Pergamon

Tetrahedron 57 (2001) 3471–3478

TETRAHEDRON

A highly efficient method for the preparation of phosphinic pseudodipeptidic blocks suitably protected for solid-phase peptide synthesis

Dimitris Georgiadis, Magdalini Matziari and Athanasios Yiotakis*

Department of Chemistry, Laboratory of Organic Chemistry, University of Athens, Panepistimiopolis Zografou, 15771 Athens, Greece

Received 23 November 2000; revised 30 January 2001; accepted 15 February 2001

Abstract—Building blocks of the general type FmocXaaΨ{PO(OAd)CH_2}YaaOH suitable for solid-phase synthesis of phosphinic peptides have been prepared using a new synthetic strategy based on mild and high-yielding reactions. The key reaction of this method is the Michael addition of activated Fmoc protected silyl aminophosphonites to benzyl acrylates at room temperature. As compared to our previous work, this method consists of less synthetic steps and doubles the overall yield, thus providing a convenient route to phosphinic synthons suitable for the solid-phase preparation of inhibitors of various metalloproteases. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

In the last decade, several studies have demonstrated that the synthesis of phosphinic peptides is a very effective approach for the development of highly potent inhibitors of zinc-metalloproteases.[1–7] In addition, development of phosphinic peptides through solid-phase synthesis using either parallel or combinatorial chemistry strategies has proven to be a fruitful approach to obtain highly potent and selective inhibitors of various zinc-metalloproteases.[8–12] Interestingly, in the case of astacin, which belongs to the zinc protease family, among different classes of pseudopeptidic inhibitors of Zn-metalloproteases, phosphinic peptides turn out to be the only compounds able to potently inhibit this protease.[13] These results illustrate that phosphinic peptides represent a unique class of Zn-metalloprotease inhibitors. Nevertheless, as compared to other classes of zinc-protease peptide inhibitors, due to the absence of a convenient synthetic method to prepare these compounds, the development of phosphinic peptides is still limited. To facilitate the preparation of phosphinic peptides, we recently proposed an approach making possible their synthesis by classical Fmoc solid-phase peptide synthesis.[8] This method relies on the synthesis of phosphinic building blocks suitably protected in order to be compatible with the Fmoc solid-phase synthetic protocol. The importance of these molecules as synthons for the preparation of phosphinopeptides and the assembly of combinatorial libraries prompted us to investigate the optimization of their synthesis. In this paper, we present a novel strategy for the synthesis of phosphinic blocks that is based on mild and high-yielding reactions.

2. Results and discussion

In previous work, we reported a method for the synthesis of compounds of type **1**, which is illustrated in Scheme 1.[8] The main disadvantage of this method is the unexpected partial cleavage of the adamantyl group during the step of Cbz removal. This problem can be partially overcome by using ammonium formate, as a hydrogen donor, in the presence of palladium/carbon catalyst.[14] Under these conditions, the extent of this unwanted side-reaction was reduced but not completely abolished. Furthermore, in many cases the isolation of the internal salts (Scheme 1, synthons type **6**) is hindered due to their co-precipitation with the excess of ammonium formate. In addition, during the Fmoc protection step of the internal salt of type **6**, the presence of ammonium formate excess was found to reduce the yield of this reaction, probably due to the ammonia produced under the alkaline conditions. All these difficulties have led us to design a novel approach to prepare synthons of type **1**.

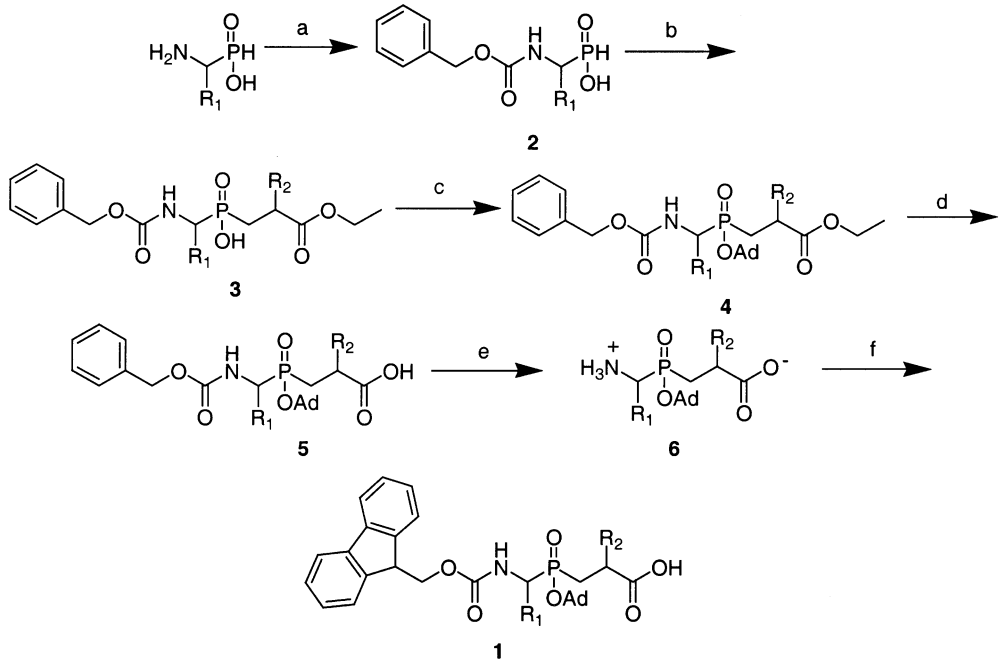
In our previous protocol, the Michael-type addition, which is the key step in the pseudodipeptide formation, was performed under conditions which were not compatible with the use of the Fmoc protecting group (Scheme 2, hexamethyldisilazane (HMDS) at 110°C, gas ammonia emission). Thus, the Fmoc group was introduced after the Michael addition, while Cbz group was used as a temporary

Keywords: phosphinic peptides; zinc metalloprotease inhibitors; Michael addition.

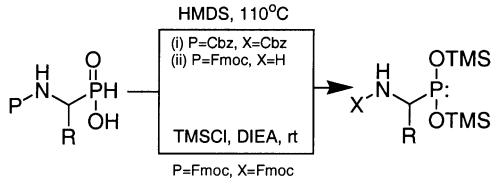
Abbreviations: Fmoc, 9-fluorenylmethyloxycarbonyl; Ad, adamantyl; Cbz, benzyloxycarbonyl; TMS, trimethylsilyl; HMDS, 1,1,1,3,3,3-hexamethyldisilazane; DIEA, diisopropylethylamine.

