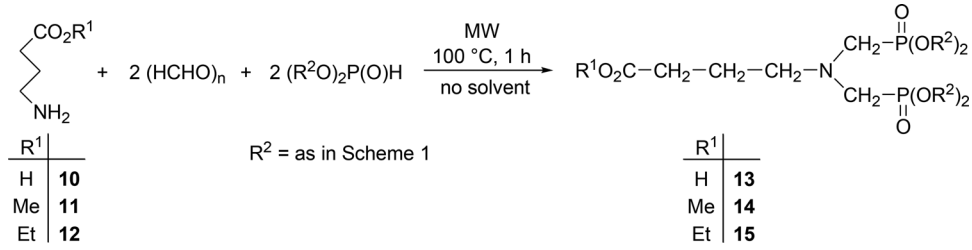
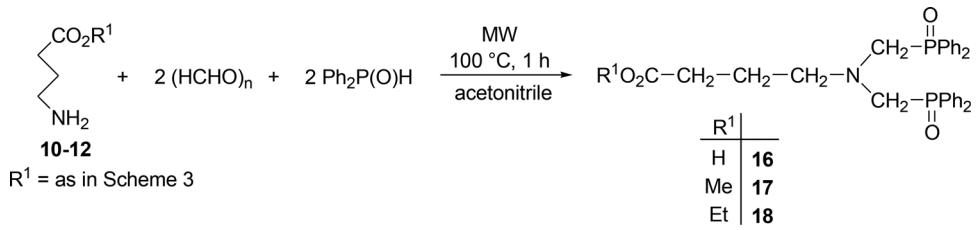
The analogous by-products were also found to have been formed in small quantities (5–-10%) in the condensation of γ–aminobutyric acid (**10**) or its esters (**11** and **12**), paraformaldehyde, and dialkyl phosphites. The pyrrolidinone-type by-products may be formed in two ways. The first possibility is that



SCHEME 6 Double Kabachnik–Fields reaction of β-alanine derivatives, paraformaldehyde, and diphenylphosphine oxide.



SCHEME 7 Double Kabachnik–Fields reaction of γ-aminobutyric acid derivatives, paraformaldehyde, and dialkyl phosphites.



SCHEME 8 Double Kabachnik–Fields reaction of γ-aminobutyric acid derivatives, paraformaldehyde, and diphenylphosphine oxide.

the amino acid is dehydrated to the lactam prior to the Kabachnik–Fields reaction (Route 1). The other possibility is that the α–aminophosphine oxide [$R^1O_2C(CH_2)_3NHCH_2P(O)Ph_2$ (**20**)] or α–aminophosphonate [$R^1O_2C(CH_2)_3NHCH_2P(O)(OR)_2$ (**21**)] intermediate formed in the first stage undergoes cyclization (Route 2). The possibility for Route 1 was investigated by a separate experiment involving the attempted cyclization of ethyl γ–aminobutyrate (**12**) under MW irradiation at 100°C for 1 h. ^{1}H NMR analysis revealed that 18% of the amino acid ester **12** was cyclized. It is worth mentioning that γ–aminobutyric acid (**10**) was more reluctant in respect of cyclization. In the reaction of **10** at 100°C for 1 h in a few drops of acetonitrile (to ensure a homogeneous medium), only a small (<3%) quantity of the pyrrolidinone could be pointed out by ^{1}H NMR analysis. From the above data, one can see that Route 2 may become predominant in respect of the formation of the ring by-product via the α–aminophosphine oxide [$R^1O_2C(CH_2)_3NHCH_2P(O)Ph_2$ (**20**)] intermediate. If R^1 = alkyl, the cyclization is more preferred, as compared to the case, when R^1 = H.

Comparative Thermal Experiments

Comparative thermal experiments were also performed in a few cases to evaluate the potential of MW irradiation in the above syntheses. The double Kabachnik–Fields reactions of β–alanine (**1**), or γ–aminobutyric acid (**10**), or their esters (**2**, **3** and **11**, **12**), paraformaldehyde, and diethyl phosphite were repeated under conventional heating at 100°C for 1 h in sealed tubes. The yields of the thermal control experiments were 7–39% lower, indicating the positive role of MW irradiation (Table 3). The acceleration observed on MW irradiation is the consequence of the beneficial effect of the local overheatings occurring statistically in the bulk of the mixture [26]. The detailed study of this effect in organophosphorus reactions means a challenge for us [27].

It is worth mentioning that in the reaction of γ–aminobutyric acid derivatives (**10–12**), paraformaldehyde, and diethyl phosphite carried out on conventional heating, a small proportion (<7%) of the pyrrolidinone-type by-products was always present. This confirms that the lactam by-product may be formed both under MW and conventional heating. The direct cyclization of γ–aminobutyric acid (**10**) to 2-pyrrolidinone involves a 5-h reflux in toluene in the presence of Al_2O_3 as the dehydrating agent [28].

TABLE 3 Yields of the MW-Assisted and Comparative Thermal Reactions

		Yield (%)	
Entry	*Compound*	*MW*	Δ
1	**4b**	85	70
2	**5b**	95	81
3	**6b**	87	80
4	**13b**	76	54
5	**14b**	89	63
6	**15b**	96	57

In summary, 30 trifunctionalized amines, comprising bis(dialkoxyphosphinoylmethyl)- or bis(diphenylphosphinoylmethyl)-β- and γ-amino acid derivatives, were synthesized under MW and, in most cases, solvent-free conditions. Among the compounds, 25 are new and two were characterized partially earlier. The accelerating effect of the MW technique was demonstrated by comparative thermal experiments.

EXPERIMENTAL

General

The ^{31}P, ^{13}C, and ^{1}H NMR spectra were obtained in $CDCl_3$ solution on a Bruker AV-300 spectrometer operating at 121.5, 75.5, and 300 MHz, respectively. Chemical shifts are downfield relative to 85% H_3PO_4 and tetramethylsilane. Mass spectra were obtained using a Thermo LTQ-FT-Ultra mass spectrometer. The reactions were carried out in a 300 W CEM Discover focused MW reactor equipped with a pressure

controller, applying 20–30 W under isothermal conditions.

The β-alanine and γ-aminobutyric acid esters were liberated from their hydrochloride salts using 20% Na_2CO_3 solution (2.0 g of Na_2CO_3 and 8 mL of water). Dichloromethane (2 × 10 mL) was used for the extraction of the free base. The organic phase was separated and dried (Na_2SO_4). Evaporation of the volatile components provided the β-alanine and γ–aminobutyric acid esters.

*General Procedure for the Preparation of Bis(>P(O)CH$_2$)-β-alanines (**4**) and Bis(>P(O)CH$_2$)-β-alanine Esters (**5** and **6**)*

A mixture of 1.70 mmol β-alanine or its esters (β-alanine: 0.15 g, β-alanine methyl ester: 0.18 g, or β-alanine ethyl ester: 0.20 g), 0.10 g (3.40 mmol) of paraformaldehyde, and 3.40 mmol of the >P(O)H species (dimethyl phosphite: 0.31 mL, diethyl phosphite: 0.44 mL, dibutyl phosphite: 0.67 mL, and dibenzyl phosphite: 0.75 mL) was heated at 100°C in a vial in the MW reactor equipped with a pressure controller for 1 h. Then, the water formed was removed in a vacuum. Column chromatography (silica gel 3% methanol in dichloromethane) of the residue afforded the products (**4a–d**, **5a–d**, **6a–d**) as oils. The following products were thus prepared.

