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Preparation of phosphinodipeptide analogs as building blocks for pseudopeptides synthesis

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Dedicated to François Mathey on the occasion of his 60th birthday

Abstract

A simple and effective preparation of phosphinodipeptides, in good overall yields, has been developed. This one pot procedure, allowing the variation of the substituents in α and/or β position to the phosphorus atom and also in α position to the nitrogen atom, consists in the addition of alkyl hypophosphites to imines, followed by Michael-addition on acrylates. To show the value of phosphinodipeptides analogs **1** as synthetic intermediates, selective deprotections of the three functional groups are described.

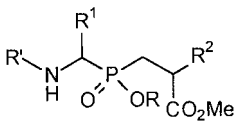
Keywords: Alkyl hypophosphite; Aminoalkylphosphinic acids; Kabachnik–Fields reaction; Michael addition; Phosphinopeptides

1. Introduction

We recently published the first results concerning a one-pot synthesis of phosphino-dipeptides [1]. Going into more details this paper describes the synthetic method applied to various *N*-diphenylmethylimines and acrylates to obtain a large number of phosphinodipeptides as building blocks for combinatorial or parallel peptides synthesis in search of new enzyme inhibitors [2].

The construction of such compounds requires the synthesis of the phosphinodipeptide analogs of type **1** as building blocks.

Compounds **1** are generally prepared in a multistep synthesis from the corresponding adequately protected 1-aminoalkylphosphonous acids by Michael additions using a basic activation [3], by Michael additions or Arbuzov reactions using silyl derivatives Ref. [3b,3c,3d,4], by nucleophilic substitution under basic conditions [3g,5].



1

The 1-aminoalkylphosphonous acids themselves can be synthesized in several ways: by Kabachnik–Fields type reactions involving addition of hypophosphorous acid or its derivatives to a C=N double bond [6–8], by the oxime procedure [9], by a Michaelis–Arbuzov reaction with the bis-(trimethylsilyl) phosphonite [6,10], by alkylation of a suitably protected 1-aminomethylphosphinic acid according to the procedure of Schöllkopf [11], by a Mitsunobu reaction on 1-hydroxyalkylphosphinates [12], by amination of chloromethylphosphinic acid [13], or by a Michael reaction of ethyl diethoxymethylphosphonite with ethyl acetamidomethylenemalonate [14].

In order to develop a convenient preparation of phosphinodipeptides of type **1**, to avoid the synthesis usually performed stepwise with purification of the various intermediates, we have developed a general one-pot synthetic method affording the possibility of

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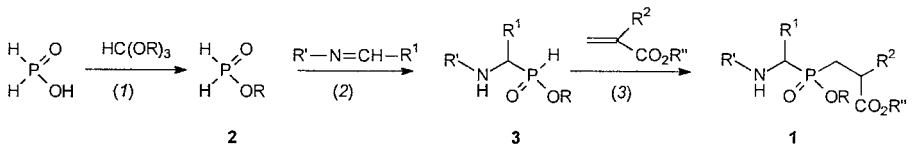


Scheme 1. General way of synthesis for compounds **1**.

variation of R^1 and R^2 groups. Each step of this reaction was improved separately until the yield was more than 90%: then, all the steps were carried out without purification, for parallel synthesis purpose.

We chose to use an in situ generated alkyl hypophosphite **2**. The addition of alkyl hypophosphite **2** to various imines afforded the corresponding alkyl phosphinates **3**. The Michael addition, to several acrylates, was performed using basic activation, and afforded the phosphinodipeptides analogs **1**.

2. Results and discussion

2.1. Synthesis of alkyl hypophosphites 2 (Step 1) (Scheme 2)

Alkyl hypophosphites, rather unstable [15] but more reactive than the hypophosphorous acid usually used [6a,6b,16], were preferred to the bis-(trimethysilyl) phosphonite which is highly pyrophoric [17] (Step 1, Scheme 1).

Such protected hypophosphorous acid derivatives as starting compounds avoid also a supplementary protection step of the phosphinic function, which is necessary if a subsequent Michael addition to an acrylate is done under basic conditions.

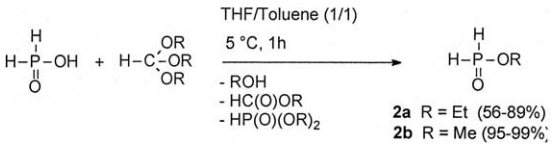
After an exhaustive study of the esterification reaction of hypophosphorous acid by alkyl orthoformates [18,19], we chose, first, to use the ethyl hypophosphite **2a**, instead of methyl hypophosphite **2b** frequently demethylated by nucleophiles.

All the reactions carried out, for the synthesis of ethyl hypophosphite **2a**, with different amounts of ethyl orthoformates, at various temperature, did not permit to get a yield more than 90%, in the presence of the diethoxymethylated compound **4a** (7–15%) as by-product (Table 1).

All the experiments, to hydrolyze selectively **4a**, failed. Also, a reaction without solvent did not permit to get more than 58% of compound **2a** together with 42% of compound **4a**. The mixture THF–toluene was the best solvent for the reaction, and a supplementary amount of ethyl orthoformate added during the reaction, allowed to get the best yield (89%) of compound **2a** with only 7% of compound **4a** (entry 2, Table 1).

To get a good yield in the preparation of alkyl phosphinates **3**, without by-product, in the next step, we decided to purify ethyl hypophosphite **2a** by distillation, but the yield was not better than 24%. Further, the pure ethyl hypophosphite **2a** has to be used immediately or stocked in dry ethanol at -75 °C, but, even at -75 °C the purity decreased to 94% after 1 week.

To check the feasibility and selectivity of the next step (Step 2) of the synthetic (Scheme 1), pure ethyl hypophosphite **2a** (purity > 99%) was directly used for the preparation of the ethyl phosphinate **3a** in the presence of *N*-diphenylmethylimine. The yield, in THF–toluene–ethanol (1/1/8) is then higher than 96%.



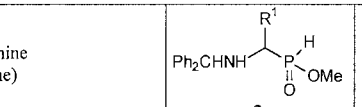
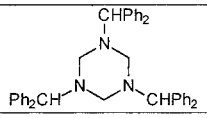
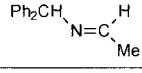
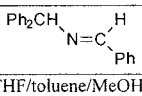
Scheme 2. Preparation of alkyl hypophosphite **2** (Step 1).

Table 1
Preparation of ethyl hypophosphite **2a**

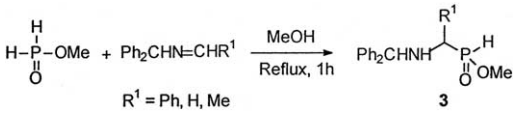
Entry	T (°C)	$H-C(OEt)_2(OEt)$ nb equiv.	$H-P(=O)(H)-OEt$ **2a** Yield (%)[a]	$(EtO)_2CH-P(=O)(H)-OEt$ **4a** Yield (%)[a]
1	5	1.05 + 0.28[b]	84	11
2	5	1.5 + 0.4[b]	89	7
3	5	2	89	8
4	5	2 + 0.1[b]	86	10
5[c]	5	4	83	6
6	- 15	2	82	15
7	28	1 + 0.1[b]	87	11

[a]Yield in toluene/THF 1/1 determined by ^{31}P-NMR.
[b]A supplementary amount of ethyl orthoformate was added during the reaction.
[c]Reaction using the conditions described by Schwabacher [19]

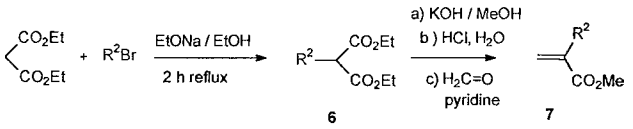
Table 2
Preparation of methyl phosphinate **3** from methyl hypophosphite **2b** and several imines or triazine

Imine (or triazine)	 **3**	R^1	$\delta^{31}P^a$	Yield[b] (%)
	**3ba**	H	40.74	79
	**3bb**	Me	44.30 45.30	39 42 } 81
	**3bc**	Ph	37.30 40.30	43 46 } 89

[a] ^{31}P NMR in THF/toluene/MeOH, 1/1/8.
[b] determined by ^{31}P-NMR.



Scheme 3. Preparation of methyl phosphinates **3** (Step 2).



Scheme 4. Synthesis of α-substituted acrylates **7** [22].

This result demonstrates the value of the foreseen synthetic strategy, concerning Step 2.

But, the poor yield in ethyl hypophosphite **2a** obtained after distillation, or the poor purity without distillation, does not permit to proceed with the synthesis using ethyl hypophosphite as starting material. For our purpose, at each step, the yields have to be around 90%, and all the steps have to be carried out without intermediate purification.

For all these reasons, we decided to use methyl hypophosphite **2b**, formed in very good yield and purity (95–99%) (Step 1, Schemes 1 and 2) [18].