* Corresponding author. Tel.: +30-1-7274498; fax: +30-1-7274761; e-mail: agiotak@cc.uoa.gr

0040–4020/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(01)00221-6

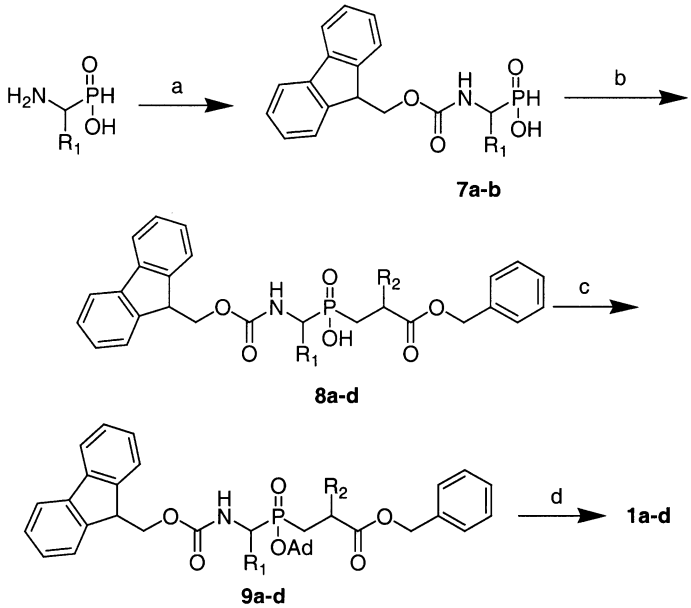


Scheme 1. (a) Z-Cl, 1 M NaOH, 82–86%; (b) HMDS 110°C, then $H_2C{=}C(R_2)COOEt$ 90°C, then EtOH 70°C, 89–96%; (c) 1-AdBr, Ag_2O, $CHCl_3$, reflux, 79–84%; (d) 0.4 M NaOH, MeOH then aq. HCl 86–98%; (e) $HCOO^-NH_4^+$, 10% Pd/C; (f) Fmoc-Cl, 10% Na_2CO_3, dioxan, H_2O, 61–67%.



Scheme 2. Behaviour of amino protecting groups of aminophosphinic acids during TMS-activation.

protecting group. The report of Boyd, which shows that the use of TMSCl/diisopropylethylamine makes it possible to perform the Michael addition of phosphinic acids to various electrophiles under milder conditions, prompted us to investigate the possibility of using directly the Fmoc, instead of the Cbz group, as the amino-protecting group of the aminophosphinic acids **7** in the conjugate addition step.[15] Indeed, Fmoc-protected aminophosphinic acids were found to be completely stable in these conditions (Scheme 2). The conjugate addition of the resulting silyl aminophosphonites to the appropriate acrylic esters (1.1 equiv.) proceeds



Scheme 3. (a) Fmoc-Cl, 10% Na_2CO_3, dioxan, 98–99%; (b) TMS-Cl, *i*-Pr_2EtN, 0°C to rt, then $H_2C{=}C(R_2)COOCH_2Ph$, 0°C to rt, then EtOH, 87–94%; (c) 1-AdBr, Ag_2O, $CHCl_3$, reflux, 97–99%; (d) H_2, 10% Pd/C, 87–90%.

Table 1. List of the compounds

Entry	R_1	R_2	Yield (%)
7a	CH_3		99
7b	$C_6H_5CH_2$		98
8a	$C_6H_5CH_2$	H	90
8b	$C_6H_5CH_2$	CH_3	87
8c	$C_6H_5CH_2$	$(CH_3)_2CHCH_2$	88
8d	CH_3	$(CH_3)_2CHCH_2$	94
9a	$C_6H_5CH_2$	H	98
9b	$C_6H_5CH_2$	CH_3	99
9c	$C_6H_5CH_2$	$(CH_3)_2CHCH_2$	97
9d	CH_3	$(CH_3)_2CHCH_2$	97
1a	$C_6H_5CH_2$	H	87
1b	$C_6H_5CH_2$	CH_3	89
1c	$C_6H_5CH_2$	$(CH_3)_2CHCH_2$	90
1d	CH_3	$(CH_3)_2CHCH_2$	90

Table 2. Overall yields for the synthesis of **1a–d** using the method illustrated in Scheme 3

Entry	Overall yield (%)
1a	77 (33)[a]
1b	77 (38)[a]
1c	75 (40)[a]
1d	81 (36)[a]

[a] The number inside the parenthesis corresponds to the overall yields for the synthesis of compounds **1a–d** by the method described in Scheme 1. These data are reported in Ref. 8.

smoothly at room temperature affording the Fmoc-protected pseudodipeptides of type **7** in high yields.

Based on the above observation, a new synthetic strategy, illustrated in Scheme 3, was designed and evaluated. The use of the Fmoc as a protecting group before the Michael addition and the adamantyl group as a protecting group of the hydroxyphospinyl moiety requires the C-terminal ethyl ester protecting group, previously used (Scheme 1), to be replaced by another group which can be removed under conditions other than saponification or acidic cleavage. Thus, the benzyl group was used, since it can be removed under classical catalytic hydrogenation conditions.[16] The introduction of the adamantyl group was easily achieved in high yields, using Ag_2O/1-AdBr in chloroform under refluxing conditions (step 3, Scheme 3). The final step involves the removal of the benzyl group by classical hydrogenation procedure. Under these conditions, the benzyl group was removed completely while Fmoc and adamantyl groups remained intact. The control of the reaction time in this step is essential, since only when short reaction times (1.5–2 h) were used, did the Fmoc group remain stable. This is consistent with the study of Atherton et al. concerning the lability of Fmoc group in hydrogenation conditions.[17] Actually, after 2 h in these conditions, **1a–d** were isolated in ~90% yield while the formation of the amino-deprotected synthon of type **6** was limited to ~10% and no starting material was detected on the TLC plate. In addition, we observed that the removal of the benzyl group by catalytic hydrogenation was not affected by the nature of the R_2 group, as this can be the case for the $B_{AC}2$ based nucleophilic removal of ethyl group during saponification described in Scheme 1. The benzyl removal reaction time is indeed independent of any steric hindrance exerted by the bulky groups present in the R_2 position.

In comparison to our previous method, this new strategy for preparing synthons of type **1** has several advantages: It reduces the synthetic steps from 6 to 4, increasing the overall yield of the synthesis of synthons of type **1** from ~40 to ~80% (Tables 1 and 2). In addition, the absence of a saponification step in the present method allows the use of other protecting groups of the hydroxyphosphinyl functionality, like methyl or isopropyl. Finally, independently of the R_2 side chain's bulkiness, the removal of benzyl ester by catalytic hydrogenation proceeds smoothly. Interestingly, the adamantyl group remains unaffected during the hydrogenation of the fully protected synthon of type **9**. This is in contrast with our previous observation showing the adamantyl group is partially removed simultaneously with the Cbz group (Scheme 1).[8] This observation strongly suggests that the presence of both free amino and free carboxylic functions in synthons **6** favors the removal of the adamantyl group during hydrogenation.[18]

3. Conclusions

In this paper, we present an improved method for the preparation of phosphinic peptide building blocks, which overcomes various problems of a previous reported methodology and, in addition, doubles the overall yield of the synthesis. Such building blocks constitute today the basis for the synthesis of phosphinic peptide libraries through which potent and selective inhibitors of various Zn-metalloproteases can be identified. Although efforts towards the construction of the pseudodipeptidic unit on solid phase have been recently reported, their applicability to the development of phosphinopeptidic libraries is yet to be evaluated.[19,20] Theretofore, the building block approach will remain the primary and safer choice for accessing this important class of pseudopeptides.