*N,N-Bis(dimethoxyphosphonylmethyl)-β-alanine (**4a**).* Yield: 70% (0.40 g); ^{31}P NMR ($CDCl_3$) δ: 25.2; ^{13}C NMR ($CDCl_3$) δ: 33.0 (CH_2C=O), 49.3 (dd, $^1J_{CP}$ = 157.1, $^3J_{CP}$ = 6.0, CH_2P), 52.7 (t, $^2J_{CP}$ = 3.0, CH_2N), 52.8 (t, $^3J_{CP}$ = 3.5, OCH_3), 174.1 (C=O); ^{1}H NMR ($CDCl_3$) δ: 2.53 (t, $^3J_{HH}$ = 6.7, 2H, CH_2C=O), 3.14 (t, $^3J_{HH}$ = 6.5, 2H, CH_2N), 3.22 (d, $^2J_{PH}$ = 8.8, 4H, CH_2P), 3.79 (d, 12H, $^2J_{PH}$ = 10.3, OCH_3); $[M + H]^+_{found}$ = 334.0804, $C_9H_{22}NO_8P_2$ requires 334.0815.

*N,N-Bis(diethoxyphosphonylmethyl)-β-alanine (**4b**).* Yield: 85% (0.56 g); ^{31}P NMR ($CDCl_3$) δ: 25.3; δ [24] ($CDCl_3$) 22.1; ^{13}C NMR ($CDCl_3$) δ: 16.3 (t, $^3J_{CP}$ = 2.7, CH_2CH_3), 33.0 (CH_2C=O), 50.1 (dd, $^1J_{CP}$ = 156.6, $^3J_{CP}$ = 6.0, CH_2P), 52.7 (t, $^3J_{CP}$ = 6.6, CH_2N), 62.3 (t, $^2J_{CP}$ = 3.3, OCH_2), 174.0 (C=O); δ [24] ($CDCl_3$) 49.63 (dd, $^1J_{CP}$ = 155.4, $^3J_{CP}$ = 5.9, CH_2P), 52.16 (t, $^3J_{CP}$ = 7.2, CH_2N), 173.53 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.29 (t, $^3J_{HH}$ = 6.8, 12H, CH_2CH_3), 2.48 (t, $^3J_{HH}$ = 6.3, 2H, CH_2C=O), 3.11 (t, $^3J_{HH}$ = 6.1, 2H, CH_2N), 3.16 (d, $^2J_{PH}$ = 8.7, 4H, CH_2P), 4.04–4.17 (m, 8H, OCH_2); δ [24] ($CDCl_3$) 2.94 (t, $^3J_{HH}$ = 7.2, 2H, CH_2N), 3.01 (d, $^2J_{PH}$ = 8.8, 4H, CH_2P); $[M + H]^+_{found}$ = 390.1447, $C_{13}H_{30}NO_8P_2$ requires 390.1441.

*N,N-Bis(dibutoxyphosphonylmethyl)-β-alanine (**4c**).* Yield: 77% (0.66 g); ^{31}P NMR ($CDCl_3$) δ: 24.7; ^{13}C NMR ($CDCl_3$) δ: 13.5 (CH_3), 18.7 ($CH_2CH_2CH_2CH_3$), 32.5 (t, $^3J_{CP}$ = 2.9, OCH_2CH_2), 33.3 (CH_2C=O), 50.0 (dd, $^1J_{CP}$ = 155.6, $^3J_{CP}$ = 5.3, CH_2P), 53.0 (t, $^3J_{CP}$ = 6.4, CH_2N), 66.0 (t, $^3J_{CP}$ = 3.5, OCH_2CH_2), 174.0 (C=O); ^{1}H NMR ($CDCl_3$) δ: 0.92 (t, $^3J_{HH}$ = 7.4, 12H, CH_3), 1.32–1.41 (m, 8H, $OCH_2CH_2CH_2$), 1.58–1.66 (m, 8H, OCH_2CH_2), 2.50 (t, $^3J_{HH}$ = 6.7, 2H, CH_2C=O), 3.13 (t, $^3J_{HH}$ = 6.7, 2H, CH_2N), 3.21(d, $^2J_{PH}$ = 8.3, 4H, CH_2P), 4.00–4.15 (m, 8H, OCH_2); $[M + H]^+_{found}$ = 502.2690, $C_{21}H_{46}NO_8P_2$ requires 502.2693.

*N,N-Bis(dibenzylyoxyphosphonylmethyl)-β-alanine (**4d**).* Yield: 96% (1.04 g); ^{31}P NMR ($CDCl_3$) δ: 25.4; ^{13}C NMR ($CDCl_3$) δ: 33.4 (CH_2C=O), 50.6 (dd, $^1J_{CP}$ = 154.7, $^3J_{CP}$ = 4.7, CH_2P), 53.1 (t, $^3J_{CP}$ = 2.7, CH_2N), 67.8 (t, $^3J_{CP}$ = 3.2, OCH_2), 128.1 (C_3),* 128.5 (C_4), 128.6 (C_2),* 135.9 (t, $^3J_{CP}$ = 2.7, C_1), 173.9 (C=O), *may be reversed; ^{1}H NMR ($CDCl_3$) δ: 2.39–2.48 (m, 2H, CH_2C=O), 3.15 (d, $^2J_{PH}$ = 8.1, 4H, .CH_2P), 3.90 (t, $^3J_{HH}$ = 5.6, 2H, CH_2N), 4.91–5.04 (m, 8H, OCH_2), 7.28–7.39 (m, 20H, ArH); $[M + H]^+_{found}$ = 638.2062, $C_{33}H_{38}NO_8P_2$ requires 638.2067.

*N,N-Bis(dimethoxyphosphonylmethyl)-β-alanine Methyl Ester (**5a**).* Yield: 73% (0.43 g); ^{31}P NMR ($CDCl_3$) δ: 26.9; ^{13}C NMR ($CDCl_3$) δ: 32.8 (CH_2C=O), 49.2 (dd, $^1J_{CP}$ = 156.1, $^3J_{CP}$ = 5.9, CH_2P), 51.6 ($COOCH_3$), 52.4 (t, $^3J_{CP}$ = 7.7, CH_2N), 52.6 (t, $^2J_{CP}$ = 3.4, OCH_3), 172.3 (C=O); ^{1}H NMR ($CDCl_3$) δ: 2.53 (t, $^3J_{HH}$ = 7.0, 2H, CH_2C=O), 3.14 (t, $^3J_{HH}$ = 6.9, 2H, CH_2N), 3.22 (d, $^2J_{PH}$ = 8.7, 4H, CH_2P), 3.68 (s, 3H, $COOCH_3$), 3.78 (d, 12H, $^2J_{PH}$ = 10.4, OCH_3); $[M + H]^+_{found}$ = 348.0968, $C_{10}H_{24}NO_8P_2$ requires 348.0972.

*N,N-Bis(diethoxyphosphonylmethyl)-β-alanine Methyl Ester (**5b**).* Yield: 95% (0.65 g); ^{31}P NMR ($CDCl_3$) δ: 24.6; ^{13}C NMR ($CDCl_3$) δ: 16.4 (t, $^3J_{CP}$ = 2.8, CH_2CH_3), 32.9 (CH_2C=O), 50.0 (dd, $^1J_{CP}$ = 155.3, $^3J_{CP}$ = 5.7, CH_2P), 51.5 ($COOCH_3$), 52.3 (t, $^3J_{CP}$ = 7.5, CH_2N), 61.9 (t, $^2J_{CP}$ = 3.4, CH_2CH_3), 172.4 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.33 (t, $^3J_{HH}$ = 7.0, 12H, CH_2CH_3), 2.54 (t, $^3J_{HH}$ = 7.2, 2H, CH_2C=O), 3.16 (t, $^3J_{HH}$ = 7.1, 2H, CH_2N), 3.20 (d, $^2J_{PH}$ = 8.4, 4H, CH_2P), 3.67 (s, 3H, $COOCH_3$), 4.09–4.18 (m, 8H, OCH_2); $[M + H]^+_{found}$ = 404.1593, $C_{14}H_{32}NO_8P_2$ requires 404.1598.