*2.2. Synthesis of methyl phosphinate **3** (Step 2) (Scheme 3)*

The intermediate 1-aminoalkylphosphonous acids **3** were prepared using the in situ generated methyl hypophosphite **2b**. Addition of methyl hypophosphite **2b** to several imines (or triazine) [derived from diphenylmethylamine and formaldehyde [6b] (75% yield), or acetaldehyde [20] (100% yield) or benzaldehyde [21] (91% yield)] in refluxing anhydrous methanol, according to the Baylis method [6b] afforded the methyl phosphinates **3** (Scheme 3) in good yield (79–89%) (Table 2).

As expected, a mixture of two diastereoisomers, in near equal amounts, is obtained when $R^1 = Ph$ or Me.

To improve the yields, the reaction conditions (temperature, solvent, ratio of reagents and rate of addition) were carefully considered.

For instance, in the case of compounds **3bb**, the normal addition of methyl hypophosphite **2b** to 1.1 equivalent of the corresponding imine in refluxing methanol affords only 51% of the mixture of diastereoisomers **3bb**. But by a dropwise addition of 1.6 equivalent of the imine (in order to lower and counterbalance the thermal degradation of the imine) the yield is increased up to 81%.

Further, the purity of the resulting compounds **3** can be increased up to 85–95%: under nitrogen, the crude reaction solution is concentrated in vacuum; to the oil obtained, dry ether is added at 0 °C and two side-products (hypophosphonous acid and dimethyl phosphonate **4b** formed likely by disproportionation of methyl hypophosphite **2b** and potentially troublesome for Step 3 of the synthesis) can be filtered out.

In the remaining solution, the main by-product is then the bis-adduct **5** of the imine on the methyl hypophosphite **2b**, which cannot react further with acrylates in the next step. The three isomers of the

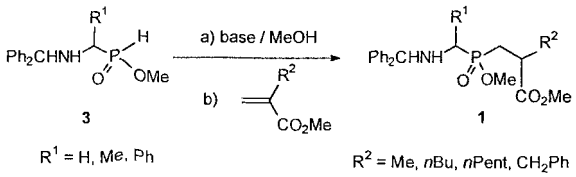
Table 3
Preparation of α-substituted acrylates [22,23]

R^2	Malonate **6** yield (%) [a]	Acrylate **7** yield (%) [b]
n-Bu	87	45
n-Pent	98	55
CH_2Ph	99	51

[a] Determined by ^{1}H-NMR.
[b] Isolated yield, after distillation.

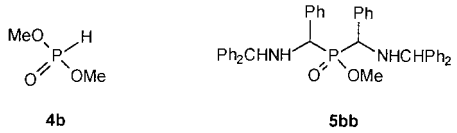
Table 4
Preparation of phosphinodipeptide analogs **1**

Compound	R^1	R^2	Base	Nb equivalent base	Product	Yield (%)
3ba	H	Me	MeONa	1.1	**1ba$_1$**	51
3bc	Ph	Me	MeONa	1.1	**1bc$_1$**	93
3ba	H	Me	*t*-BuOK	0.1	**1ba$_1$**	71
3bb	Me	Me	*t*-BuOK	0.1	**1bb$_1$**	86
3bb	Me	*n*-Bu	*t*-BuOK	0.1	**1bb$_2$**	78
3bb	Me	*n*-Pent	*t*-BuOK	0.1	**1bb$_3$**	86
3bb	Me	CH_2Ph	*t*-BuOK	0.1	**1bb$_4$**	87



Scheme 5. Preparation of phosphinodipeptides analogs **1** (Step 3).

bis-adduct **5bb** (overall yield 8.5%) were isolated, separated and fully characterized.



Products **3ba**, **3bb** and **3bc** were directly used, without additional purification, in the Step 3 of the synthesis.

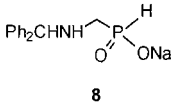
2.3. Synthesis of phosphinodipeptide analogs *1* (Step 3) (Scheme 5)

The last step of the synthesis consists in a Michael addition of the phosphinates **3** to various α-substituted acrylates **7**, which are prepared according to the method proposed by Steller [22] (Scheme 4, Tables 3 and 4).

The last step (Step 3) of the synthesis was first performed according to the method developed by Parsons et al. [3a], using sodium methanolate as basic activating agent.

With the phenyl-substituted phosphinate **3bc** (R^1 = Ph) the yield in the adduct **1bc$_1$** corresponding to the methyl methacrylate (R^2 = Me) is high (92%), using 1.1 equivalent of sodium methanolate as base.

But in the case of unsubstituted phosphinate **3ba** (R^1 = Me) the same conditions give only 51% yield, because a side reaction takes place corresponding to the demethylation of the methyl phosphinate and resulting in the formation of the sodium phosphinate **8** as by-product.



To lower the demethylation process, we have used *t*-BuOK, an overcrowded base, in catalytic amount (0.1 equivalent) as activating agent. The yield in **1ba$_1$** increases then up to 71% and the adducts **1bb** from differently substituted acrylates are obtained in 78–87% yields.

2.4. Selective and total deprotection of phosphinodipeptide analog *1*

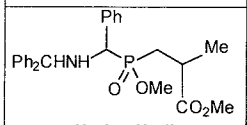
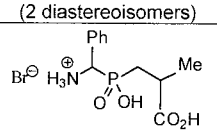
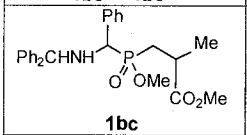
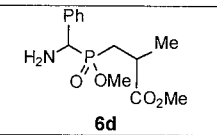
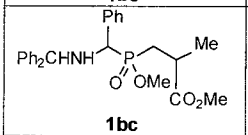
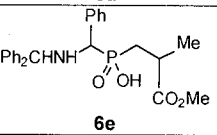
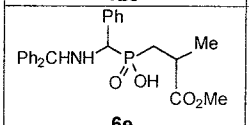
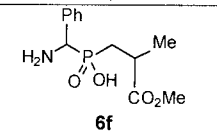
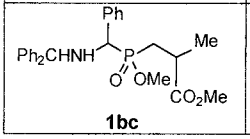
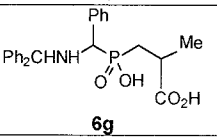
In order to show the value of phosphinodipeptide analog **1** as building blocks, examples of selective deprotection of the various protective groups were performed, in usual ways, on compounds **1bc** and **6e**, to obtain either totally deprotected **6c**, free amino **6d**, free phosphinic **6e**, free amino and phosphinic **6f** or free phosphinic and carboxylic analogs **6g**, in quantitative yields (Table 5).

The separation of two pairs of diastereoisomers was achieved on compounds **1bc** by chromatography on silica gel. Two compounds were isolated as a white solid (**1bc′** and **1bc″**). These compounds were completely deprotected by using an excess of 47% bromhydric acid at 100 °C, affording compounds **6c** in a quantitative yield as a mixture of two diastereoisomers.

3. Conclusions

A general three step synthesis has been developed for the one-pot preparation of phosphinodipeptides **1** by careful adjusting of each step: (i) preparation of methyl hypophosphite **2b** in high yield and purity (preferred to ethyl ester), by esterification of hypophosphorous acid with methyl orthoformate; (ii) dropwise addition of an excess of imines (or triazin) to a refluxing methanolic solution of compound **2b** for the preparation of compound **3**, which can also be partially purified by simple falling out of by-products; (iii) basic catalysis by *t*-

Table 5
Selective and total deprotection of phosphinodipeptides analogs **1**

Starting compound	Conditions	Products (2 diastereoisomers)	Yield %
 **1bc' + 1bc"**	47 % aq. HBr at 100 °C	 **6c**	100
 **1bc**	H_2 / Pd / C in MeOH	 **6d**	95
 **1bc**	1) $BrSi(Me)_3$ 2) MeOH	 **6e**	100
 **6e**	H_2, Pd / C in MeOH	 **6f**	100
 **1bc**	1) NaOH 1N 2) HCl 1N	 **6g**	100

BuOK in order to reduce side reactions, for the addition of compound **3** on various α-substituted methyl acrylates.

This method allows the one-pot preparation of phosphinodipeptides as a mixture of diastereoisomers, in 60–80% overall yields, and allows moreover the variation of the substituents on the carbon in α and/or β positions to the phosphorus.

Last, in order to show the value of phosphinodipeptides analogs **1** as synthetic building blocks for combinatorial or parallel synthesis, selective or complete deprotections of the various protective groups were performed in almost quantitative yields.

4. Experimental

4.1. General

Solvents and substrates were purified by conventional methods immediately before use. The NMR spectra were obtained on Bruker AC-200, AC-250 instruments (^{1}H-NMR at 200.13 and 250.13 MHz, ^{13}C-NMR at 50.32 MHz and ^{31}P-NMR at 81.0 MHz. IR spectra were recorded using a Perkin–Elmer 377 spectrometer. MS were obtained using a JEOL JMS DX-300 (FAB +). Elemental analyses were performed by the 'Service de Microanalyse du CNRS au Département Analyse Elémentaire, à Vernaison'. The crude products were purified by HPLC preparative chromatography on Merck 15–40 μm, flash chromatography on Merck 40–63 μm or liquid chromatography at normal pressure on Merck 70–200 μm.