4. Experimental

4.1. General

All of the compounds, for which analytical and spectroscopic data are quoted, were homogenous by TLC. TLC analyses were performed using silica gel plates (E. Merck silica gel 60 F-254), and components were visualized by the following methods: ultraviolet light absorbance, iodine vapor, charring after spraying with a solution of $(NH_4)HSO_4$ and ninhydrin spray. The solvents systems used for TLC developments were (a) 1-butanol–acetic acid–water (4:1:1), (b) chloroform–methanol–acetic acid (7:2:1), (c) chloroform–methanol–acetic acid (7:0.5:0.5), (d) chloroform–2-propanol (9.8:0.2), (e) hexane–ethyl acetate–acetic acid (3:3:0.2), (f) chloroform–methanol (9.5:0.5). In most solvent systems close, but different, R_f values have been observed for the various stereoisomers of these compounds, due to the presence of asymmetric centers in these compounds. Thus, the R_f values correspond to an average value. Column chromatography was carried

out on silica gel (E. Merck, 70–230 mesh). All the compounds were characterized by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. The presence of asymmetric centers in these compounds complicates the interpretation of the spectra, especially when the hydroxyphosphinyl function is protected by the adamantyl group. Numbers I and II were used to describe the ^{13}C resonance corresponding to the different set of diastereoisomers. Assignment of the NMR signals was done using DQ-COSY, HETCOR and DEPT experiments. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a 200 MHz Mercury Varian spectrometer. ^{13}C and ^{31}P NMR spectra are fully proton decoupled. ^{31}P-chemical shifts are reported on δ scale (in ppm) downfield from 85% H_3PO_4. Melting points provided are uncorrected. Mass spectroscopy and analytical data are also provided. Before microanalyses, samples were dried under high vacuum at 40°C for 24 h in a dry pistol. These analyses were obtained from the Laboratory of Inorganic Chemistry, University of Athens, 15771, Athens, Greece. Electron spray mass spectroscopy (ES-MS) was performed on a Micromass Platform II instrument with positive ionization mode by Dr Reto Stöcklin (Atheris Laboratories, 314 CH-1233 Bernex, Geneva, Switzerland).

4.2. General procedures

(*R*,*S*)-(1-(Amino)-2-phenylethyl)phosphinic acid and (*R*,*S*)-(1-(amino)ethyl)phosphinic acid were synthesized as described by Baylis et al.[21] 2-Isobutylpropenoic acid was prepared according to the method reported by Stetter and Kuhlmann.[22] 2-Isobutyl-propenoic acid benzyl esters were prepared from the corresponding acids with introduction of the benzyl group using phase transfer catalysis.[23] Propenoic benzyl ester and 2-methylpropenoic acid benzyl ester were purchased from Aldrich. All benzyl acrylates were distilled before use.

4.3. General method for the synthesis of compounds of type 7

α-Aminophosphinic acid (5 mmol) was dissolved in 10% solution of sodium carbonate (12.5 mmol, 13.2 ml) containing dioxan (7.5 ml). The mixture was cooled to 0°C and then Fmoc chloride (5 mmol, 1.3 g), dissolved in dioxan (3.7 ml), was added dropwise to the mixture over a period of 1 h. After the end of the addition, the mixture was stirred for 1 h at 0°C and then for five additional hours at room temperature. Then, dioxan was removed in vacuo and H_2O (10 ml) was added to the residue. The resulting solution was acidified with 2 M HCl to pH 1. After standing for 24 h at 0°C, the solid precipitate was filtered, washed with cold water (2×5 ml) and Et_2O (3×10 ml).

4.3.1. (*R*,*S*)-(1-(*N*-(9-Fluorenylmethoxycarbonyl)amino)-ethyl) phosphinic acid (7a). White solid, mp 185–187°C; TLC R_f(a) 0.31, R_f(b) 0.63; IR ν_{max}(KBr) 3650–3150 (br), 3070, 3021, 2980, 2396, 1694, 1514, 1449, 1021, 931, 856, 741, 661, 623 cm^{-1}; ^{1}H NMR (200 MHz, d_6-DMSO) δ 1.23 (dd, $^{3}J_{HH}$=7.1 Hz, $^{3}J_{PH}$=16.0 Hz, 3H, C*H*$_3$), 3.65–3.80 (m, 1H, PC*H*), 4.16–4.39 (m, 3H, C*H*CH$_2$O, CHC*H*$_2$O), 6.83 (d, $^{1}J_{PH}$=534 Hz, 1H, P*H*), 7.28–7.89 (m, 8H, aryl); ^{13}C NMR (50 MHz, d_6-DMSO) δ 12.8 (d, $^{2}J_{PC}$=1.9 Hz, *C*H$_3$), 45.9 (d, $^{1}J_{PC}$=105.0 Hz, P*C*H), 46.7 (*C*HCH$_2$O), 65.9 (CH*C*H$_2$O), 120.2, 125.4, 127.2, 140.8, 143.9 (aryl), 156.0 (d, $^{3}J_{PC}$=3.7 Hz, *C*O); ^{31}P NMR (81 MHz, d_6-DMSO) δ 29.40; ESMS *m*/*z* calcd for $C_{17}H_{18}NO_4PNa$ $(M+Na)^+$ 354.3, found 353.9; Anal. Calcd for $C_{17}H_{18}NO_4P+3H_2O$ (385.3); C, 52.99; H, 6.28; N, 3.63. Found: C, 53.15; H, 5.95; N, 3.61.

4.3.2. (*R*,*S*)-(1-(*N*-(9-Fluorenylmethoxycarbonyl)amino)-2-phenylethyl) phosphinic acid (7b). White solid, mp 188–190°C; TLC R_f(a) 0.26, R_f(b) 0.59; IR ν_{max}(KBr) 3630–3120 (br), 3067, 3018, 2982, 2395, 1689, 1556, 1514, 1449, 1018, 927, 856, 740, 662, 623 cm^{-1}; ^{1}H NMR (200 MHz, d_6-DMSO) δ 2.73–2.90 (m, 1H, PhC*H*H), 2.99–3.09 (m, 1H, PhCH*H*), 3.69–3.83 (m, 1H, PC*H*), 4.10–4.18 (m, 3H, C*H*CH$_2$O, CHC*H*$_2$O), 6.89 (d, 1H, $^{1}J_{PH}$= 527 Hz, P*H*), 7.15–7.89 (m, 13H, aryl); ^{13}C NMR (50 MHz, d_6-DMSO) δ 31.9 (d, $^{2}J_{PC}$=1.8 Hz, *C*H$_2$Ph), 46.6 (*C*HCH$_2$O), 52.3 (d, $^{1}J_{PC}$=104.5 Hz, P*C*H), 65.7 (CH*C*H$_2$O), 120.1, 125.3, 125.4, 126.2, 127.1, 127.6, 128.1, 129.1, 138.2, 138.5, 140.7, 143.7 (aryl), 156.0 (d, $^{3}J_{PC}$=2.9 Hz, *C*O); ^{31}P NMR (81 MHz, d_6-DMSO) δ 26.59; ESMS *m*/*z* calcd for $C_{23}H_{22}NO_4PNa$ $(M+Na)^+$ 430.4, found 430.1; Anal. Calcd for $C_{23}H_{22}NO_4P+H_2O$ (425.4); C, 64.94; H, 5.69; N, 3.29. Found: C, 64.81; H, 5.46; N, 3.31.

4.4. General method for the synthesis of compounds of type 8

To an ice cold suspension of compound **7** (1 mmol) in CH_2Cl_2 (2.5 ml) diisopropylethylamine (3.2 mmol, 0.45 g) and chlorotrimethylsilane (3.2 mmol, 0.34 g) were added, under argon atmosphere. This solution was stirred for 3 h at room temperature. Then, the mixture was cooled to 0°C and the appropriate benzyl acrylate was added (1.1 mmol) dropwise for 30 min. When the addition was over, the solution was stirred for 24 h at room temperature. Then, absolute ethanol (0.8 ml) was added dropwise and the mixture was stirred for 15 min. The solvents were evaporated. To the residue, H_2O was added and the resulting suspension was acidified with 0.5 M HCl to pH 1 and extracted with ethyl acetate (3×10 ml). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness. The oily residue was purified by column chromatography using chloroform–methanol–acetic acid (7:0.4:0.4) as eluent.