*N,N-Bis(dibutoxyphosphonylmethyl)-β-alanine Methyl Ester (**5c**).* Yield: 90% (0.79 g); ^{31}P NMR ($CDCl_3$) δ: 24.8; ^{13}C NMR ($CDCl_3$) δ: 13.5 ($CH_2CH_2CH_2CH_3$), 18.7 ($CH_2CH_2CH_2CH_3$), 32.5 (t, $^3J_{CP}$

= 2.9, OCH_2CH_2), 32.9 ($CH_2C{=}O$), 49.9 (dd, $^1J_{CP}$ = 154.7, $^3J_{CP}$ = 5.4, CH_2P), 51.5 ($COOCH_3$), 52.2 (t, $^3J_{CP}$ = 7.3, CH_2N), 65.6 (t, $^3J_{CP}$ = 3.5, OCH_2), 172.3 (C=O); ^{1}H NMR ($CDCl_3$) δ: 0.90 (t, $^3J_{HH}$ = 7.3, 12H, $CH_2CH_2CH_2CH_3$), 1.30–1.43 (m, 8H, $OCH_2CH_2CH_2$), 1.55–1.70 (m, 8H, OCH_2CH_2), 2.50 (t, $^3J_{HH}$ = 7.2, 2H, $CH_2C{=}O$), 3.13 (t, $^3J_{HH}$ = 7.2, 2H, CH_2N), 3.17 (d, $^2J_{PH}$ = 8.3, 4H, CH_2P), 3.63 (s, 3H, $COOCH_3$), 3.96–4.10 (m, 8H, OCH_2); $[M + H]^+_{found}$ = 516.2845, $C_{22}H_{48}NO_8P_2$ requires 516.2848.

*N,N-Bis(dibenzylyoxyphosphonylmethyl)-β-alanine Methyl Ester (***5d***).* Yield: 99% (1.10 g); ^{31}P NMR ($CDCl_3$) δ: 25.4; ^{13}C NMR ($CDCl_3$) δ: 32.8 ($CH_2C{=}O$), 50.4 (dd, $^1J_{CP}$ = 155.1, $^3J_{CP}$ = 6.2, CH_2P), 51.5 ($COOCH_3$), 52.3 (t, $^3J_{CP}$ = 7.3, CH_2N), 67.4 (t, $^3J_{CP}$ = 3.4, OCH_2) 127.9 (C_3),* 128.3 (C_4), 128.5 (C_2),* 136.2 (t, $^3J_{CP}$ = 2.9, C_1), 172.2 (C=O), *may be reversed; ^{1}H NMR ($CDCl_3$) δ: 2.42 (t, $^3J_{HH}$ = 7.1, 2H, $CH_2C{=}O$), 3.12 (t, $^3J_{HH}$ = 7.0, 2H, CH_2N), 3.21 (d, $^2J_{PH}$ = 8.1, 4H, CH_2P), 3.57 (s, 3H, $COOCH_3$), 4.91–5.07 (m, 8H, OCH_2), 7.25–7.38 (m, 20H, ArH); $[M + H]^+_{found}$ = 652.2213, $C_{34}H_{40}NO_8P_2$ requires 652.2224.

*N,N-Bis(dimethoxyphosphonylmethyl)-β-alanine Ethyl Ester (***6a***).* Yield: 76% (0.47 g); ^{31}P NMR ($CDCl_3$) δ: 27.0; ^{13}C NMR ($CDCl_3$) δ: 14.1 (CH_2CH_3), 33.1 ($CH_2C{=}O$), 49.2 (dd, $^1J_{CP}$ = 156.0, $^3J_{CP}$ = 5.8, CH_2P), 52.5 (t, $^3J_{CP}$ = 7.6, CH_2N), 52.6 (t, $^2J_{CP}$ = 3.3, OCH_3), 60.5 (OCH_2), 171.9 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.24 (t, $^3J_{HH}$ = 7.4, 3H, OCH_2CH_3), 2.49 (t, $^3J_{HH}$ = 7.0, 2H, $CH_2C{=}O$), 3.11 (t, $^3J_{HH}$ = 7.0, 2H, CH_2N), 3.19 (d, $^2J_{PH}$ = 8.6, 4H, CH_2P), 3.75 (d, 12H, $^2J_{PH}$ = 10.4, OCH_3), 4.11 (q, 2H, OCH_2); $[M + H]^+_{found}$ = 362.1141, $C_{11}H_{26}NO_8P_2$ requires 362.1128.

*N,N-Bis(diethoxyphosphonylmethyl)-β-alanine Ethyl Ester (***6b***).* Yield: 87% (0.66 g); ^{31}P NMR ($CDCl_3$) δ: 24.6; δ [24] ($CDCl_3$) 24.2; ^{13}C NMR ($CDCl_3$) δ: 14.0 ($C(O)OCH_2CH_3$), 16.3 (t, $^3J_{CP}$ = 2.6, CH_2CH_3), 32.9 ($CH_2C{=}O$), 49.9 (dd, $^1J_{CP}$ = 155.5, $^3J_{CP}$ = 5.7, CH_2P), 52.2 (t, $^3J_{CP}$ = 7.5, CH_2N), 60.2 ($C(O)OCH_2$), 61.9 (t, $^2J_{CP}$ = 3.3, CH_2CH_3), 171.8 (C=O); δ [24] ($CDCl_3$) 50.40 (dd, $^1J_{CP}$ = 154.8, $^3J_{CP}$ = 6.0, CH_2P), 52.94 (t, $^3J_{CP}$ = 8.4, CH_2N), 171.73 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.26 (t, $^3J_{HH}$ = 7.1, 3H, $C(O)OCH_2CH_3$), 1.33 (t, $^3J_{HH}$ = 7.0, 12H, CH_2CH_3), 2.53 (t, $^3J_{HH}$ = 7.1, 2H, $CH_2C{=}O$), 3.14 (t, $^3J_{HH}$ = 7.0, 2H, CH_2N), 3.22 (d, $^2J_{PH}$ = 8.5, 4H, CH_2P), 4.05–4.18 (m, 10H, OCH_2); δ [24] ($CDCl_3$) 3.25 (k, $^3J_{HH}$ = 7.8, 2H, CH_2N), 3.28 (d, $^2J_{PH}$ = 9.0, 4H, CH_2P); $[M + H]^+_{found}$ = 418.1757, $C_{15}H_{34}NO_8P_2$ requires 418.1752.