All reactions were performed under dry nitrogen in a flask, magnetic stirrer and a pressure equalizing addition funnel.

4.2. Synthesis of alkyl hypophosphites *2*

4.2.1. Synthesis of ethyl hypophosphite *2a*

To a solution of anhydrous hypophosphorous acid (0.66 g, 10 mmol) in dry THF (2.4 ml) and toluene (2.4 ml) stirred at 5 °C under N_2 was added triethyl orthoformate (6.65 ml, 40 mmol). After 1 h at 5 °C, the mixture was allowed to warm to room temperature (r.t.) and stirred for 2 h to afford 83% of **2a** together with 6% of anhydrous hypophosphorous acid and 6% ethyl (diethoxymethyl) hydrogenophosphinate **4a**.

4.2.1.1. Hypophosphorous acid. ^{31}P-NMR (THF–toluene): δ 5.20 (t, $^1J_{P-H} = 543.8$).

*4.2.1.2. Ethyl (diethoxymethyl) hydrogenophosphinate **4a**.* ^{31}P-NMR (THF–toluene): δ 27.02 (ddt, $^1J_{P-H} = 551.7$, $^2J_{P-H} = {}^3J_{P-H} = 8.5$).

*4.2.1.3. Ethyl hypophosphite **2a**.* ^{31}P-NMR (THF–toluene): δ 13.16 (tt, $^1J_{P-H} = 562.4$, $^3J_{P-H} = 9.9$). Eb: 31 °C, 2 mmHg.

*4.2.2. Synthesis of methyl hypophosphite **2b***

To a solution of anhydrous hypophosphorous acid (0.66 g, 10 mmol) in a mixture of dry THF (2.4 ml) and toluene (2.4 ml) stirred at 5 °C under N_2 is added trimethyl orthoformate (4.4 ml, 40 mmol). After 1 h at 5 °C, the mixture was allowed to warm to r.t. and stirred for 2 h to afford 98% of **2b** (together with 2% of dimethyl hydrogenophosphinate **4b**).

*4.2.2.1. Methyl hypophosphite **2b**.* ^{31}P-NMR (THF–toluene): δ 16.8 (tq, $^1J_{P-H} = 565.6$, $^3J_{P-H} = 12.7$).

*4.2.2.2. Dimethyl hydrogenophosphinate **4b**.* ^{31}P-NMR (THF–toluene): δ 10.70 (dhept, $^1J_{P-H} = 696.2$, $^3J_{P-H} = 11.8$).

The *N*-diphenylmethylimines are prepared according to the literature: $R^1 = H$ [6], $R^1 = CH_3$ [19], $R^1 = Ph$ [19].

4.2.2.3. Tris(diphenylmethyl) hexahydro 1,3,5-triazine. Melting point (m.p.): 241.5–245 °C (toluene) (lit. 252 °C) [6b], ^{1}H-NMR ($CDCl_3$): δ 3.34 (s, 6H, CH_2), 4.72 (s, 3H, C*H*), 6.99–7.33 (m, 30H, CH_{ar}), ^{13}C-NMR: ($CDCl_3$): δ 70.02 (*C*H), 71.89 (*C*H_2), 126.66, 127.58, 128.29, 142.39 (*C*$_{ar}$), IR ($CHCl_3$): 3064, 3029, 3009, 2813, 1599, 1492, 1452, 1187, 1175.

4.2.2.4. N-(Diphenylmethyl) ethanimine (colorless oil). ^{1}H-NMR ($CDCl_3$): δ 2.10 (d, 3H, $^3J_{HH} = 4.8$, CH_3), 5.40 (s, 1H, C*H*Ph_2), 7.23–7.39 (m, 10H, *C*H$_{ar}$), 7.92 ppm (q, 1H, $^3J_{HH} = 4.8$, *C*H=N), ^{13}C-NMR: ($CDCl_3$): δ 22.50 (*C*H_3), 78.71 (*C*HPh_2), 127.07, 127.74, 128.56, 143.86, 161.36.

4.2.2.5. N-(Diphenylmethyl) phenylmethanimine. m.p.: 99–101 °C (EtOH) (lit. 98–100 °C) [21], ^{1}H-NMR ($CDCl_3$): δ 5.62 (s, C*H*Ph_2), 7.19–7.44 and 7.83–7.88 (m, CH_{ar}), 8.44 (s, C*H*=N), ^{13}C-NMR: ($CDCl_3$): δ 78.03 (*C*HPh_2); 127.11, 127.81, 128.57, 128.59, 128.65, 130.88, 136.45, 144.04 (*C*$_{ar}$), 160.91 (*C*=N), IR ($CHCl_3$): 3090, 3065, 3029, 3009, 2846, 1951, 1889, 1810, 1644, 1599, 1580, 1492, 1452, 1025.

*4.3. Synthesis of phosphinates **3***

*4.3.1. Synthesis of ethyl (1-diphenylmethylamino)-1-phenyl-methyl hydrogenophosphinate (**3a**)*

To a solution of pure ethyl hypophosphite **2a** (1.14 g, 12 mmol, one equivalent), obtained after distillation, in dry EtOH (10 ml) is added a solution of 3.29 g (12 mmol, one equivalent) of *N*-(diphenylmethyl) phenyl methanimine in dry EtOH. After 4 h reflux, ^{31}P-NMR shows two diastereoisomers (in a ratio 48/52) corresponding to a 96% overall yields in **3a**.

*4.3.2. Ethyl (1-diphenylmethylamino)-1phenyl-methyl hydrogenophosphinate (**3a**)*

^{31}P-NMR (EtOH): δ 34.05 (ddt, $^1J_{PH} = 564.5$, $^2J_{PH} = 16.7$, $^3J_{PH} = 8.4$), 37.63 (ddt, $^1J_{PH} = 562.2$, $^2J_{PH} = 17.0$, $^3J_{PH} = 8.5$), ^{1}H-NMR ($CDCl_3$): δ 1.16 and 1.29 (2t, 3H, $^3J_{HH} = 7.1$, OCH_2CH_3), 2.71 (s, 1H, N*H*), 3.83–4.22 (m, 3H, CH_2 and NC*H*P), 4.82 and 4.83 (2s, 1H, C*H*Ph_2), 7.01 and 7.14 (2d, 1H, $^1J_{PH} = 557.0$ and $^1J_{PH} = 559.5$, P*H*), 7.25–7.44 (m, 15H, CH_{ar}), ^{13}C-NMR: ($CDCl_3$): δ 16.25 and 16.37 (2d, $^3J_{PC} = 5.6$ and $^3J_{PC} = 5.8$, *C*H_3), 59.59 and 59.76 (2d, $^1J_{PC} = 104.2$ and $^1J_{PC} = 106.1$, HN*C*HP), 62.45 and 63.09 (2d, $^2J_{PC} = 7.4$ and $^2J_{PC} = 7.5$, *C*H_2), 63.60 and 63.79 (2d, $^3J_{PC} = 15.3$ and 16.5, Ph_2CH), 127.04–129.07 (m, *C*H$_{ar}$), 133.99 and 134.13 (2d, $^2J_{PC} = 1.8$ and $^2J_{PC} = 3$, *C*$_{ar}$), 141.76, 141.90, 143.45 et 143.48 (4s, *C*$_{ar}$).

*4.3.2.1. Synthesis of methyl 1-diphenylmethylamino-methyl phosphinate (**3ba**).* To the reaction mixture of methyl hypophosphite **2b** (9.78 mmol) is then added dry MeOH (20 ml) and 2.24 g (3.75 mmol) of 1,3,5-tris-(diphenylmethyl) hexahydro-triazine. After 7 h reflux, the solution stays under nitrogen at r.t. The excess in triazine is filtered out and compound **3ba** is obtained in 79% yield in the filtrate which will be used for the next synthetic step. ^{31}P-NMR (THF–toluene–MeOH, 1/1/8): δ 40.74, ^{1}H-NMR ($CDCl_3$): δ 2.98 (d, 2H, $^2J_{PH} = 11.2$, CH_2), 3.81 (d, $^3J_{PH} = 8.8$, 3H, CH_3), 4.86 (s, 1H, C*H*), 7.07–7.40 (m, 10H, CH_{ar}), 7.08 (d, 1H, $^1J_{PH} = 546.3$, P*H*), ^{13}C-NMR: ($CDCl_3$): δ 45.44 (d, $^1J_{PC} = 106.8$, *C*H_2), 52.97 (d, $^2J_{PC} = 7.3$, *C*H_3), 68.24 (d, $^3J_{PC} = 16.2$, *C*H), 127.28–129.26 (m, *C*$_{ar}$), 142.47 (*C*$_{ar}$), 142.66 (*C*$_{ar}$).