4.4.1. (*R*,*S*)-3-((1-(*N*-(9-Fluorenylmethoxycarbonyl)amino)-2-phenylethyl)-hydroxyphosphinyl) propanoic acid, benzyl ester (8a). White solid, mp 124–126°C; TLC R_f(b) 0.69, R_f(c) 0.64; IR ν_{max} (liquid film) 3660–3150 (br), 3072, 3014, 2979, 1731, 1692, 1549, 1503, 1445, 1024, 931, 847, 731, 702, 660, 621 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.04–2.17 (m, 2H, PC*H*$_2$), 2.53–2.99 (m, 3H, C*H*$_2$COOBzl, PhC*H*H), 3.24–3.39 (m, 1H, PhCH*H*), 3.97–4.17 (m, 2H, CHC*H*$_2$O), 4.20–4.38 (m, 2H, C*H*CH$_2$O, PC*H*), 5.10 (s, 2H, OC*H*$_2$Ph), 5.47 (d, $^{3}J_{HH}$=9.7 Hz, 1H, N*H*), 7.17–7.75 (m, 18H, aryl); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.9 (d, $^{1}J_{PC}$=92.9 Hz, P*C*H$_2$), 26.5 (*C*H$_2$CO), 33.8 (*C*H$_2$Ph), 47.0 (*C*HCH$_2$O), 50.8 (d, $^{1}J_{PC}$=105.6 Hz, P*C*H), 66.9 (O*C*H$_2$Ph), 67.2 (CH*C*H$_2$O), 119.9, 125.0, 125.1, 126.9, 127.0, 127.6, 128.2, 128.5, 129.1, 135.5, 136.2, 141.2, 143.5, 143.7 (aryl), 156.1 (d, $^{3}J_{PC}$=4.9 Hz, O*C*ONH), 172.1 (d, $^{3}J_{PC}$=14.2 Hz, *C*OOBzl); ^{31}P NMR (81 MHz, $CDCl_3$) δ 54.30; ESMS *m*/*z*

calcd for $C_{33}H_{33}NO_6P$ $(M+H)^+$ 570.6, found 570.2; Anal. Calcd for $C_{33}H_{32}NO_6P$ (569.6); C, 69.59; H, 5.66; N, 2.46. Found: C, 69.31; H, 5.75; N, 2.67.

4.4.2. (*R*,*R*,*S*,*S*)-2-Methyl-3-((1-(*N*-(9-fluorenylmethoxycarbonyl)amino)-2-phenylethyl)-hydroxyphosphinyl) propanoic acid, benzyl ester (8b). White solid, mp 127–129°C; TLC R_f(b) 0.72, R_f(c) 0.68; IR ν_{max} (liquid film) 3650–3120 (br), 3068, 3020, 2983, 1737, 1689, 1550, 1503, 1444, 1021, 934, 849, 730, 702, 658, 622 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 (d, $^3J_{HH}$=7.0 Hz, 3H, CH_3), 1.78–1.95 (m, 1H, PC*H*H), 2.24–2.39 (m, 1H, PCH*H*), 2.74–3.11 (m, 2H, PhC*H*H, C*H*COOBzl), 3.26–3.51 (m, 1H, PhCH*H*), 3.97–4.20 (m, 2H, CHCH_2O), 4.22–4.39 (m, 2H, C*H*CH_2O, PC*H*), 5.13 (s, 2H, OCH_2Ph), 5.42 (d, $^3J_{HH}$=9.9 Hz, 1H, N*H*), 7.19–7.76 (m, 18H, aryl); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.0 (d, $^3J_{PC}$=9.5 Hz, *C*H_3), 29.8 (d, $^1J_{PC}$=91.4 Hz, P*C*H_2, I), 30.3 (d, $^1J_{PC}$=91.4 Hz, P*C*H_2, II), 33.8 (*C*H_2Ph), 34.7 (d, $^2J_{PC}$=42.7 Hz, *C*HCOOBzl), 46.9 (*C*HCH_2O), 51.6 (d, $^1J_{PC}$=104.7 Hz, P*C*H), 66.8 (O*C*H_2Ph), 67.2 (CH*C*H_2O), 119.9, 125.0, 125.1, 126.9, 127.0, 127.6, 128.1, 128.2, 128.5, 129.1, 135.6, 136.3, 136.5, 141.1, 143.4, 143.8 (aryl), 156.0 (d, $^3J_{PC}$=5.9 Hz, O*C*ONH), 175.3 (d, $^3J_{PC}$=9.1 Hz, *C*OOBzl); ^{31}P NMR (81 MHz, $CDCl_3$) δ 53.17, 53.23; ESMS *m*/*z* calcd for $C_{34}H_{35}NO_6P$ $(M+H)^+$ 584.6, found 584.3; Anal. Calcd for $C_{34}H_{34}NO_6P$ (583.6); C, 69.97; H, 5.87; N, 2.40. Found: C, 70.09; H, 5.74; N, 2.44.

4.4.3. (*R*,*R*,*S*,*S*)-2-Isobutyl-3-((1-(*N*-(9-fluorenylmethoxycarbonyl)amino)-2-phenylethyl)-hydroxyphosphinyl) propanoic acid, benzyl ester (8c). White solid, mp 131–133°C; TLC R_f(b) 0.81, R_f(c) 0.77; IR ν_{max} (liquid film) 3640–3120 (br), 3065, 3020, 2983, 1742, 1689, 1543, 1503, 1445, 1362, 1023, 930, 847, 726, 704, 663, 621 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.78 (dd, $^3J_{HH}$=5.8 Hz, A_3B_3X, J_{AB}=11.6 Hz, 6H, CH(CH_3)$_2$), 1.22–1.48 (m, 2H, C*H*HCH(CH$_3$)$_2$, C*H*(CH$_3$)$_2$), 1.51–1.63 (m, 1H, CH*H*CH(CH$_3$)$_2$), 1.77–1.92 (m, 1H, PC*H*H), 2.02–2.34 (m, 1H, PCH*H*), 2.75–3.01 (m, 2H, PhC*H*H, C*H*COOBzl), 3.27–3.36 (m, 1H, PhCH*H*), 3.96–4.09 (m, 2H, CHCH_2O), 4.11–4.39 (m, 1H, PC*H*), 4.33–4.44 (m, 1H, C*H*CH_2O), 5.12 (s, 2H, OCH_2Ph), 5.41 (d, $^3J_{HH}$=9.7 Hz, 1H, N*H*), 7.08–7.83 (m, 18H, aryl); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.2 (d, ABX, J_{AB}=35.6 Hz, CH(*C*H$_3$)$_2$), 25.7 (*C*H(CH$_3$)$_2$), 29.1 (d, $^1J_{PC}$=85.6 Hz, P*C*H_2, I), 29.6 (d, $^1J_{PC}$=85.6 Hz, P*C*H_2, II), 33.9 (*C*H_2Ph), 37.3 (br, *C*HCOOBzl), 43.2 (d, $^3J_{PC}$=10.8 Hz, *C*H_2CH(CH$_3$)$_2$), 46.9 (*C*HCH_2O), 51.7 (d, $^1J_{PC}$=102.5 Hz, P*C*H), 66.7 (O*C*H_2Ph), 67.2 (CH*C*H_2O), 119.9, 125.0, 125.2, 126.8, 127.0, 127.6, 128.2, 128.3, 128.4, 128.5, 129.2, 135.7, 136.4, 136.7, 141.1, 143.5, 143.8 (aryl), 156.0 (d, $^3J_{PC}$=6.1 Hz, O*C*ONH), 175.2 (d, $^3J_{PC}$=4.9 Hz, *C*OOBzl); ^{31}P NMR (81 MHz, $CDCl_3$) δ 51.93, 52.40; ESMS *m*/*z* calcd for $C_{37}H_{41}NO_6P$ $(M+H)^+$ 626.7, found 626.3; Anal. Calcd for $C_{37}H_{40}NO_6P+0.25H_2O$ (629.8); C, 70.52; H, 6.48; N, 2.22. Found: C, 70.47; H, 6.45; N, 2.37.