*N,N-Bis(dibutoxyphosphonylmethyl)-β-alanine Ethyl Ester (***6c***).* Yield: 77% (0.69 g); ^{31}P NMR ($CDCl_3$) δ: 24.8; ^{13}C NMR ($CDCl_3$) δ: 13.5 (CH_2 $CH_2CH_2CH_3$), 14.1 (CH_2CH_3), 18.7 ($CH_2CH_2CH_2CH_3$), 32.6 (t, $^3J_{CP}$ = 2.9, OCH_2CH_2), 33.2 ($CH_2C{=}O$), 49.9 (dd, $^1J_{CP}$ = 154.8, $^3J_{CP}$ = 5.6, CH_2P), 52.3 (t, $^3J_{CP}$ = 7.3, CH_2N), 60.4 (OCH_2CH_3), 65.7 (t, $^3J_{CP}$ = 3.5, OCH_2CH_2), 171.9 (C=O); ^{1}H NMR ($CDCl_3$) δ: 0.92 (t, $^3J_{HH}$ = 7.3, 12H, $CH_2CH_2CH_2CH_3$), 1.24 (t, $^3J_{HH}$ = 7.2, 3H, OCH_2CH_3), 1.31–1.46 (m, 8H, $OCH_2CH_2CH_2$), 1.56–1.71 (m, 8H, OCH_2CH_2), 2.50 (t, $^3J_{HH}$ = 7.0, 2H, $CH_2C{=}O$), 3.13 (t, $^3J_{HH}$ = 7.3, 2H, CH_2N), 3.19 (d, $^2J_{PH}$ = 8.2, 4H, CH_2P), 3.98–4.17 (m, 10H, OCH_2); $[M + H]^+_{found}$ = 530.3069, $C_{23}H_{50}NO_8P_2$ requires 530.3062.

*N,N-Bis(dibenzylyoxyphosphonylmethyl)-β-alanine Ethyl Ester (***6d***).* Yield: 91% (1.03 g); ^{31}P NMR ($CDCl_3$) δ: 25.4; ^{13}C NMR ($CDCl_3$) δ: 14.1 (OCH_2CH_3), 32.9 ($CH_2C{=}O$), 50.4 (dd, $^1J_{CP}$ = 155.0, $^3J_{CP}$ = 5.8, CH_2P), 52.3 (t, $^3J_{CP}$ = 7.3, CH_2N), 60.3 (OCH_2CH_3), 67.4 (t, $^3J_{CP}$ = 3.4, OCH_2) 127.9 (C_3),* 128.3 (C_4), 128.5 (C_2),* 136.2 (t, $^3J_{CP}$ = 2.9, C_1), 171.7 (C=O), *may be reversed; ^{1}H NMR ($CDCl_3$) δ: 1.19 (t, $^3J_{HH}$ = 7.1, 3H, OCH_2CH_3), 2.41 (t, $^3J_{HH}$ = 7.2, 2H, $CH_2C{=}O$), 3.12 (t, $^3J_{HH}$ = 6.9, 2H, CH_2N), 3.21 (d, $^2J_{PH}$ = 8.1, 4H, CH_2P), 4.04 (q, 2H, $C(O)OCH_2$), 4.88–5.09 (m, 8H, OCH_2), 7.26–7.33 (m, 20H, ArH); $[M + H]^+_{found}$ = 666.2374, $C_{35}H_{42}NO_8P_2$ requires 666.2380.

*General Procedure for the Synthesis of N,N-Bis-(diphenylphosphinoylmethyl)-β-alanine (***7***) and N,N-Bis(diphenylphosphinoylmethyl)-β-alanine Esters (***8*** and ***9***)*

A mixture of 0.85 mmol β-alanine or its esters (β-alanine: 0.08 g, β-alanine methyl ester: 0.09 g, or β-alanine ethyl ester: 0.10 g), 0.05 g (1.7 mmol) of paraformaldehyde, 0.34 g (1.7 mmol) of diphenylphosphine oxide in 3 mL of acetonitrile was heated at 100°C in a closed vial in the MW reactor for 1 h. The work-up was similar as above to provide products **7**, **8**, and **9** as oils.

*N,N-bis(diphenylphosphinoylmethyl)-β-alanine (***7***).* Yield: 61% (0.27 g); ^{31}P NMR ($CDCl_3$) δ: 30.1; δ [25] ($CDCl_3$) 30.0; ^{13}C NMR ($CDCl_3$) δ: 32.3 ($CH_2C{=}O$), 54.6 (t, $^3J_{CP}$ = 6.7, CH_2N), 55.2 (dd, $^1J_{CP}$ = 82.4, $^3J_{CP}$ = 6.5, CH_2P), 128.6 (d, $^3J_{CP}$ = 12.0, C_3),* 131.1 (d, $^3J_{CP}$ = 9.6, C_2),* 131.2 (d, $^3J_{CP}$ = 97.9, C_1), 131.9 (C_4), 174.5 (C=O), *may be reversed; ^{1}H NMR ($CDCl_3$) δ: 2.47 (t, $^3J_{HH}$ = 6.6, 2H, $CH_2C{=}O$), 3.23 (t, $^3J_{HH}$ = 6.5, 2H, CH_2N), 3.76 (d, $^2J_{PH}$ = 4.3,

4H, CH_2P), 7.32–7.78 (m, 20H, ArH); δ [25]* ($CDCl_3$) 2.53 (t, 2H, CH_2), 3.23 (s, 2H, CH_2N), 3.79 (s, 4H, CH_2P), 7.36–7.73 (m, 20H, ArH); $[M + H]^+_{found}$ = 518.1638, $C_{29}H_{29}NO_4P_2$ requires 518.1645.

*N,N-Bis(diphenylphosphinoylmethyl)-β-alanine Methyl Ester (**8**).* Yield: 89% (0.40 g); ^{31}P NMR ($CDCl_3$) δ: 29.1; ^{13}C NMR ($CDCl_3$) δ: 31.5 ($CH_2C{=}O$), 51.5 ($COOCH_3$), 53.9 (t, $^3J_{CP} = 6.6$, CH_2N), 55.6 (dd, $^1J_{CP} = 83.3$, $^3J_{CP} = 6.8$, CH_2P), 128.4 (d, $^3J_{CP} = 11.7$, C_3),* 131.1 (d, $^3J_{CP} = 9.3$, C_2),* 131.7 (C_4), 131.9 (d, $^3J_{CP} = 88.2$, C_1), 172.8 (C=O), *may be reversed; ^1H NMR ($CDCl_3$) δ: 1.50–1.62 (m, 2H, $CH_2CH_2CH_2$), 1.88 (t, $^3J_{HH} = 7.4$, 2H, $CH_2C{=}O$), 2.98 (t, $^3J_{HH} = 6.4$, 2H, CH_2N), 3.59 (s, 3H, $COOCH_3$), 3.72 (d, $^2J_{PH} = 5.8$, 4H, CH_2P), 7.34–7.78 (m, 20H, ArH); $[M + H]^+_{found}$ = 532.1806, $C_{30}H_{32}NO_4P_2$ requires 532.1811.

*N,N-Bis(diphenylphosphinoylmethyl)-β-alanine Ethyl Ester (**9**).* Yield: 85% (0.40 g); ^{31}P NMR ($CDCl_3$) δ: 29.2; ^{13}C NMR ($CDCl_3$) δ: 14.1 (OCH_2CH_3), 31.6 ($CH_2C{=}O$), 53.8 (t, $^3J_{CP}$ = 7.0, CH_2N), 55.6 (dd, $^1J_{CP} = 83.3$, $^3J_{CP} = 7.0$, CH_2P), 60.4 (OCH_2CH_3), 128.4 (d, $^3J_{CP} = 11.7$, C_3),* 131.1 (d, $^3J_{CP} = 9.4$, C_2),* 131.7 (C_4), 131.9 (d, $^3J_{CP}$ = 87.6, C_1), 172.4 (C=O), *may be reversed; ^1H NMR ($CDCl_3$) δ: 1.15 (t, $^3J_{HH} = 7.2$, 3H, OCH_2CH_3), 2.39 (t, $^3J_{HH} = 6.9$, 2H, $CH_2C{=}O$), 3.32 (t, $^3J_{HH} = 6.7$, 2H, CH_2N), 3.76 (d, $^2J_{PH} = 5.81$, 4H, CH_2P), 3.98 (q, 2H, $C(O)OCH_2$), 7.33–7.79 (m, 20H, ArH); $[M + H]^+_{found}$ = 546.1960, $C_{31}H_{34}NO_4P_2$ requires 546.1958.