*4.3.2.2. Synthesis of methyl 1-diphenylmethylaminoethyl phosphinate (**3bb**).* To a solution of crude methyl hypophosphite **2b** (9.78 mmol) in dry MeOH (13 ml), under reflux, is added drop-wise in 30 min, a 2 N solution in MeOH of *N*-(diphenylmethyl) methanimine (15.6 mmol) until the disappearing of methyl hypophosphite, observed by ^{31}P-NMR. Two isomers of compounds **3bb** are observed in 81% overall yield [δ ^{31}P: 44.30 ppm (39.5%), 45.30 ppm (41.5%)] in the presence of hypophosphorus acid [δ ^{31}P: 2.50 ppm (3.9%)] and dimethylhydrogenophosphinate [δ ^{31}P: 11.9 ppm (2.4%)].

^{31}P-NMR (THF–toluene–MeOH, 1/1/8): δ 44.30 and 45.30, ^{1}H-NMR ($CDCl_3$): δ 1.35 (dd, 3H, $^3J_{PH} = 17.7$, $^3J_{HH} = 7.1$, $CHCH_3$), 2.86–3.05 (m, 1H, C*H*CH_3), 3.80 and 3.83 (2d, $^3J_{PH} = 11.2$, OCH_3), 5.16 and 5.18 (2s, 1H, Ph_2CH), 6.97 (d, H, $^1J_{PH} = 538.1$, P*H*), 7.25–7.44 (m, 10H, CH_{ar}), ^{13}C-NMR($CDCl_3$): δ 12.80 (d, $^2J_{PC} = 2.1$, $CHCH_3$), 48.64 and 48.75 (2d, $^1J_{PC} = 108.0$, $^1J_{PC} = 109.6$, CH_3CH), 52.59 and 52.92 (2d, $^2J_{PC} = 7.7$, $^2J_{PC} = 7.9$, OCH_3), 64.23 and 64.32 (2d, $^3J_{PC} = 11.3$,

$^3J_{PC} = 11.9$, Ph_2CH), 127.12–128.75 (m, CH_{ar}), 142.47, 142.61, 143.15 and 143.21 (4s, CH_{ar}).

*4.3.2.3. Synthesis of methyl 1-diphenylmethylamino-1-phenyl-methyl phosphinate (**3bc**).* A solution of crude methyl hypophosphite **2b** (9.67 mmol) in dry MeOH (20 ml) and 2.62 g (9.67 mmol) of *N*-(diphenylmethyl) phenylmetanimine is heated for 1 h at reflux. After cooling under nitrogen at r.t., two isomers are obtained in 89% overall yield, observed by ^{31}P-NMR, [δ ^{31}P: 37.30 ppm (43%), 40.30 ppm (46%)], in the presence of 8.5% of **5bb**: three compounds, **5bb$_1$** (4.3%), **5bb$_2$** (2.5%) and **5bb$_3$** (1.7%). **3bc**: ^{31}P-NMR (THF–toluene–MeOH, 1/1/8): δ 37.30 and 40.30.

Compounds **5bb** are obtained, as a mixture of three compounds because of the chirality of the central phosphorus atom. After the neutralization of the crude solution, with HCl 1 N, until pH 7, concentration, and extraction with ethyl acetate, chromatography on silica gel (hexane–AcOEt 90/10 to 40/60) each diastereisomer is isolated pure. **5bb$_1$**: $R_f = 0.33$, **5bb$_2$**: $R_f = 0.30$, and **5bb$_3$**: $R_f = 0.14$ (hexane–AcOEt 50/50).

*Methyl bis-(1-diphenylmethylamino-1-phenyl-methyl) phosphinates (**5bb**).*

5bb$_1$ (DL isomers)

m.p.: 137–138 °C, ^{31}P-NMR ($CDCl_3$): δ 46.02, ^{1}H-NMR ($CDCl_3$): δ 3.17 (d, 6H, $^3J_{PH} = 9.9$, OCH_3), 4.11 and 4.17 (2d, 2H, $^2J_{PH} = 14.0$ and $^2J_{PH} = 18.4$, PCHPh), 4.63 and 4.91 (s, 2H, Ph_2CH), 7.14–7.40 (m, 30H, CH_{ar}), ^{13}C-NMR ($CDCl_3$): δ 52.29 (d, $^2J_{PC} = 7.5$, OCH_3), 57.57 (d, $^1J_{PC} = 95.9$, PCHN), 59.97 (d, $^1J_{PC} = 96.2$, PCHN), 63.54 (d, $^3J_{PC} = 14.6$, Ph_2CH), 63.98 (d, $^3J_{PC} = 12.3$, Ph_2CH), 126.98–129.03 (m, CH_{ar}), 134.71 (d, $^2J_{PC} = 3.5$ Hz, C_{ar}), 135.46 (s, C_{ar}), 141.75, 141.98, 143.36 and 143.69 (4s, C_{ar}).

5bb$_2$ (*meso*)

m.p.: 136–138 °C, ^{31}P-NMR ($CDCl_3$): δ 47.19, ^{1}H-NMR ($CDCl_3$): δ 3.03 (d, 6H, $^3J_{PH} = 9.9$, OCH_3), 4.09 (d, 2H, $^2J_{PH} = 12.7$, PCHPh), 4.69 (s, 2H, Ph_2CH), 7.14–7.40 (m, 30H, CH_{ar}), ^{13}C-NMR ($CDCl_3$): δ 52.38 (d, $^2J_{PC} = 7.6$, OCH_3), 57.67 (d, $^1J_{PC} = 98.3$, PCHN), 63.49 (d, $^3J_{PC} = 14.9$, Ph_2CH), 127.12–129.06 (m, CH_{ar}), 135.53 (d, $^2J_{PC} = 4.5$ Hz, C_{ar}), 142.08 (s, $2C_{ar}$), 143.6 (s, $2C_{ar}$).

5bb$_3$ (*meso*)

m.p.: 165–169 °C, ^{31}P-NMR (THF–toluene): δ 48.30, ^{1}H-NMR ($CDCl_3$): δ 3.99 (d, 6H, $^3J_{PH} = 9.8$, OCH_3), 4.08 (d, 2H, $^2J_{PH} = 15.1$, PCHPh), 4.68 (s, 2H, Ph_2CH), 7.16–7.37 (m, 30H, CH_{ar}), ^{13}C-NMR ($CDCl_3$): δ 54.02 (d, $^2J_{PC} = 7.6$, OCH_3), 58.06 (d, $^1J_{PC} = 99.2$, PCHN), 63.54 (d, $^3J_{PC} = 14.1$, Ph_2CH), 126.99–128.98 (m, CH_{ar}), 134.64 (s, C), 141.41 (s, $2C_{ar}$), 143.76 (s, $2C_{ar}$).

Acrylates **7** (colorless oils) were prepared using the method proposed by Steller and by Deslongchamps [22,23]:

Methyl α-butyl acrylate (yield 45%)

Eb: 70 °C 20 mmHg, ^{1}H-NMR ($CDCl_3$): δ 0.91 (t, 3H, $^3J_{HH} = 7.0$, CH_3), 1.28–1.49 (m, 4H, CH_2), 2.30 (t, 2H, $^3J_{HH} = 7.1$, C=CCH_2), 3.75 (s, 3H, OCH_3), 5.52 and 6.13 (2m, 2H, =CH_2), ^{13}C-NMR ($CDCl_3$): δ 13.48 (CH_3), 22.04 (CH_2), 30.38 (CH_2), 31.39 (CH_2), 51.18 (OCH_3), 123.85 (=CH_2), 140.65 (C=), 167.22 (C=O).

Methyl α-pentyl acrylate (yield 55%)

Eb: 95 °C 20 mmHg, ^{1}H-NMR ($CDCl_3$): δ 0.90 (t, 3H, $^3J_{HH} = 6.6$, CH_3), 1.18–1.54 (m, 6H, CH_2), 2.30 (t, 2H, $^3J_{HH} = 7.4$, C=CCH_2); 3.76 (s, 3H, OCH_3), 5.53 and 6.13 (2m, 2H, =CH_2), ^{13}C-NMR ($CDCl_3$): δ 13.61 (CH_3), 22.21 (CH_2), 27.90 (CH_2), 31.20 (CH_2), 31.65 (CH_2), 51.15 (OCH_3), 123.82 (=CH_2), 140.68 (C=), 167.16 (C=O).

Methyl α-benzyl acrylate (yield 51%)

Eb: 130–132 °C 20 mmHg, ^{1}H-NMR ($CDCl_3$): δ 3.68 (m, 2H, CH_2), 3.74 (s, 3H, OCH_3), 5.46 and 6.24 (2m, 2H, =CH_2), 7.19–7.35 (m, 5H, CH_{ar}), ^{13}C-NMR ($CDCl_3$): δ 38.30 (CH_2), 51.86 (OCH_3), 126.20 (CH_2), 128.55 (C_{ar}), 129.07 (C_{ar}), 138.90 (C_{ipso}), 140.00 (C=), 166.70 (C=O).