4.4.4. (*R*,*R*,*S*,*S*)-2-Isobutyl-3-((1-(*N*-(9-fluorenylmethoxycarbonyl)amino)-ethyl)-hydroxyphosphinyl) propanoic acid, benzyl ester (8d). White solid, mp 130–132°C; TLC R_f(b) 0.77, R_f(c) 0.71; IR ν_{max} (liquid film) 3660–3150 (br), 3074, 3014, 2986, 1734, 1692, 1551, 1506, 1444, 1021, 931, 846, 730, 702, 663, 620 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.84 (dd, $^3J_{HH}$=6.0 Hz, A_3B_3X, J_{AB}=8.6 Hz, 6H, CH(CH_3)$_2$), 1.35 (dd, $^3J_{HH}$=6.7 Hz, $^3J_{PH}$=13.8 Hz, 3H, CH_3), 1.36–1.50 (m, 2H, C*H*HCH(CH$_3$)$_2$, C*H*(CH$_3$)$_2$), 1.52–1.69 (m, 1H, CH*H*CH(CH$_3$)$_2$), 1.77–1.96 (m, 1H, PC*H*H), 2.15–2.37 (m, 1H, PCH*H*), 2.86–3.01 (m, 1H, C*H*COOBzl), 3.97–4.15 (m, 1H, PC*H*), 4.17–4.25 (m, 1H, C*H*CH_2O), 4.33–4.48 (m, 2H, CHCH_2O), 5.14 (s, 2H, OCH_2Ph), 5.42 (d, $^3J_{HH}$=9.3 Hz, 1H, N*H*), 7.24–7.79 (m, 13H, aryl); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.9 (d, $^2J_{PC}$=12.6 Hz, *C*H_3), 22.2 (d, ABX, J_{AB}=37.9, CH(*C*H$_3$)$_2$), 25.7 (*C*H(CH$_3$)$_2$), 28.6 (d, $^1J_{PC}$=91.2 Hz, P*C*H_2, I), 29.0 (d, $^1J_{PC}$=91.2 Hz, P*C*H_2, II), 37.2 (d, $^2J_{PC}$=3.9 Hz, *C*HCOOBzl, I), 37.3 (d, $^2J_{PC}$=3.9 Hz, *C*HCOOBzl, II), 43.2 (d, $^3J_{PC}$=11.1 Hz, *C*H_2CH(CH$_3$)$_2$), 45.1 (d, $^1J_{PC}$=105.2 Hz, P*C*H, I), 45.9 (d, $^1J_{PC}$=105.2 Hz, P*C*H, II), 47.1 (*C*HCH_2O), 66.7 (O*C*H_2Ph), 67.2 (CH*C*H_2O), 119.9, 125.0, 127.0, 127.4, 127.7, 128.1, 128.2, 128.4, 135.7, 141.2, 143.7 (aryl), 156.0 (d, $^3J_{PC}$=6.8 Hz, O*C*ONH), 175.2 (d, $^3J_{PC}$=5.4 Hz, *C*OOBzl); ^{31}P NMR (81 MHz, $CDCl_3$) δ 53.01, 53.41; ESMS *m*/*z* calcd for $C_{31}H_{37}NO_6P$ $(M+H)^+$ 550.6, found 550.3; Anal. Calcd for $C_{31}H_{36}NO_6P$ (549.6); C, 67.75; H, 6.60; N, 2.55. Found: C, 67.89; H, 6.26; N, 2.50.

4.5. General method for the synthesis of compounds of type 9

Compound **8** (1 mmol) and 1-adamantyl bromide (1.2 mmol) were dissolved in chloroform (10 ml), and the reaction mixture was refluxed. To this refluxing mixture, silver oxide (1.2 mmol) was added in five equal portions over 50 min. The reaction mixture was refluxed for two additional hours. Then the solvents were removed in vacuo and the residue was treated with diethylether. The silver bromide and the excess of silver oxide were removed by filtration through celite. The filtrates were concentrated to dryness and the residue was purified by column chromatography using chloroform–2-propanol (98:2) as eluent.

4.5.1. (*R*,*S*)-3-((1-(*N*-(9-Fluorenylmethoxycarbonyl)amino)-2-phenylethyl)-adamantyloxyphosphinyl) propanoic acid, benzyl ester (9a). White solid, mp 127–129°C; TLC R_f(d) 0.73, R_f(e) 0.84; IR ν_{max} (liquid film) 3650–3120 (br), 3071, 3010, 2978, 1740, 1693, 1551, 1504, 1445, 1016, 930, 841, 732, 700, 661, 620 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.53–1.71 (m, 6H, CHCH_2CH of Ad group), 2.01–2.26 (m, 11H, CCH_2 of Ad group, C*H* of Ad group, PCH_2), 2.50–2.77 (m, 2H, CH_2CO), 2.85–3.08 (m, 1H, PhC*H*H), 3.22–3.41 (m, 1H, PhCH*H*), 4.07–4.24 (m, 3H, CHCH_2O, PC*H*), 4.27–4.46 (m, 1H, C*H*CH_2O), 5.12 (s, 2H, OCH_2Ph), 5.58 (d, $^3J_{HH}$=10.1 Hz, 1H, N*H*), 7.17–7.78 (m, 18H, aryl); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.8 (d, $^1J_{PC}$=91.4 Hz, P*C*H_2, I), 24.2 (d, $^1J_{PC}$=91.4 Hz, P*C*H_2, II), 27.4 (d, $^2J_{PC}$=17.3 Hz, *C*H_2CO), 31.2 (*C*H of Ad group), 33.8 (*C*H_2Ph), 35.6 (CH*C*H_2CH of Ad group), 44.5 (d, $^3J_{PC}$=4.8 Hz, C*C*H_2 of Ad group), 46.9 (*C*HCH_2O), 50.5 (d, $^1J_{PC}$=111.3 Hz, P*C*H), 66.7 (O*C*H_2Ph), 67.2 (CH*C*H_2O), 83.8 (d, $^2J_{PC}$=10.3 Hz, PO*C*), 119.9, 125.0, 125.1, 126.7, 127.0, 127.6, 128.2, 128.5, 129.1, 135.5, 136.7, 141.2, 143.6, 143.8 (aryl), 156.1 (d, $^3J_{PC}$=6.0 Hz, O*C*ONH), 172.1 (d, $^3J_{PC}$=17.2 Hz, *C*OOBzl); ^{31}P NMR (81 MHz, $CDCl_3$) δ 49.16, 49.97; ESMS *m*/*z* calcd for $C_{43}H_{47}NO_6P$ $(M+H)^+$ 704.8, found

704.4; Anal. Calcd for $C_{43}H_{46}NO_6P$ (703.8); C, 73.38; H, 6.59; N, 1.99. Found: C, 73.12; H, 6.83; N, 1.95.