*General Procedure for the Preparation of Bis(>P(O)CH$_2$)-γ-aminobutyric Acids (**13**) and Bis(>P(O)CH$_2$)-γ-aminobutyric Acid Esters (**14** and **15**)*

A mixture of 1.7 mmol γ-aminobutyric acid or its esters (γ–aminobutyric acid: 0.18 g, γ–aminobutyric acid methyl ester: 0.20 g, or γ–aminobutyric acid ethyl ester: 0.22 g), 0.10 g (3.4 mmol) of paraformaldehyde, and 3.4 mmol of the >P(O)H species (dimethyl phosphite: 0.31 mL, diethyl phosphite: 0.44 mL, dibutyl phosphite: 0.67 mL, and dibenzyl phosphite: 0.75 mL) was heated at 100°C in a vial in the MW reactor equipped with a pressure controller for 1 h. Then, the water formed was removed in a vacuum. Column chromatography (silica gel 3% methanol in dichloromethane) of the residue afforded the products (**13a–d**, **14a–-d**, **15a–d**) as oils. The following products were thus prepared.

*N,N-Bis(dimethoxyphosphonylmethyl)-γ-aminobutyric Acid (**13a**).* Yield: 79% (0.47 g); ^{31}P NMR ($CDCl_3$) δ: 24.9; δ [23] ($CDCl_3$) 30.7; ^{13}C NMR ($CDCl_3$) δ: 22.6 ($CH_2CH_2CH_2N$), 31.2 ($CH_2C{=}O$), 49.4 (dd, $^1J_{CP} = 158.5$, $^3J_{CP} = 7.3$, CH_2P), 52.7 (t, $^3J_{CP} = 3.4$, OCH_3), 56.0 (t, $^2J_{CP} = 7.5$, CH_2N), 176.1 (C=O); δ [23] ($CDCl_3$) 22.6 ($CH_2CH_2CH_2N$), 31.1 ($CH_2C{=}O$), 49.3 (dd, $^1J_{CP} = 158.0$, $^3J_{CP} = 7.3$, CH_2P), 52.8 (d, $^2J_{CP} = 7.2$, OCH_3), 56.0 (t, $^2J_{CP}$ = 7.5, CH_2N), 176.1 (C=O); ^1H NMR ($CDCl_3$) δ: 1.79 (t, $^3J_{HH} = 7.2$, 2H, $CH_2CH_2CH_2N$), 2.41 (t, $^3J_{HH}$ = 7.4, 2H, $CH_2C{=}O$), 2.83 (t, $^3J_{HH} = 6.8$, 2H, CH_2N), 3.16 (d, $^2J_{PH} = 8.9$, 4H, CH_2P), 3.79 (d, 12H, $^2J_{PH}$ = 10.6, OCH_3); δ [23] ($CDCl_3$) 1.74 (q, $^3J_{HH} = 7.1$, 2H, $CH_2CH_2CH_2N$), 2.36 (t, $^3J_{HH} = 7.1$, 2H, $CH_2C{=}O$), 2.78 (t, $^3J_{HH} = 7.1$, 2H, CH_2N), 3.10 (d, $^2J_{PH}$ = 8.8, 4H, CH_2P), 3.74 (d, 12H, $^2J_{PH} = 10.7$, OCH_3); $[M + H]^+_{found}$ = 348.0971, $C_{10}H_{24}NO_8P_2$ requires 348.0972.

*N,N-Bis(diethoxyphosphonylmethyl)-γ-aminobutyric Acid (**13b**).* Yield: 76% (0.52 g); ^{31}P NMR ($CDCl_3$) δ: 25.9; δ [24] ($CDCl_3$) 22.2; ^{13}C NMR ($CDCl_3$) δ: 16.3 (t, $^3J_{CP} = 2.8$, CH_2CH_3), 22.6 ($CH_2CH_2CH_2N$), 31.2 ($CH_2C{=}O$), 50.0 (dd, $^1J_{CP}$ = 157.6, $^3J_{CP} = 7.0$, CH_2P), 55.8 (t, $^3J_{CP} = 7.3$, CH_2N), 62.0 (t, $^2J_{CP} = 3.4$, OCH_2), 175.8 (C=O); δ [24] ($CDCl_3$) 49.56 (dd, $^1J_{CP} = 156.4$, $^3J_{CP} = 7.1$, CH_2P), 55.50 (t, $^3J_{CP} = 7.5$), 175.14 (C=O); ^1H NMR ($CDCl_3$) δ: 1.25 (t, $^3J_{HH} = 7.0$, 12H, CH_2CH_3), 1.71 (t, $^3J_{HH}$ = 7.0, 2H, $CH_2CH_2CH_2N$), 2.31 (t, $^3J_{HH} = 7.0$, 2H, $CH_2C{=}O$), 2.76 (t, $^3J_{HH} = 6.5$, 2H, CH_2N), 3.08 (d, $^2J_{PH} = 8.9$, 4H, CH_2P), 4.01–4.16 (m, 8H, OCH_2); δ [24] ($CDCl_3$) 2.61 (t, $^3J_{HH} = 6.6$, 2H, CH_2N), 2.94 (d, $^2J_{PH} = 8.8$, 4H, CH_2P); $[M + H]^+_{found}$ = 404.1592, $C_{14}H_{32}NO_8P_2$ requires 404.1598.

*N,N-Bis(dibutoxyphosphonylmethyl)-γ-aminobutyric Acid (**13c**).* Yield: 77% (0.68 g); ^{31}P NMR ($CDCl_3$) δ: 25.7; ^{13}C NMR ($CDCl_3$) δ: 13.5 (CH_2 $CH_2CH_2CH_3$), 18.7 ($CH_2CH_2CH_2CH_3$), 22.9 ($CH_2CH_2CH_2N$), 31.5 ($CH_2C{=}O$), 32.5 (t, $^3J_{CP}$ = 2.8, OCH_2CH_2), 50.0 (dd, $^1J_{CP} = 156.9$, $^3J_{CP} = 6.6$, CH_2P), 55.7 (t, $^3J_{CP} = 6.9$, CH_2N), 65.8 (t, $^3J_{CP} = 3.5$, OCH_2CH_2), 176.1 (C=O); ^1H NMR ($CDCl_3$) δ: 0.93 (t, $^3J_{HH} = 7.3$, 12H, $CH_2CH_2CH_2CH_3$), 1.34–1.45 (m, 8H, $OCH_2CH_2CH_2$), 1.57–1.70 (m, 8H, OCH_2CH_2), 1.79 (t, $^3J_{HH} = 6.9$, 2H, $CH_2CH_2CH_2N$), 2.40 (t, $^3J_{HH}$ = 7.3, 2H, $CH_2C{=}O$), 2.85 (t, $^3J_{HH} = 6.0$, 2H, CH_2N), 3.15 (d, $^2J_{PH} = 8.5$, 4H, CH_2P), 4.01–4.15 (m, 8H, OCH_2); $[M + H]^+_{found}$ = 516.2844, $C_{22}H_{48}NO_8P_2$ requires 516.2850.