4.4. Synthesis of phosphinodipeptides analogs **1**

4.4.1. General procedure

The solution containing methyl phosphinate **3** (10 mmol), is concentrated under vacuum. At 0 °C dry ether (15 ml) is added to the yellow oil under agitation for 45 min. The white solid is filtrated under nitrogen. The solid corresponds to hypophosphorous acid and dimethyl phosphinate. At −5 °C, the solution is, once again, concentrated under vacuum, and 20 ml of dry THF are added. To the solution containing **3**, was added, dropwise, at 0 °C, first a solution of 1.1 equivalents of α-alkyl acrylate in dry THF, then, 0.1 equivalent of a solution of sublimed *t*-BuOK in dry THF. The reaction mixture was then stirred for 2 h at 0 °C and at r.t. overnight. The reaction was quenched with 1 N HCl and extracted with EtOAc. The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The crude product, by chromatography on silica gel (15–40 μm) with hexane–EtOAc (90/10) as the starting eluent, gives compounds **1** as a viscous oil.

4.4.2. Methyl (1-diphenylmethylaminomethyl) (2-methoxycarbonyl-propyl) phosphinate **1ba$_1$** (yield 51%)

^{31}P-NMR (AcOEt): δ 51.56 (s) (28%) and 52.05 (s) (23%), ^{1}H-NMR ($CDCl_3$): δ 1.34 (d, 6H, $^3J_{HH} = 7.1$, CH_3), 1.90 and 2.38 (m, 2H, ABMX system, CH_2C), 1.97 and 2.43 (m, 2H, ABMX system, CH_2C), 2.47 (s, 1H, NH), 2.84–3.00 (m, 3H, CHCO and CH_2N), 3.68 and 3.69 (2s, 3H, CO_2CH_3), 3.70 and 3.73 (2d, 3H, $^3J_{PH} = 10.4$ and $^3J_{PH} = 10.4$ Hz, $POCH_3$), 4.81 (s, 1H, CHPh$_2$), 7.22–7.41 (m, 10H, CH_{ar}), ^{13}C-NMR

($CDCl_3$): δ 19.53 and 19.56 (2d, $^3J_{PC} = 9.1$ and $^3J_{PC} = 9.1$, CH_3), 30.32 and 30.41 (2d, $^1J_{PC} = 92$ and $^1J_{PC} = 92$, CH_2C), 34.05 and 34.16 (2d, $^2J_{PC} = 3.6$ and $^2J_{PC} = 2.4$, $CHCO$), 45.53 and 46.07 (2d, $^1J_{PC} = 104.1$ and $^1J_{PC} = 102.9$ Hz, CH_2N), 51.80 and 52.01 (2d, $^2J_{PC} = 7.3$ and $^2J_{PC} = 6.7$, $POCH_3$), 52.49 (s, $COCH_3$), 69.10 and 69.16 (2d, $^3J_{PC} = 16.3$ and $^3J_{PC} = 16.9$, $CHPh_2$), 127.64, 127.68, 127.77, 127.81, 129.03, 129.06, 143.15, 143.22, 143.32, 176.28 and 176.31 ppm (2d, $^3J_{PC} = 10.3$ $^3J_{PC} = 9.7$ Hz, C=O), MS FAB$^+$(NBA): $[M + H]^+$: 376.

*4.4.3. Methyl (1-diphenylmethylaminoethyl) (2-methoxycarbonyl-propyl) phosphinate (**1bb$_1$**) (yield 86%)*

^{31}P-NMR (Acetone) δ: 54.71 (s), 54.82 (s), 54.95 (s), 55.15 (s), ^{1}H-NMR ($CDCl_3$): δ 1.25–1.37 (m, 6H, 2 CH_3), 1.76–2.53 (m, 3H, CH_2 and NH), 2.69–3.04 (m, 2H, $CHCO$ and CHP), 3.63 (d, 3H, $^3J_{PH} = 10.1$, $POCH_3$), 3.65 (s, 3H, $COCH_3$), 3,66 (d, 3H, $^3J_{PH} = 10.1$, $POCH_3$), 3.67 and 3.69 (2s, 6H, $COCH_3$), 3.72 and 3.74 (2d, $^3J_{PH} = 10.1$ and $^3J_{PH} = 11.2$, $POCH_3$), 5.04, 5.05, 5.06 and 5.07 (4s, $CHPh_2$), 7.20–7.35 (m, 10H, CH_{ar}), ^{13}C-NMR ($CDCl_3$): δ 12.95 and 13.17 (2d, $^2J_{PC} = 3.5$ and $^2J_{PC} = 5.5$, CCH_3), 18.71, 19.20 and 19.22 ppm (3d, $^3J_{PC} = 7.0$, $^3J_{PC} = 9.0$ and $^3J_{PC} = 9.2$, CH_3), 28.16, 28.33, 28.63 and 28.81 (4d, $^1J_{PC} = 88.1$, $^1J_{PC} = 88.3$, $^1J_{PC} = 88.3$ and $^1J_{PC} = 88.7$, CH_2), 33.74, 33.86 and 33.91 (3d, $^2J_{PC} = 3.0$, $^2J_{PC} = 3.2$ and $^2J_{PC} = 4.0$, CH), 48.63, 49.18 and 49.39 (3d, $^1J_{PC} = 109.2$, $^1J_{PC} = 107.4$ and $^1J_{PC} = 108.8$, CH), 51.48, 51.67 and 51.93 (3d, $^2J_{PC} = 6.9$, $^2J_{PC} = 7.0$ and $^2J_{PC} = 6.8$, OCH_3), 51.93, 51.94, 51.95 and 51.96 (4s, CH_3), 64.08 and 64.11 (2d, $^3J_{PC} = 13.8$ and $^3J_{PC} = 13.1$, CH), 127.06–128.59 (m, CH_{ar}), 142.35, 142.54, 142.56, 143.55, 143.58, 143.80 and 143.83 (7s, C_{ar}), 175.90, 175.93, 176.02 and 176.08 (4d, $^3J_{PC} = 9.0$, $^3J_{PC} = 11.5$, $^3J_{PC} = 8.4$ and $^3J_{PC} = 8.7$, CO), MS FAB$^+$: $[M + H]^+$(GT): 390, IR ($CHCl_3$): 3318, 3086, 3067, 3028, 2975, 2946, 2849, 1741, 1601, 1495, 1466, 1219, 1166, 1117, 1045. Elemental microanalysis ($C_{21}H_{28}NO_4P$): Found: C, 63.28; H, 7.21; N, 3.60; P, 8.37. Calc.: C, 64.77; H, 7.25; N, 3.60; P, 7.95%

*4.4.4. Methyl (1-diphenylmethylamino-1-phenyl-methyl) (2-methoxycarbonyl-propyl) phosphinate (**1bc$_1$**) (yield 93%)*

^{31}P-NMR (Toluene–THF–MeOH): δ: 51.92 (s) (26%), 52.11 (s) (24%), 52.51 (s) (22%), 52.93 (s) (21%), The crude product, by chromatography on silica gel (15–40 μm) with hexane–EtOAc (90/10) as the starting eluent to hexane–EtOAc (60/40), gives two pairs of diastereoisomers **1bc$'_1$** as a white solid and **1bc$''_1$** as a yellow oil.