4.5.2. (*R*,*R*,*S*,*S*)-2-Methyl-3-((1-(*N*-(9-fluorenylmethoxycarbonyl)amino)-2-phenylethyl)-adamantyloxyphosphinyl) propanoic acid, benzyl ester (9b). White solid, mp 134–136°C; TLC R_f(d) 0.76, R_f(e) 0.85; IR ν_{max} (liquid film) 3640–3100 (br), 3072, 3015, 2981, 1736, 1689, 1550, 1502, 1442, 1012, 932, 841, 732, 699, 660, 621 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (d, $^3J_{HH}$=7.0 Hz, 3H, C*H*$_3$), 1.56–1.67 (m, 6H, CHC*H*$_2$CH of Ad group), 1.78–1.96 (m, 1H, PC*H*H), 2.09–2.24 (m, 9H, C*H* of Ad group, CC*H*$_2$ of Ad group), 2.41–2.61 (m, 1H, PCH*H*), 2.87–3.16 (m, 2H, PhC*H*H, C*H*COOBzl), 3.24–3.38 (m, 1H, PhCH*H*), 4.01–4.16 (m, 2H, CHC*H*$_2$O), 4.22–4.41 (m, 2H, C*H*CH$_2$O, PC*H*), 5.18 (s, 2H, OC*H*$_2$Ph), 5.92 (d, $^3J_{HH}$=9.9 Hz, 1H, N*H*), 7.19–7.76 (m, 18H, aryl); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.0 (d, $^3J_{PC}$=10.7 Hz, *C*H$_3$), 28.9 (d, $^1J_{PC}$=92.9 Hz, P*C*H$_2$, I), 30.7 (d, $^1J_{PC}$=92.9 Hz, P*C*H$_2$, II), 30.9 (*C*H of Ad group), 33.7 (*C*H$_2$Ph), 34.9 (*C*HCO), 35.3 (CH*C*H$_2$CH of Ad group), 44.1 (d, $^3J_{PC}$=4.8 Hz, C*C*H$_2$ of Ad group), 46.7 (*C*HCH$_2$O), 51.4 (d, $^1J_{PC}$=109.3 Hz, P*C*H), 66.8 (O*C*H$_2$Ph), 67.5 (CH*C*H$_2$O), 83.6 (d, $^2J_{PC}$=10.3 Hz, PO*C*), 119.9, 125.2, 125.4, 126.9, 127.1, 127.6, 128.2, 128.5, 129.1, 135.4, 135.6, 136.3, 136.6, 141.2, 143.6, 143.9 (aryl), 155.9 (d, $^3J_{PC}$=5.3 Hz, O*C*ONH), 175.3 (d, $^3J_{PC}$=12.2 Hz, *C*OOBzl); ^{31}P NMR (81 MHz, $CDCl_3$) δ 48.36, 48.4, 48.82, 49.77; ESMS *m*/*z* calcd for $C_{44}H_{49}NO_6P$ $(M+H)^+$ 718.8, found 718.4; Anal. Calcd for $C_{44}H_{48}NO_6P$ (717.8); C, 73.62; H, 6.74; N, 1.95. Found: C, 73.56; H, 6.84; N, 1.88.

4.5.3. (*R*,*R*,*S*,*S*)-2-Isobutyl-3-((1-(*N*-(9-fluorenylmethoxycarbonyl)amino)-2-phenylethyl)-adamantyloxyphosphinyl) propanoic acid, benzyl ester (9c). White solid, mp 135–137°C; TLC R_f(d) 0.78, R_f(e) 0.87; IR ν_{max} (liquid film) 3650–3150 (br), 3070, 3016, 2981, 1743, 1694, 1550, 1506, 1442, 1020, 932, 840, 741, 699, 660, 617 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.78–0.97 (m, 6H, CH(C*H*$_3$)$_2$), 1.38–1.57 (m, 2H, C*H*HCH(CH$_3$)$_2$, C*H*(CH$_3$)$_2$), 1.52–1.66 (m, 7H, CH*H*CH(CH$_3$)$_2$, CHC*H*$_2$CH of Ad group), 1.82–1.96 (m, 1H, PC*H*H), 2.09–2.24 (m, 9H, CC*H*$_2$ of Ad group, C*H* of Ad group), 2.32–2.48 (m, 1H, PCH*H*), 2.87–3.06 (m, 2H, PhC*H*H, C*H*COOBzl), 3.22–3.38 (m, 1H, PhCH*H*), 3.98–4.09 (m, 2H, CHC*H*$_2$O), 4.21–4.43 (m, 2H, C*H*CH$_2$O, PC*H*), 5.16 (s, 2H, OC*H*$_2$Ph), 5.40 (d, $^3J_{HH}$=10.3 Hz, 1H, N*H*), 7.12–7.82 (m, 18H, aryl); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.4 (d, ABX, J_{AB}=43.6 Hz, CH(*C*H$_3$)$_2$), 25.8 (*C*H(CH$_3$)$_2$), 28.5 (d, $^1J_{PC}$=81.3 Hz, P*C*H$_2$, I), 29.1 (d, $^1J_{PC}$=81.3 Hz, P*C*H$_2$, II), 31.2 (*C*H of Ad group), 34.6 (*C*H$_2$Ph), 35.6 (CH*C*H$_2$CH of Ad group), 37.9 (d, $^2J_{PC}$=37.7 Hz, *C*HCOOBzl), 43.6 (d, $^3J_{PC}$=10.7 Hz, *C*H$_2$CH(CH$_3$)$_2$), 44.3 (d, $^3J_{PC}$=4.8 Hz, C*C*H$_2$ of Ad group), 46.9 (*C*HCH$_2$O), 51.4 (d, $^1J_{PC}$= 107.8 Hz, P*C*H, I), 52.2 (d, $^1J_{PC}$=107.8 Hz, P*C*H, II), 66.6 (O*C*H$_2$Ph), 67.2 (CH*C*H$_2$O), 83.9 (d, $^2J_{PC}$=10.7 Hz, PO*C*), 119.9, 125.0, 125.3, 126.7, 127.0, 127.6, 128.2, 128.3, 129.3, 135.8, 136.5, 136.7, 141.2, 143.6, 143.8 (aryl), 156.0 (d, $^3J_{PC}$=7.4 Hz, O*C*ONH), 175.2 (d, $^3J_{PC}$=5.3 Hz, *C*OOBzl); ^{31}P NMR (81 MHz, $CDCl_3$) δ 46.91, 47.55, 48.60, 49.90; ESMS *m*/*z* calcd for $C_{47}H_{55}NO_6P$ $(M+H)^+$ 760.8, found 760.4; Anal. Calcd for $C_{47}H_{54}NO_6P+0.5H_2O$ (768.9); C, 73.42; H, 7.21; N, 1.82. Found: C, 73.52; H, 7.04; N, 1.91.