*N,N-Bis(dibenzylyoxyphosphonylmethyl)-γ-aminobutyric Acid (**13d**).* Yield: 81% (0.90 g); ^{31}P NMR ($CDCl_3$) δ: 26.5; ^{13}C NMR ($CDCl_3$) δ: 22.7

($CH_2CH_2CH_2$), 31.3 (CH_2C=O), 50.5 (dd, $^1J_{CP}$ = 157.2, $^3J_{CP}$ = 7.2, CH_2P), 55.8 (t, $^3J_{CP}$ = 7.0, CH_2N), 67.6 (t, $^3J_{CP}$ = 3.4, OCH_2) 128.0 (C_3),* 128.4 (C_4), 128.5 (C_2),* 136.0 (t, $^3J_{CP}$ = 2.9, C_1), 176.2 (C=O), *may be reversed; ^{1}H NMR ($CDCl_3$) δ: 1.69 (t, $^3J_{HH}$ = 6.9, 2H, $CH_2CH_2CH_2$), 2.29 (t, $^3J_{HH}$ = 7.3, 2H, CH_2C=O), 2.78 (t, $^3J_{HH}$ = 6.2, 2H, CH_2N), 3.12 (d, $^2J_{PH}$ = 8.3, 4H, CH_2P), 4.90–5.01 (m, 8H, OCH_2), 7.23–7.30 (m, 20H, ArH); $[M + H]^+_{found}$ = 652.2211, $C_{34}H_{40}NO_8P_2$ requires 652.2224.

*N,N-Bis(dimethoxyphosphonylmethyl)-γ-aminobutyric Acid Methyl Ester (***14a***).* Yield: 86% (0.52 g); ^{31}P NMR ($CDCl_3$) δ: 24.7; ^{13}C NMR ($CDCl_3$) δ: 22.5 ($CH_2CH_2CH_2$), 30.9 (CH_2C=O), 49.2 (dd, $^1J_{CP}$ = 157.9, $^3J_{CP}$ = 7.1, CH_2P), 51.5 ($COOCH_3$), 52.6 (t, $^2J_{CP}$ = 6.9, OCH_3), 55.9 (t, $^3J_{CP}$ = 7.6, CH_2N), 173.8 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.65–1.82 (m, 2H, $CH_2CH_2CH_2$), 2.40 (t, $^3J_{HH}$ = 7.4, 2H, CH_2C=O), 2.82 (t, $^3J_{HH}$ = 6.7, 2H, CH_2N), 3.16 (d, $^2J_{PH}$ = 9.0, 4H, CH_2P), 3.67 (s, 3H, $COOCH_3$), 3.78 (d, 12H, $^2J_{PH}$ = 10.6, OCH_3); $[M + H]^+_{found}$ = 362.1126, $C_{11}H_{26}NO_8P_2$ requires 362.1128.

*N,N-Bis(diethoxyphosphonylmethyl)-γ-aminobutyric Acid Methyl Ester (***14b***).* Yield: 89% (0.63 g); ^{31}P NMR ($CDCl_3$) δ: 26.0; δ [24] ($CDCl_3$) 24.4; ^{13}C NMR ($CDCl_3$) δ: 16.4 (t, $^3J_{CP}$ = 2.8, CH_2CH_3), 22.6 ($CH_2CH_2CH_2$), 31.0 (CH_2C=O), 50.0 (dd, $^1J_{CP}$ = 157.1, $^3J_{CP}$ = 6.9, CH_2P), 51.4 ($COOCH_3$), 55.7 (t, $^3J_{CP}$ = 7.7, CH_2N), 61.9 (t, $^2J_{CP}$ = 3.4, OCH_2), 173.8 (C=O); δ [24] ($CDCl_3$) 50.45 (dd, $^1J_{CP}$ = 156.9, $^3J_{CP}$ = 7.1, CH_2P), 56.18 (t, $^3J_{CP}$ = 8.3, CH_2N), 173.07 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.30 (t, $^3J_{HH}$ = 7.0, 12H, CH_2CH_3), 1.70–1.81 (m, 2H, $CH_2CH_2CH_2$), 2.37 (t, $^3J_{HH}$ = 7.4, 2H, CH_2C=O), 2.81 (t, $^3J_{HH}$ = 6.6, 2H, CH_2N), 3.12 (d, $^2J_{PH}$ = 8.9, 4H, CH_2P), 3.64 (s, 3H, $COOCH_3$), 4.05–4.14 (m, 8H, OCH_2); δ [24] ($CDCl_3$) 3.18 (d, $^2J_{PH}$ = 9.1, 4H, CH_2P), 3.27 (k, $^3J_{HH}$ = 6.7, 2H, CH_2N); $[M + H]^+_{found}$ = 418.1749, $C_{15}H_{34}NO_8P_2$ requires 418.1754.

*N,N-Bis(dibutoxyphosphonylmethyl)-γ-aminobutyric Acid Methyl Ester (***14c***).* Yield: 84% (0.76 g); ^{31}P NMR ($CDCl_3$) δ: 25.7; ^{13}C NMR ($CDCl_3$) δ: 13.5 (CH_2 $CH_2CH_2CH_3$), 18.7 ($CH_2CH_2CH_2CH_3$), 22.7 ($CH_2CH_2CH_2N$), 31.1 (CH_2C=O), 32.5 (t, $^3J_{CP}$ = 2.9, OCH_2CH_2), 49.8 (dd, $^1J_{CP}$ = 156.1, $^3J_{CP}$ = 6.6, CH_2P), 51.4 ($COOCH_3$), 55.7 (t, $^3J_{CP}$ = 7.5, CH_2N), 65.4–65.7 (m, OCH_2CH_2), 173.9 (C=O); ^{1}H NMR ($CDCl_3$) δ: 0.89 (t, $^3J_{HH}$ = 7.3, 12H, $CH_2CH_2CH_2CH_3$), 1.29–1.42 (m, 8H, $OCH_2CH_2CH_2$), 1.54–1.68 (m, 8H, OCH_2CH_2), 1.74 (t, $^3J_{HH}$ = 7.2, 2H, $CH_2CH_2CH_2N$), 2.34 (t, $^3J_{HH}$ = 7.4, 2H, CH_2C=O), 2.78 (t, $^3J_{HH}$ = 6.7, 2H, CH_2N), 3.10 (d, $^2J_{PH}$ = 8.5, 4H, CH_2P), 3.62 (s, 3H, $COOCH_3$), 3.96–4.09 (m, 8H, OCH_2); $[M + H]^+_{found}$ = 530.2998, $C_{23}H_{50}NO_8P_2$ requires 530.3006.