*4.4.4.1. Fraction 1: **1bc$'_1$**.*

M.p.: 92–96 °C, ^{31}P-NMR (AcOEt): δ 49.01 (s), 49.07 (s), ^{1}H-NMR ($CDCl_3$): δ 1.30 and 1.35 (2d, 3H, $^3J_{HH} = 7.0$ and $^3J_{HH} = 7.1$, $CHCH_3$), 1.94 and 2.32 (m, 2H, ABMX system, $OPCH_2$), 2.17 and 2.56 (m, 2H, ABMX system, $OPCH_2$), 2.74 (s, NH), 2.80–3.06 (m, 1H, $CHCH_3$), 3.13 and 3.14 (2d, 3H, $^3J_{PH} = 10.1$ and $^3J_{PH} = 10.1$, OCH_3), 3.68 (d, 1H, $^2J_{PH} = 15.3$, $HNCHPh$), 3.69 and 3.70 (2s, 3H, OCH_3), 3.71 (d, 1H, $^2J_{PH} = 14.9$, $HNCHPh$), 4.64 and 4.65 (2s, 1H, Ph_2CH), 7.19–7.40 (m, 15H, CH_{ar}), ^{13}C-NMR ($CDCl_3$): δ: 18.97 and 19.19 (2d, $^3J_{PC} = 8.4$ and $^3J_{PC} = 9.1$, $CHCH_3$), 30.16 and 30.30 (2d, $^1J_{PC} = 92.2$ and $^1J_{PC} = 92.4$, $OPCH_2$), 33.83 and 34.02 (2d, $^2J_{PC} = 4.4$ and $^2J_{PC} = 3.8$, $OCCH$), 51.86 (d, $^2J_{PC} = 7.6$, OCH_3), 51.98 (s, OCH_3), 52.01 (d, $^2J_{PC} = 7.3$, OCH_3), 59.76 and 60.17 (2d, $^1J_{PC} = 103.0$ and $^1J_{PC} = 103.0$, $HNCHP$), 63.64 and 63.68 (2d, $^3J_{PC} = 16.0$ and $^3J_{PC} = 16.0$, $CHPh_2$), 127.04, 127.25, 127.56, 127.95, 128.24, 128.51, 128.70, 128.73, 128.77, 128.81, 128.94 (C_{ar}), 135.20 [d, $^2J_{PC} = 3.8$, $(HN)CH(P)C_{ar}$], 141.97, 142.01, 143.51, 175.83 and 176.03 (2d, $^3J_{PC} = 10.4$ and $^3J_{PC} = 9.2$, C=O), MS FAB$^+$(NBA): $[M + H]^+$ 452, IR (KBr): 3260, 3080, 3060, 3020, 2940, 2880, 2840, 1720, 1600, 1560, 1495, 1450, 1200, 1160, 1100, 1030, Elemental microanalysis ($C_{26}H_{30}NO_4P$): Found: C, 68.99; H, 6.68; N, 3.21; P, 6.53. Calc.: C, 69.17; H, 6.70; N, 3.10; P, 6.86%.

*4.4.4.2. Fraction 2: **1bc$''_1$**.*

^{31}P-NMR (AcOEt): δ 49.50 (s), 50.09 (s), ^{1}H-NMR ($CDCl_3$): δ 1.20 and 1.23 (2d, 3H, $^3J_{HH} = 7.9$ and $^3J_{HH} = 7.4$, $CHCH_3$), 1.60 and 2.22 (m, 2H, ABMX system, $OPCH_2$), 1.72 and 2.16 (m, 2H, ABMX system, $OPCH_2$), 2.68–2.86 (m, 1H, $CHCH_3$), 3.09 (s, NH), 3.67 (s, 6H, OCH_3), 3.80 and 3.87 (2d, 3H, $^3J_{PH} = 10.1$ and $^3J_{PH} = 10.2$, OCH_3), 3.82 and 3.92 (2d, 1H, $HNCHPh$), 4.66 and 4.69 (2s, 1H, Ph_2CH), 7.24–7.47 (m, 15H, CH_{ar}), ^{13}C-NMR ($CDCl_3$): δ 18.69 and 19.14 (2d, $^3J_{PC} = 7.3$ and $^3J_{PC} = 9.3$, $CHCH_3$), 29.54 and 29.68 (2d, $^1J_{PC} = 92.7$ and $^1J_{PC} = 92.9$, $OPCH_2$), 33.50 and 33.58 (2d, $^2J_{PC} = 4.3$ and $^2J_{PC} = 3.6$, $OCCH$), 51.95 (s, OCH_3), 52.63 and 53.04 (2d, $^2J_{PC} = 7.0$ and $^2J_{PC} = 7.1$, OCH_3), 60.20 and 60.58 (2d, $^1J_{PC} = 99.8$ and $^1J_{PC} = 99.6$, $HNCHP$), 63.79 ($^3J_{PC} = 14.4$, $CHPh_2$), 127.07, 127.26, 127.48, 127.90, 128.20, 128.23, 128.54, 128.70, 128.92, 128.93, 128.94, 128.95 (C_{ar}), 135.23 (d, $^2J_{PC} = 3.4$, $(HN)CH(P)C_{ipso}$), 141.80, 141.84, 143.70, 175.73 and 175.93 (2d, $^3J_{PC} = 11.5$ and $^3J_{PC} = 8.9$, C=O), MS FAB$^+$(NBA): $[M + H]^+$: 452, IR: (KBr): 33.23, 3062, 3028, 2980, 2946, 2849, 1737, 1601, 1495, 1451, 1234, 1180, 1100, 1040, Elemental microanalysis ($C_{26}H_{30}NO_4P$): Found: C, 68.68; H, 6.71; N, 3.22; P, 6.30. Calc.: C, 69.17; H, 6.70; N, 3.10; P, 6.86%.

*Sodium 1-diphenylmethylaminomethyl hydrogenophosphinate (**8**).*

^{31}P-NMR (H_2O): δ 23.49 (dt, $^1J_{PH} = 515.4$ and $^2J_{PH} = 12.3$), ^{1}H-NMR: (D_2O): δ 2.65 (d, 2H, $^2J_{PH} = 12.4$, $HNCH_2PO$), 4.95 (s, 1H, $CHPh_2$), 7.03 (d, $^1J_{PH} = 514.7$, PH), 7.27–7.51 ppm (10H, CH_{ar}), ^{13}C-NMR (D_2O), 50.98 (d, $^1J_{PC} = 98.1$, $HNCH_2$), 70.57 (d, $^3J_{PC} = 14.3$,

Ph_2CH), 130.19 (s, *C*H), 130.31 (s, *C*H), 131.62 (s, *C*H), 144.74 (s, *C*), IR (KBr): 3610, 3410, 3280, 2810, 2310, 1620, 1600, 1390, 1360, 1200, 1170, 1110, 1100, 820, 710, MS FAB$^+$(NBA): $[M+H]^+$: 284.

*4.4.5. Methyl 1-diphenylmethylaminoethyl 2-methoxycarbonyl-hexyl phosphinate (**1bb$_2$**)*

^{31}P-NMR (AcOEt): δ 53.94 (s), 54.01 (s), 54.16 (s), 54.37 (s), ^{1}H-NMR ($CDCl_3$): δ 0.84–0.92 (m, 3H, CH_2CH_3), 1.21–1.35 (m, 7H, $HNCHCH_3$, $CH_2CH_2CH_2CH_3$), 1.55–2.39 (m, 5H, $CHCH_2CH_2$, $OPCH_2CH$, N*H*), 2.57–2.95 (m, 2H, $OPCHCH_3$, $OCCH$), 3.62 (d, 3H, $^3J_{PH}=10.1$, $POCH_3$), 3.63 and 3.64 (2s, 3H, $COCH_3$), 3.64 (d, $^3J_{PH}=10.1$, $POCH_3$), 3.65 and 3.68 (2s, 3H, $COOCH_3$), 3.71 and 3.72 (2d, 3H, $^3J_{PH}=10.1$, $POCH_3$), 5.04, 5.05, 5.06 and 5.09 ppm (4s, 1H, Ph_2CH), 7.19–7.40 (m, CH_{ar}), ^{13}C-NMR ($CDCl_3$): δ 12.95 and 13.30 (2s, $HNCHCH_3$), 13.91 and 13.92 (2s, CH_2CH_3), 22.44, 22.46 and 22.52 (3s, CH_2CH_3), 27.14, 27.49, 27.59 and 27.77 (4d, $^1J_{PC}=87.8$, $^1J_{PC}=87.3$, $^1J_{PC}=87.7$ and $^1J_{PC}=88.3$, PCH_2CH), 29.04, 29.06, 29.07 and 29.14 (4s, CH_2CH_3), 33.47, 34.00, 34.09 and 34.11 (4d, $^3J_{PC}=9.3$, $^3J_{PC}=11.0$, $^3J_{PC}=11.2$ and $^3J_{PC}=11.4$, $CHCH_2CH_2$), 39.06, 39.20, 39.22 and 39.34 (4d, $^2J_{PC}=3.6$, $^2J_{PC}=4.5$, $^2J_{PC}=3.2$ and $^2J_{PC}=3.4$, CH_2CHCH_2), 48.41, 49.31, 49.35 and 49.60 (4d, $^1J_{PC}=109.0$, $^1J_{PC}=107.4$, $^1J_{PC}=106.3$ and $^1J_{PC}=109.1$, $HNCHCH_3$), 51.54 and 51.64 (2d, $^2J_{PC}=6.9$ and $^2J_{PC}=6.9$, $POCH_3$), 51.72, 51.75, 51.76 and 51.78 (4s, CO_2CH_3), 51.78 and 51.92 (2d, $^2J_{PC}=6.9$ and $^2J_{PC}=6.9$ Hz, $POCH_3$), 64.08, 64.09, 64.10 and 64.16 (4d, $^3J_{PC}=14.2$, $^3J_{PC}=14.2$, $^3J_{PC}=14.2$ and $^3J_{PC}=12.7$, Ph_2CH), 127.10–128.62 (m, CH_{ar}), 142.41, 142.56, 142.62, 143.59, 143.65, 143.86 and 143.89 (7s, C_{ar}), 175.47, 175.54, 175.74 and 175.85 (4d, $^3J_{PC}=5.8$, $^3J_{PC}=7.9$, $^3J_{PC}=5.2$ and $^3J_{PC}=5.6$, CO_2), IR (CCl_4): 3328, 3086, 3067, 3028, 2955, 2931, 2859, 1737, 1601, 1495, 1451, 1219, 1156, 1040, MS FAB$^+$(NBA) $[M+H]^+$: 432, Elemental microanalysis ($C_{24}H_{34}NO_4P$): Found: C, 66.91; H, 8.01; N, 3.37; P, 2.00. Calc.: C, 66.80; H, 7.94; N, 3.25; P, 2.18%.