4.5.4. (*R*,*R*,*S*,*S*)-2-Isobutyl-3-((1-(*N*-(9-fluorenylmethoxycarbonyl)amino)-ethyl)-adamantyloxyphosphinyl) propanoic acid, benzyl ester (9d). Mp 139–141°C; TLC R_f(d) 0.67, R_f(e) 0.85; IR ν_{max} (liquid film) 3660–3130 (br), 3071, 3010, 2978, 1740, 1693, 1551, 1504, 1445, 1016, 930, 841, 732, 700, 661, 620 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.80–0.98 (m, 6H, CH(C*H*$_3$)$_2$), 1.22–1.52 (m, 5H, C*H*HCH(CH$_3$)$_2$, C*H*$_3$, C*H*(CH$_3$)$_2$), 1.49–1.67 (m, 7H, CHC*H*$_2$CH of Ad group, CH*H*CH(CH$_3$)$_2$), 1.82–1.97 (m, 1H, PC*H*H), 2.04–2.19 (m, 9H, CC*H*$_2$ of Ad group, C*H* of Ad group), 2.22–2.40 (m, 1H, PCH*H*), 2.85–3.02 (m, 1H, C*H*COOBzl), 3.97–4.25 (m, 2H, PC*H*, C*H*CH$_2$O), 4.31–4.44 (m, 2H, CHC*H*$_2$O), 5.14 (s, 2H, OC*H*$_2$Ph), 5.94 (d, $^3J_{HH}$=9.7 Hz, 1H, N*H*), 7.24–7.79 (m, 13H, aryl); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0 (d, $^2J_{PC}$=13.1 Hz, *C*H$_3$), 22.4 (d, ABX, J_{AB}=45.9 Hz, CH(*C*H$_3$)$_2$), 25.9 (*C*H(CH$_3$)$_2$), 28.3 (d, $^1J_{PC}$=84.7 Hz, P*C*H$_2$, I), 29.3 (d, $^1J_{PC}$=84.7 Hz, P*C*H$_2$, II), 31.1 (*C*H of Ad group), 35.5 (CH*C*H$_2$CH of Ad group), 37.2 (d, $^2J_{PC}$=37.7 Hz, *C*HCOOBzl), 43.5 (d, $^3J_{PC}$=10.1 Hz, *C*H$_2$CH(CH$_3$)$_2$), 44.2 (d, $^3J_{PC}$=4.8 Hz, C*C*H$_2$ of Ad group), 45.6 (d, $^1J_{PC}$=104.6 Hz, P*C*H, I), 46.1 (d, $^1J_{PC}$= 107.8 Hz, P*C*H, II), 47.5 (*C*HCH$_2$O), 66.7 (O*C*H$_2$Ph), 67.5 (CH*C*H$_2$O), 83.3 (d, $^2J_{PC}$=10.7 Hz, PO*C*), 119.9, 125.0, 127.0, 127.4, 127.8, 128.1, 128.4, 135.6, 141.4, 143.7 (aryl), 156.1 (d, $^3J_{PC}$=6.8 Hz, O*C*ONH), 175.3 (d, $^3J_{PC}$= 7.7 Hz, *C*OOBzl); ^{31}P NMR (81 MHz, $CDCl_3$) δ 47.43, 48.24, 48.39, 49.15; ESMS *m*/*z* calcd for $C_{41}H_{51}NO_6P$ $(M+H)^+$ 684.8, found 684.4; Anal. Calcd for $C_{41}H_{50}NO_6P$ (683.8); C, 72.01; H, 7.37; N, 2.05. Found: C, 72.33; H, 7.40; N, 1.93.

4.6. General method for the synthesis of compounds of type 1

Compound **9** (1 mmol) was dissolved in absolute ethanol (5 ml). To this solution, Pd/C 10% (300 mg) was carefully added. Then, H_2 was introduced in a pressure of 1 atm. After 1.5–2 h, the catalyst was removed by filtration through celite and the filtrates were concentrated to dryness giving the crude compounds of type **1** as white foam. Further purification was achieved by column chromatography using chloroform–methanol (9.6:0.4) as eluent.

4.6.1. (*R*,*R*,*S*,*S*)-3-((1-(*N*-(9-Fluorenylmethoxycarbonyl)-amino)-2-phenylethyl)-adamantyloxyphosphinyl) propanoic acid (1a). White solid, mp 128–130°C; TLC R_f(e) 0.37, R_f(f) 0.84; IR ν_{max} (liquid film) 3610–3150 (br), 3074, 3013, 2986, 1742, 1694, 1552, 1503, 1441, 1014, 932, 741, 698, 660, 621 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.54–1.63 (m, 6H, CHC*H*$_2$CH of Ad group), 2.04–2.18 (m, 11H, C*H*of Ad group, CC*H*$_2$ of Ad group, PC*H*$_2$), 2.62–2.78 (m, 2H, C*H*$_2$CO), 2.81–3.00 (m, 1H, PhC*H*H), 3.19–3.33 (m, 1H, PhCH*H*), 4.01–4.13 (m, 2H, CHC*H*$_2$O), 4.16–4.37 (m, 2H, C*H*CH$_2$O, PC*H*), 6.65 (d, $^3J_{HH}$=10.1 Hz, 1H, N*H*), 7.16–7.79 (m, 13H, aryl); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.6 (bd, $^1J_{PC}$=89.8 Hz, P*C*H$_2$), 30.7 (*C*H$_2$COOH), 31.2 (*C*H of Ad group), 33.6 (*C*H$_2$Ph), 35.5 (CH*C*H$_2$CH of Ad group), 44.7 (d, $^3J_{PC}$=2.9 Hz, C*C*H$_2$ of Ad group), 46.9 (*C*HCH$_2$O), 51.5 (d, $^1J_{PC}$=115.5 Hz, P*C*H), 67.2

(CHCH$_2$O), 84.2 (d, $^2J_{PC}$=10.4 Hz, POC), 119.8, 125.3, 126.7, 127.0, 127.6, 128.4, 128.5, 129.2, 135.5, 136.7, 141.2, 143.7, (aryl), 157.2 (d, $^3J_{PC}$=7.1 Hz, OCONH), 172.1 (d, $^3J_{PC}$=18.1 Hz, COOH); ^{31}P NMR (81 MHz, $CDCl_3$) δ 50.51, 50.79; ESMS *m/z* calcd for $C_{36}H_{41}NO_6P$ $(M+H)^+$ 614.7, found 614.3; Anal. Calcd for $C_{36}H_{40}NO_6P+H_2O$ (631.7); C, 68.45; H, 6.64; N, 2.22. Found: C, 68.53; H, 7.01; N, 2.32.

4.6.2. (*R*,*R*,*S*,*S*)-2-Methyl-3-((1-(*N*-(9-fluorenylmethoxycarbonyl)amino)-2-phenylethyl)-adamantyloxyphosphinyl) propanoic acid (1b). White solid, mp 128–130°C; TLC R_f(d) 0.40, R_f(e) 0.41; IR ν_{max} (liquid film) 3630–3120 (br), 3078, 3010, 2981, 1744, 1693, 1550, 1504, 1444, 1020, 931, 846, 741, 700, 668, 624 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.24 (d, $^3J_{HH}$=6.8 Hz, 3H, CH_3), 1.48–1.69 (m, 6H, CH_2 of Ad group), 1.81–2.08 (m, 1H, PCHH), 2.04–2.18 (m, 9H, CHCH_2CH of Ad group, CH of Ad group), 2.31–2.62 (m, 1H, PCHH), 2.79–3.02 (m, 2H, CHCOOH, PhCHH), 3.20–3.32 (m, 1H, PhCHH), 3.94–4.16 (m, 2H, CHCH_2O), 4.19–4.37 (m, 2H, CHCH$_2$O, PCH), 6.68 (d, $^3J_{HH}$=10.3 Hz, 1H, NH), 7.12–7.78 (m, 13H, aryl); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.7 (d, $^3J_{PC}$=10.7 Hz, CH_3), 25.9 (d, $^1J_{PC}$=116.3 Hz, PCH$_2$, I), 26.3 (d, $^1J_{PC}$=116.3 Hz, PCH$_2$, II), 31.1 (CH of Ad group), 33.7 (CH_2Ph), 34.7 (CHCOOH), 35.5 (CHCH_2CH of Ad group), 44.2 (d, $^3J_{PC}$=4.8 Hz, CCH$_2$ of Ad group), 46.8 (CHCH$_2$O), 51.6 (d, $^1J_{PC}$=116.3 Hz, PCH, I), 52.5 (d, $^1J_{PC}$=116.3 Hz, PCH, II), 67.3 (CHCH$_2$O), 83.9 (d, $^2J_{PC}$=12.8 Hz, POC), 119.8, 125.1, 125.5, 127.0, 127.5, 128.3, 129.2, 136.8, 137.1, 137.4, 141.1, 143.4, 144.0 (aryl), 156.6 (d, $^3J_{PC}$=5.2 Hz, OCONH), 179.1 (d, $^3J_{PC}$=5.5 Hz, COOH); ^{31}P NMR (81 MHz, $CDCl_3$) δ 48.42, 48.57, 49.84, 51.21; ESMS *m/z* calcd for $C_{37}H_{43}NO_6P$ $(M+H)^+$ 628.7, found 628.4; Anal. Calcd for $C_{37}H_{42}NO_6P$ (627.7); C, 70.80; H, 6.74; N, 2.23. Found: C, 70.42; H, 7.16; N, 2.12.