*N,N-Bis(dibenzylyoxyphosphonylmethyl)-γ-aminobutyric Acid Methyl Ester (***14d***).* Yield: 88% (1.0 g); ^{31}P NMR ($CDCl_3$) δ: 26.0; ^{13}C NMR ($CDCl_3$) δ: 22.5 ($CH_2CH_2CH_2$), 31.0 (CH_2C=O), 50.4 (dd, $^1J_{CP}$ = 156.4, $^3J_{CP}$ = 7.1, CH_2P), 51.4 ($COOCH_3$), 55.7 (t, $^3J_{CP}$ = 7.4, CH_2N), 67.2–67.5 (m, OCH_2), 127.9 (C_3),* 128.3 (C_4), 128.5 (C_2),* 136.2 (t, $^3J_{CP}$ = 2.9, C_1), 173.7 (C=O), *may be reversed; ^{1}H NMR ($CDCl_3$) δ: 1.71 (t, $^3J_{HH}$ = 7.1, 2H, $CH_2CH_2CH_2$), 2.27 (t, $^3J_{HH}$ = 7.5, 2H, CH_2C=O), 2.81 (t, $^3J_{HH}$ = 6.7, 2H, CH_2N), 3.17 (d, $^2J_{PH}$ = 8.6, 4H, CH_2P), 4.95–5.20 (m, 8H, OCH_2), 7.28–7.32 (m, 20H, ArH); $[M + H]^+_{found}$ = 666.2383, $C_{35}H_{42}NO_8P_2$ requires 666.2380.

*N,N-Bis(dimethoxyphosphonylmethyl)-γ-aminobutyric Acid Ethyl Ester (***15a***).* Yield: 74% (0.47 g); ^{31}P NMR ($CDCl_3$) δ: 24.7; ^{13}C NMR ($CDCl_3$) δ: 14.1 (CH_2CH_3), 22.5 ($CH_2CH_2CH_2$), 31.2 (CH_2C=O), 49.2 (dd, $^1J_{CP}$ = 157.8, $^3J_{CP}$ = 7.1, CH_2P), 52.5 (t, $^2J_{CP}$ = 3.4, OCH_3), 55.9 (t, $^3J_{CP}$ = 7.7, CH_2N), 60.2 (OCH_2), 173.3 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.20 (t, $^3J_{HH}$ = 7.1, 3H, OCH_2CH_3), 1.67–1.79 (m, 2H, $CH_2CH_2CH_2$), 2.33 (t, $^3J_{HH}$ = 7.3, 2H, CH_2C=O), 2.76 (t, $^3J_{HH}$ = 6.7, 2H, CH_2N), 3.11 (d, $^2J_{PH}$ = 9.0, 4H, CH_2P), 3.73 (d, 12H, $^2J_{PH}$ = 10.5, OCH_3), 4.11 (q, 2H, OCH_2); $[M + H]^+_{found}$ = 376.1276, $C_{12}H_{28}NO_8P_2$ requires 376.1285.

*N,N-Bis(diethoxyphosphonylmethyl)-γ-aminobutyric Acid Ethyl Ester (***15b***).* Yield: 96% (0.70 g); ^{31}P NMR ($CDCl_3$) δ: 24.9; ^{13}C NMR ($CDCl_3$) δ: 14.1 ($C(O)OCH_2CH_3$), 16.4 (t, $^3J_{CP}$ = 2.9, CH_2CH_3), 22.6 ($CH_2CH_2CH_2$), 31.3 (CH_2C=O), 50.0 (dd, $^1J_{CP}$ = 156.9, $^3J_{CP}$ = 6.9, CH_2P), 55.8 (t, $^3J_{CP}$ = 7.8, CH_2N), 60.2 ($C(O)OCH_2$), 61.8 (t, $^2J_{CP}$ = 3.4, CH_2CH_3),173.5 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.25 (t, $^3J_{HH}$ = 7.1, 3H, $C(O)OCH_2CH_3$), 1.33 (t, $^3J_{HH}$ = 7.0, 12H, CH_2CH_3), 1.75–1.83 (m, 2H, $CH_2CH_2CH_2$), 2.38 (t, $^3J_{HH}$ = 7.4, 2H, CH_2C = O), 2.84 (t, $^3J_{HH}$ = 6.7, 2H, CH_2N), 3.15 (d, $^2J_{PH}$ = 8.8, 4H, CH_2P), 4.07–4.17 (m, 10H, OCH_2); $[M + H]^+_{found}$ = 432.1919, $C_{16}H_{36}NO_8P_2$ requires 432.1911.

*N,N-Bis(dibutoxyphosphonylmethyl)-γ-aminobutyric Acid Ethyl Ester (***15c***).* Yield: 79% (0.73 g); ^{31}P NMR ($CDCl_3$) δ: 25.6; ^{13}C NMR ($CDCl_3$) δ: 13.5 (CH_2 $CH_2CH_2CH_3$), 14.2 (OCH_2CH_3), 18.7 ($CH_2CH_2CH_2CH_3$), 22.7 ($CH_2CH_2CH_2N$), 31.4 (CH_2C=O), 32.6 (t, $^3J_{CP}$ = 2.9, OCH_2CH_2), 49.8

(dd, $^1J_{CP}$ = 156.0, $^3J_{CP}$ = 6.4, CH_2P), 55.7 (t, $^3J_{CP}$ = 7.3, CH_2N), 60.1 (OCH_2CH_3), 65.5 (t, $^3J_{CP}$ = 3.5, OCH_2CH_2), 173.4 (C=O); ^{1}H NMR ($CDCl_3$) δ: 0.92 (t, $^3J_{HH}$ = 7.2, 12H, $CH_2CH_2CH_2CH_3$), 1.23 (t, $^3J_{HH}$ = 7.0, 3H, OCH_2CH_3), 1.33–1.42 (m, 8H, $OCH_2CH_2CH_2$), 1.57–1.68 (m, 8H, OCH_2CH_2), 1.77 (t, $^3J_{HH}$ = 7.1, 2H, $CH_2CH_2CH_2N$), 2.35 (t, $^3J_{HH}$ = 7.3, 2H, CH_2C=O), 2.81 (t, $^3J_{HH}$ = 6.6, 2H, CH_2N), 3.13 (d, $^2J_{PH}$ = 8.7, 4H, CH_2P), 4.00–4.13 (m, 10H, OCH_2); $[M + H]^+_{found}$ = 544.3165, $C_{24}H_{52}NO_8P_2$ requires 544.3163.

*N,N-Bis(dibenzylyoxyphosphonylmethyl)-γ-aminobutyric Acid Ethyl Ester (***15d***).* Yield: 97% (1.1 g); ^{31}P NMR ($CDCl_3$) δ: 26.4; ^{13}C NMR ($CDCl_3$) δ: 14.1 (OCH_2CH_3), 22.5 ($CH_2CH_2CH_2$), 31.2 (CH_2C=O), 50.4 (dd, $^1J_{CP}$ = 156.4, $^3J_{CP}$ = 7.0, CH_2P), 55.7 (t, $^3J_{CP}$ = 7.4, CH_2N), 60.1 (OCH_2CH_3), 67.3 (t, $^3J_{CP}$ = 3.4, OCH_2) 127.8 (C_3),* 128.2 (C_4), 128.4 (C_2),* 136.2 (t, $^3J_{CP}$ = 2.9, C_1), 173.2 (C=O), *may be reversed; ^{1}H NMR ($CDCl_3$) δ: 1.21 (t, $^3J_{HH}$ = 7.1, 3H, OCH_2CH_3), 1.69 (t, $^3J_{HH}$ = 7.1, 2H, $CH_2CH_2CH_2$), 2.23 (t, $^3J_{HH}$ = 7.5, 2H, CH_2C=O), 2.79 (t, $^3J_{HH}$ = 6.6, 2H, CH_2N), 3.16 (d, $^2J_{PH}$ = 8.9, 4H, CH_2P), 4.07 (q, 2H, $C(O)OCH_2$), 4.90–5.06 (m, 8H, OCH_2), 7.23–7.34 (m, 20H, ArH); $[M + H]^+_{found}$ = 680.2532, $C_{36}H_{44}NO_8P_2$ requires 680.2537.