*4.4.6. Methyl 1-diphenylmethylaminoethyl 2-methoxycarbonyl-heptyl phosphinate (**1bb$_3$**)*

^{31}P-NMR (THF): δ 53.35 (s), 53.43 (s), 53.57(s), 53.82 (s). No purification.

*4.4.7. Methyl 1-diphenylmethylaminoethyl 2-benzyl-2-methoxycarbonyl-ethyl phosphinate (**1bb$_4$**)*

^{31}P-NMR (AcOEt): δ 53.82 (s), 53.92 (s), 53.98 (s), 54.26 (s), ^{1}H-NMR ($CDCl_3$): δ 1.20–1.33 (m, 3H, $CHCH_3$), 1.88–2.40 (m, 3H, PCH_2, N*H*), 2.65–2.86 (m, 4H, $OCCH$, CH_2CH, $PhCH_2$), 3.57, 3.59, 3.60 and 3.64 (4s, 3H, OCH_3), 3.62, 3.65, 3.69 and 3.73 (4d, 3H, $^3J_{PH}=10.1$, $^3J_{PH}=10.1$, $^3J_{PH}=10.0$ and $^3J_{PH}=10.1$, $POCH_3$), 5.01, 5.06 and 5.08 (3s, 1H, Ph_2CH), 7.15–7.38 (m, CH_{ar}), ^{13}C-NMR ($CDCl_3$): δ 12.63, 12.96 and 13.24 ppm (3s,$CHCH_3$), 26.33, 26.56, 26.76 and 26.82 (4d, $^1J_{PC}=87.5$, $^1J_{PC}=87.2$, $^1J_{PC}=88.2$ and $^1J_{PC}=87.4$, PCH_2CH), 39.42, 39.88 and 40.02 (3d, $^3J_{PC}=10.0$, $^3J_{PC}=11.2$ and $^3J_{PC}=11.9$, $PhCH_2$), 41.21, 41.33, 41.37 and 41.61 (4d, $^2J_{PC}=3.4$, $^2J_{PC}=3.1$, $^2J_{PC}=3.2$ and $^2J_{PC}=4.1$, CH_2CHCH_2), 48.72, 49.32, 49.41 and 49.50 (4d, $^1J_{PC}=109.1$, $^1J_{PC}=107.0$, $^1J_{PC}=107.5$ and $^1J_{PC}=110.6$, $HNCHP$), 51.58, 51.68, 51.84 and 51.96 (4d, $^2J_{PC}=6.9$, $^2J_{PC}=7.0$, $^2J_{PC}=7.0$, $^2J_{PC}=7.0$, $POCH_3$), 51.82, 51.84, 51.88 and 51.90 (4s, CO_2CH_3), 63.96, 64.09, 64.12 and 64.17 (4d, $^3J_{PC}=14.4$, $^3J_{PC}=13.9$, $^3J_{PC}=12.9$ and $^3J_{PC}=12.9$, Ph_2CH), 126.77–129.18 (m, CH_{ar}), 138.03 and 138.11 (2s, C_{ar}), 142.34, 142.40, 142.52, 143.59, 143.63, 143.85 and 143.89 (7s, C_{ar}), 174.73, 174.74, 174.98 and 175.20 (4d, $^3J_{PC}=6.0$, $^3J_{PC}=7.0$, $^3J_{PC}=43.9$ and $^3J_{PC}=5.0$, O=*C*), IR (CCl_4): 3323, 3086, 3062, 3028, 2950, 2849, 1742, 1601, 1500, 1451, 1219, 1170, 1137, 1040, MS FAB$^+$(NBA): $[M+H]^+$: 466, Elemental microanalysis ($C_{27}H_{32}NO_4P$): Found: C, 69.60; H, 7.02; N, 3.17; P, 6.30. Calc.: C, 69.66; H, 6.93; N, 3.01; P, 6.65%.

*4.5. Selective and total deprotection of phosphinodipeptide analog **1***

*4.5.1. Total deprotection of phosphinodipeptides analogs **1***

The pair of diastereoisomers **1bc′** + **1bc″** (0.6 g, 1.33 mmol) was heated together with an excess of 47% HBr (2 ml) at 100 °C for 1–2 h until two distinct phases have separated. The mixture was evaporated to dryness under reduced pressure and the residue taken up in water. The aqueous solution was washed several times with ether to remove diphenylmethyl bromide and then evaporated to dryness. Deprotected compounds were obtained as their hydrobromide salts **6c** in a quantitative yield.

*4.5.1.1. 1-Amino-1-phenyl-methyl 2-carboxyl-propyl phosphinic acid hydrobromide salt (**6c**).*

M.p.: 172–175 °C, ^{31}P-NMR (D_2O + NaOH): δ 40.14 (s), 40.41 (s), ^{1}H-NMR (D_2O + NaOH): δ 1.24 (d, $^3J_{HH}=7.0$, $CHCH_3$), 1.50 and 1.94 (m, 1H, ABMX system, PCH_2), 1.54 and 2.14 (m, 1H, ABMX system,PCH_2), 2.47–2.73 (m, $CHCH_3$), 3.98 and 4.02 (2d, 1H, $^2J_{PH}=11.2$ and $^2J_{PH}=11.5$, $PhCH$), 7.37–7.52 (m, CH_{ar}), ^{13}C-NMR (D_2O + NaOH): 22.11 and 22.48 (2d, $^3J_{PC}=3.8$ and $^3J_{PC}=6.2$, $CHCH_3$), 34.06 and 34.31 (2d, $^1J_{PC}=89.2$ and $^1J_{PC}=88.9$, PCH_2), 39.85 and 40.12 (2d, $^2J_{PC}=3.7$ and $^2J_{PC}=3.2$, O=C*C*H), 58.82 and 59.39 (2d, $^1J_{PC}=90.4$ and $^1J_{PC}=90.5$, $HNCH$), 130.00 and 130.04 (2d, $^5J_{PC}=2.0$ and $^5J_{PC}=2.1$, CH_{ar}), 130.50 and 130.63 (2d, $^3J_{PC}=4.5$ and $^3J_{PC}=4.5$, CH_{ar}), 131.24 and 131.31 (2d, $^4J_{PC}=2.1$ and $^4J_{PC}=2.2$, CH_{ar}), 141.54 and 141.95 (2d, $^2J_{PC}=3.1$ and $^2J_{PC}=2.2$, C_{ar}),

188.63 and 188.67 (2d, $^3J_{PC} = 11.1$ and $^3J_{PC} = 13.4$ Hz, O=*C*).

*4.5.2. Hydrogenolysis of compound **1bc***

To a solution of **1bc** (0.4 g, 0.89 mmol) in dry MeOH (3 ml), was added Pd–C (191 mg, 0.18 mmol). After consumption of the required volume of hydrogen, the mixture was filtered on celite, and the filtrate concentrated. The crude product, by chromatography on silica gel with EtOAc as eluent, gives compounds **6d** (a mixture of two diastereoisomers, 241 mg) as a viscous oil in 95% yield.

*4.5.2.1. Methyl 1-amino-1-phenyl-methyl 2-methoxycarbonyl-propyl phosphinate (**6d**).*

^{31}P-NMR ($CDCl_3$): δ 52.29 (s), 52.38 (s), ^{1}H-NMR ($CDCl_3$): δ 1.23 (d, 3H, $^3J_{HH} = 7{,}1$ Hz, CHCH_3), 1.92 (s, 2H, NH_2), 1.68–2.00 and 2.21–2.44 (2m, 2H, 2 ABMX systems, PCH_2), 2.72–2.92 (m, CHCH$_3$), 3.39 and 3.40 (2d, 3H, $^3J_{PH} = 10.1$ and $^3J_{PH} = 10.1$, POCH_3), 3.66 (s, CO_2CH_3), 4.12 and 4.15 (2d, $^2J_{PH} = 13.0$ and $^2J_{PH} = 12.3$, PhCH), 7.26–7.43 (m, CH_{ar}), ^{13}C-NMR ($CDCl_3$): δ 18.95 and 19.13 (2d, $^3J_{PC} = 7.4$ and $^3J_{PC} = 8.1$, CHCH$_3$), 28.75 and 29.19 (2d, $^1J_{PC} = 89.9$ and $^1J_{PC} = 89.9$, PCH$_2$), 33.71 and 33.85 (2d, $^2J_{PC} = 4.4$ and $^2J_{PC} = 3.6$, CHCH$_3$), 51.86 (d, $^2J_{PC} = 7.4$, POCH$_3$), 51.94 (s, CO_2CH_3), 51.97 (d, $^2J_{PC} = 7.0$, POCH$_3$), 56.34 and 56.37 (2d, $^1J_{PC} = 98.7$ and $^1J_{PC} = 98.7$, PhCH), 127.65 and 127.69 (2d, $^3J_{PC} = 5.1$ and $^3J_{PC} = 5.1$, CH$_{ar}$), 127.88 and 127.89 (2d, $^5J_{PC} = 2.9$ and $^5J_{PC} = 3.0$, CH$_{ar}$), 128.56 and 129.56 (2d, $^4J_{PC} = 2.3$ and $^4J_{PC} = 2.3$, CH$_{ar}$), 137.90 and 138.14 (2d, $^2J_{PC} = 4.2$ and $^2J_{PC} = 4.2$, C_{ar}), 175.86 and 175.95 (2d, $^3J_{PC} = 9.7$ and $^3J_{PC} = 8.3$, O=*C*), IR (CCl_4): 3405, 3052, 3000, 2951, 2883, 2849, 1737, 1263, 1214, 1045, MS FAB$^+$ (NBA): $[M + H]^+$ 286.

*4.5.3. Diphenylmethylamino-1-phenyl-methyl 2-methoxycarbonyl-propyl phosphinic acid (**6e**)*

A solution containing 0.2 g of **1bc** (0.443 mmol) with 64.3 μl (0.487 mmol) trimethylsilylbromine in 2.2 ml of dry CH_2Cl_2 was stirred at r.t. for 3 h. After concentration of the solution the mixture is dissolved in EtOAc and an excess of MeOH is added. After another concentration of the solution, 194 mg of compounds **6e** are obtained in quantitative yield as a mixture of two isomers.

M.p.: 81.2–85.5 °C, ^{31}P-NMR ($CDCl_3$): δ 39.31 (s), 39.70 (s), ^{1}H-NMR ($CDCl_3$): δ 1.00 and 1.13 (2d, 3H, $^3J_{HH} = 7.1$ and $^3J_{HH} = 7.1$, CHCH_3), 1.14 and 1.75 (m, 1H, ABMX system, PCH_2CH), 1.41 and 1.86 (m, 1H, ABMX system, PCH_2CH), 2.41–2.56 (m, 1H, CHCH$_3$), 3.54 and 3.56 (2s, 3H, CO_2CH_3), 4.10 and 4.16 (2d, 1H, $^2J_{PH} = 11.6$ and $^2J_{PH} = 11.3$, HNCHPh), 5.21 and 5.30 (2s, Ph$_2$CH), 7.28–7.57 (m, 15H, CH_{ar}), ^{13}C-NMR ($CDCl_3$): δ 19.27 and 19.29 (2d, $^3J_{PC} = 6.4$ and $^3J_{PC} = 9.2$, CHCH$_3$), 31.42 and 31.88 (2d, $^1J_{PC} = 101.7$ and $^1J_{PC} = 102.3$, PCH$_2$CH), 33.98 and 34.18 (2d, $^2J_{PC} = 3.4$ and $^2J_{PC} = 3.6$, CHCH$_3$), 52.43 (s, CO_2CH_3), 61.99 (d, $^1J_{PC} = 87.3$, HNCHPh), 65.84 (d, $^3J_{PC} = 6.8$, Ph$_2$$C$H), 128.92–130.74 (m, CH$_{ar}$), 131.47 and 131.69 (2s, C_{ar}), 136.27 and 136.58 (2s, C_{ar}), 176.31 and 176.66 (2d, $^3J_{PC} = 11.8$ and $^3J_{PC} = 10.0$, CO_2), MS FAB$^+$ (NBA): $[M + H]^+$ 438.

*4.5.4. Hydrogenolysis of compound **6e***

To a solution of **6e** (0.4 g, 0.91 mmol) in dry MeOH (3 ml), was added Pd–C (146 mg, 0.44 mmol). After consumption of the required volume of hydrogen, the mixture was filtered on celite, and the filtrate concentrated. The crude product, washed with ether to remove diphenylmethane gives compounds **6f** (a mixture of two diastereoisomers, 246.8 mg) as a white solid in quantitative yield.

*4.5.4.1. 1-Amino-1-phenyl-methyl 2-methoxycarbonyl-propyl phosphic acid (**6d**).*

M.p.: 125–133 °C, ^{31}P-NMR (D_2O): δ 31.24 (s), 31.32 (s), ^{1}H-NMR (D_2O): δ 1.19 (d, 3H, $^3J_{HH} = 7.0$, CHCH_3), 1.50–1.69 and 1.92–2.11 (2m, 2H, 2 ABMX systems, PCH_2), 2.56–2.78 (m, CHCH$_3$), 3.69 and 3.70 (2s, 3H, CO_2CH_3), 4.41(d, 2H, $^2J_{PH} = 10.3$, HNCH), 7.41–7.57 (m, 5H, CH_{ar}), ^{13}C-NMR (D_2O): δ 21.19 and 21.27 (2d, $^3J_{PC} = 8.9$ and $^3J_{PC} = 9.3$, CHCH$_3$), 34.17 and 34.24 (2d, $^1J_{PC} = 97.1$ and $^1J_{PC} = 97.5$, PCH$_2$), 36.82 and 36.91 (2d, $^2J_{PC} = 4.1$ and $^2J_{PC} = 4.5$, CHCH$_3$), 55.32 (s, CO_2CH_3), 58.13 (d, $^1J_{PC} = 86.3$, HNCH), 130.48 and 130.57 (2d, $^4J_{PC} = 4.8$ and $^4J_{PC} = 4.5$, CH$_{ar}$), 131.75 and 131.78 (2d, $^5J_{PC} = 1.9$ and $^5J_{PC} = 1.9$, CH$_{ar}$), 131.96 (d, $^3J_{PC} = 1.5$, CH$_{ar}$), 135.05 and 135.12 (2d, $^2J_{PC} = 3.7$ and $^2J_{PC} = 3.7$, C_{ar}), 181.84 and 181.85 (2d, $^3J_{PC} = 9.3$ and $^3J_{PC} = 8.2$, CO_2), MS FAB$^+$ (NBA): $[M + H]^+$ 272.

*4.5.5. 1-Diphenylmethylamino-1-phenyl-methyl 2-carboxyl-propyl phosphinic acid (**6g**)*

The pair of diastereoisomers **1bc′** + **1bc″** (0.2 g, 0.44 mmol) in 2 ml of MeOH, is added to 1 ml of NaOH 1 N and stirring 4 h at r.t. The mixture was evaporated to dryness under reduced pressure and the residue acidified by HCl solution 1 N. The aqueous solution was washed several times with ether and then evaporated to dryness. Deprotected compounds **6g** were obtained as a white solid as a mixture of two diastereoisomers (186 mg) in a quantitative yield.

M.p.: 119.0–132.2 °C, ^{31}P-NMR (D_2O): δ 34.30 (s), 34.67 (s), ^{1}H-NMR (D_2O + NaOH): δ 1.14 and 1.16 (2d, 3H, $^3J_{HH} = 6.9$ and $^3J_{HH} = 6.9$, CHCH_3), 1.48–1.76 and 1.91–2.22 ppm (2m, 2H, 2 ABMX systems, PCH_2), 2.38–2.64 (m, 1H, CHCH$_3$), 3.58 and 3.59 (2d, 1H, $^2J_{PH} = 15.0$ and $^2J_{PH} = 15.5$, HNCHPh), 4.45 and 4.46 (2s, 1H, Ph$_2$CH), 6.85–7.35 (m, 15H, CH_{ar}), ^{13}C-NMR (D_2O + NaOH): δ 22.19 and 22.28 (2d, $^3J_{PC} =$

7.3 and $^{3}J_{PC} = 8.2$, $CHCH_3$), 34.92 and 35.08 (2d, $^{1}J_{PC} = 91.8$ and $^{1}J_{PC} = 91.7$, PCH_2), 39.82 and 40.09 (2d, $^{2}J_{PC} = 3.2$ and $^{2}J_{PC} = 3.1$, $CHCH_3$), 64.55 and 64.67 (2d, $^{1}J_{PC} = 97.5$ and $^{1}J_{PC} = 97.7$, $HNCHPh$), 66.34 and 66.34 (2d, $^{3}J_{PC} = 13.5$ and $^{3}J_{PC} = 13.5$, Ph_2CH), 129.22–131.46 (m, CH_{ar}), 140.29 and 141.29 (2d, $^{2}J_{PC} = 3.3$ and $^{2}J_{PC} = 3.3$, C_{ar}), 144.73 and 146.50 (2s, CH_{ar}), 188.71 (d, $^{3}J_{PC} = 12.7$, CO_2), MS FAB$^+$ (NBA): $[M + H]^+$ 424.

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