*General Procedure for the Synthesis of N,N-Bis-(diphenylphosphinoylmethyl)-γ–aminobutyric Acid (***16***) and N,N-Bis(diphenylphosphinoylmethyl)-γ–aminobutyric Acid Esters (***17*** and* ***18****)*

A mixture of 0.85 mmol γ-aminobutyric acid or its esters (γ–aminobutyric acid: 0.09 g, γ–aminobutyric acid methyl ester: 0.10 g, or γ-aminobutyric acid ethyl ester: 0.11 g), 0.05 g (1.7 mmol) of paraformaldehyde, 0.34 g (1.7 mmol) of diphenylphosphine oxide in 3 mL of acetonitrile was heated at 100°C in a closed vial in the MW reactor for 1 h. The work-up was similar as above to provide products **10**, **11**, and **12** as oils.

*N,N-Bis(diphenylphosphinoylmethyl)-γ-aminobutyric Acid (***16***).* Yield: 60% (0.27 g); ^{31}P NMR ($CDCl_3$) δ: 30.2; δ [25] ($CDCl_3$) 30.0; ^{13}C NMR ($CDCl_3$) δ: 21.6 ($CH_2CH_2CH_2$), 31.1 (CH_2C=O), 55.4 (dd, $^1J_{CP}$ = 84.6, $^3J_{CP}$ = 7.6, CH_2P), 57.3 (t, $^3J_{CP}$ = 6.8, CH_2N), 128.5 (d, $^3J_{CP}$ = 11.8, C_3),* 130.9 (d, $^3J_{CP}$ = 9.4, C_2),* 131.0 (d, $^3J_{CP}$ = 98.6, C_1), 131.9 (C_4), 175.7 (C=O), *may be reversed; ^{1}H NMR ($CDCl_3$) δ: 1.56–1.69 (m, 2H, $CH_2CH_2CH_2$), 2.10 (t, $^3J_{HH}$ = 7.1, 2H, CH_2C=O), 2.94 (t, $^3J_{HH}$ = 6.4, 2H, CH_2N), 3.72 (d, $^2J_{PH}$ = 5.4, 4H, CH_2P), 7.33–7.78 (m, 20H, ArH); δ [25]* ($CDCl_3$) 1.69 (m, 2H, CH_2), 2.15 (t, 2H, CH_2), 2.97 (t, 2H, CH_2N), 3.76 (d, $^2J_{PH}$ = 3.6, 4H, CH_2P), 7.32–7.86 (m, 20H, ArH); $[M + H]^+_{found}$ = 532.1801, $C_{30}H_{32}NO_4P_2$ requires 532.1801.

*N,N-Bis(diphenylphosphinoylmethyl)-γ-aminobutyric Acid Methyl Ester (***17***).* Yield: 94% (0.44 g); ^{31}P NMR ($CDCl_3$) δ: 29.5; ^{13}C NMR ($CDCl_3$) δ: 21.8 ($CH_2CH_2CH_2$), 30.7 (CH_2C=O), 51.3 ($COOCH_3$), 55.7 (dd, $^1J_{CP}$ = 84.8, $^3J_{CP}$ = 7.8, CH_2P), 57.3 (t, $^3J_{CP}$ = 7.2, CH_2N), 128.4 (d, $^3J_{CP}$ = 11.7, C_3),* 131.0 (d, $^3J_{CP}$ = 9.2, C_2),* 131.7 (C_4), 131.8 (d, $^3J_{CP}$ = 84.8, C_1), 174.0 (C=O), *may be reversed; ^{1}H NMR ($CDCl_3$) δ: 1.50–1.62 (m, 2H, $CH_2CH_2CH_2$), 1.88 (t, $^3J_{HH}$ = 7.4, 2H, CH_2C=O), 2.98 (t, $^3J_{HH}$ = 6.4, 2H, CH_2N), 3.59 (s, 3H, $COOCH_3$), 3.72 (d, $^2J_{PH}$ = 5.8, 4H, CH_2P), 7.34–7.78 (m, 20H, ArH); $[M + H]^+_{found}$ = 546.1945, $C_{31}H_{34}NO_4P_2$ requires 546.1958.

*N,N-Bis(diphenylphosphinoylmethyl)-γ-aminobutyric Acid Ethyl Ester (***18***).* Yield: 80% (0.38 g); ^{31}P NMR ($CDCl_3$) δ: 29.2; ^{13}C NMR ($CDCl_3$) δ: 14.2 (OCH_2CH_3), 21.8 ($CH_2CH_2CH_2$), 31.1 (CH_2C=O), 55.8 (dd, $^1J_{CP}$ = 84.9, $^3J_{CP}$ = 7.8, CH_2P), 57.5 (t, $^3J_{CP}$ = 6.8, CH_2N), 60.0 (OCH_2CH_3), 128.4 (d, $^3J_{CP}$ = 11.7, C_3),* 131.1 (d, $^3J_{CP}$ = 9.2, C_2),* 131.6 (C_4), 132.0 (d, $^3J_{CP}$ = 97.9, C_1), 173.6 (C=O), *may be reversed; ^{1}H NMR ($CDCl_3$) δ: 1.22 (t, $^3J_{HH}$ = 4.6, 3H, OCH_2CH_3), 1.51–1.66 (m, 2H, $CH_2CH_2CH_2$), 1.90 (t, $^3J_{HH}$ = 7.6, 2H, CH_2C=O), 3.00 (t, $^3J_{HH}$ = 6.7, 2H, CH_2N), 3.72 (d, $^2J_{PH}$ = 6.0, 4H, CH_2P), 4.05 (q, 2H, $C(O)OCH_2$), 7.32–7.85 (m, 20H, ArH); $[M + H]^+_{found}$ = 560.2111, $C_{32}H_{36}NO_4P_2$ requires 560.2114.

*N-Diphenylphosphinoylmethyl)pyrrolodin-2-one (***19***).* ^{31}P NMR ($CDCl_3$) δ: 30.3; ^{13}C NMR ($CDCl_3$) δ: 17.9 (C_4), 29.9 (C_3=O), 43.3 (d, J_{CP} = 43.3, CH_2P), 48.5 (C_5N), 128.7 (d, $^3J_{CP}$ = 11.8, $C_{3'}$),* 130.7 (d, $^3J_{CP}$ = 98.4, $C_{1'}$), 130.9 (d, $^3J_{CP}$ = 9.7, $C_{2'}$),* 132.2 (d, $^3J_{CP}$ = 2.8, $C_{4'}$), 174.9 (d, $^3J_{CP}$ = 2.7, C=O), *may be reversed; ^{1}H NMR ($CDCl_3$) δ: 1.83–1.92 (m, 2H, C_4H), 2.20 (t, $^3J_{HH}$ = 8.4, 2H, C_3H), 3.65 (t, $^3J_{HH}$ = 7.0, 2H, C_5H), 4.23 (d, $^2J_{PH}$ = 5.6, 2H, CH_2P), 7.44–7.88 (m, 10H, ArH); δ [29] ($CDCl_3$) 1.9 (m, 2H, CH_2), 2.2 (t, $^3J_{HH}$ = 6.2, 2H, CH_2), 3.6 (t, $^3J_{HH}$ = 6.9, 2H, CH_2), 4.2 (d, $^2J_{PH}$ = 5.7, 2H, CH_2P), 7.1–8.0 (m, 10H, ArH); $[M + H]^+_{found}$ = 300.1146, $C_{17}H_{19}NO_2P$ requires 300.1153.

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