4.6.3. (*R*,*R*,*S*,*S*)-2-Isobutyl-3-((1-(*N*-(9-fluorenylmethoxycarbonyl)amino)-2-phenylethyl)-adamantyloxyphosphinyl) propanoic acid (1c). White solid, mp 140–142°C; TLC R_f(d) 0.44, R_f(e) 0.46; IR ν_{max} (liquid film) 3630–3140 (br), 3072, 3016, 2988, 1742, 1689, 1550, 1506, 1445, 1020, 930, 842, 740, 699, 660, 624 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.82–1.01 (m, 6H, CH(CH_3)$_2$), 1.21–1.38 (m, 1H, CHHCH(CH$_3$)$_2$), 1.51–1.74 (m, 8H, CH_2 of Ad group, CH(CH$_3$)$_2$, CHHCH(CH$_3$)$_2$), 1.82–2.08 (m, 1H, PCHH), 2.04–2.21 (m, 9H, CHCH_2CH, CH of Ad group), 2.36–2.44 (m, 1H, PCHH), 2.93–3.02 (m, 2H, PhCHH, CHCOOH), 3.16–3.37 (m, 1H, PhCHH), 3.87–4.11 (m, 2H, CHCH_2O), 4.18–4.42 (m, 2H, CHCH$_2$O, PCH), 6.86 (d, $^3J_{HH}$=10.0 Hz, 1H, NH), 7.16–7.80 (m, 13H, aryl); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.4 (d, ABX, J_{AB}=43.6 Hz, CH(CH_3)$_2$), 25.7 (CH(CH$_3$)$_2$), 29.6 (d, $^1J_{PC}$=86.9 Hz, PCH$_2$, I), 30.6 (d, $^1J_{PC}$=86.9 Hz, PCH$_2$, II), 31.2 (CH of Ad group), 34.1 (CH_2Ph), 35.5 (CHCH_2CH of Ad group), 38.9 (d, $^2J_{PC}$=37.7 Hz, CHCO), 42.4 (d, $^3J_{PC}$=10.7 Hz, CH$_2$CH(CH$_3$)$_2$), 44.3 (d, $^3J_{PC}$=3.7 Hz, CCH$_2$ of Ad group), 46.9 (CHCH$_2$O), 51.7 (d, $^1J_{PC}$=111.8 Hz, PCH, I), 52.3 (d, $^1J_{PC}$=111.8 Hz, PCH, II), 67.2 (CHCH$_2$O), 83.9 (d, $^2J_{PC}$=10.7 Hz, POC), 119.8, 125.1, 125.5, 126.9, 127.0, 127.5, 128.3, 129.3, 136.8, 137.2, 141.1, 143.7, 144.0 (aryl), 156.0 (d, $^3J_{PC}$=7.9 Hz, OCONH), 175.2 (d, $^3J_{PC}$=7.2 Hz, COOH); ^{31}P NMR (81 MHz, $CDCl_3$) δ 48.45, 49.32, 51.30, 51.91; ESMS *m/z* calcd for $C_{40}H_{49}NO_6P$ $(M+H)^+$ 670.8, found 670.4 $(M+H)^+$; Anal. Calcd for $C_{40}H_{48}NO_6P+0.5H_2O$ (678.8); C, 70.78; H, 7.27; N, 2.06. Found: C, 70.87; H, 7.47; N, 2.12.

4.6.4. (*R*,*R*,*S*,*S*)-2-Isobutyl-3-((1-(*N*-(9-fluorenylmethoxycarbonyl)amino)-ethyl)-adamantyloxyphosphinyl) propanoic acid (1d). White solid, mp 140–142°C; TLC R_f(d) 0.41, R_f(e) 0.53; IR ν_{max} (liquid film) 3650–3130 (br), 3070, 3014, 2990, 1736, 1692, 1554, 1505, 1441, 1017, 932, 738, 702, 664, 621 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80–0.98 (m, 6H, CH(CH_3)$_2$), 1.27–1.42 (m, 4H, CHHCH(CH$_3$)$_2$, CH_3), 1.46–1.71 (m, 8H, CHCH_2CH of Ad group, CH(CH$_3$)$_2$, CHHCH(CH$_3$)$_2$), 1.77–1.93 (m, 1H, PCHH), 1.97–2.18 (m, 9H, CCH$_2$ of Ad group, CH of Ad group), 2.21–2.33 (m, 1H, PCHH), 2.77–2.96 (m, 1H, CHCOOH), 3.88–4.16 (m, 2H, PCH, CHCH$_2$O), 4.18–4.39 (m, 2H, CHCH_2O), 6.84 (d, $^3J_{HH}$=9.1 Hz, 1H, NH), 7.24–7.79 (m, 10H, aryl); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.6 (d, $^2J_{PC}$=11.9 Hz, CH_3), 22.4 (d, ABX, J_{AB}=29.2 Hz, CH(CH_3)$_2$), 25.6 (CH(CH$_3$)$_2$), 28.6 (d, $^1J_{PC}$=102.4 Hz, PCH$_2$, I), 29.1 (d, $^1J_{PC}$=102.4 Hz, PCH$_2$, II), 31.1 (CH of Ad group), 35.5 (CHCH_2CH of Ad group), 38.4 (d, $^2J_{PC}$=25.2 Hz, CHCO), 44.3 (d, $^3J_{PC}$=3.3 Hz, CCH$_2$ of Ad group), 42.4 (d, $^3J_{PC}$=13.3 Hz, CH$_2$CH(CH$_3$)$_2$), 45.3 (bd, $^1J_{PC}$=101.2 Hz, PCH), 47.0 (CHCH$_2$O), 67.5 (CHCH$_2$O), 84.4 (d, $^2J_{PC}$=9.8 Hz, POC), 119.8, 123.6, 125.1, 125.4, 127.0, 127.6, 127.9, 128.9, 137.7, 141.2, 143.7 (aryl), 157.2 (d, $^3J_{PC}$=7.5 Hz, OCONH), 177.4 (d, $^3J_{PC}$=6.8 Hz, COOH); ^{31}P NMR (81 MHz, $CDCl_3$) δ 48.96, 50.06, 50.43, 51.69; ESMS *m/z* calcd for $C_{34}H_{45}NO_6P$ $(M+H)^+$ 594.7, found 594.4; Anal. Calcd for $C_{34}H_{44}NO_6P+H_2O$ (611.7); C, 66.76; H, 7.58; N, 2.29. Found: C, 67.08; H, 7.63; N, 2.27.

Acknowledgements

This work was supported in part by funds from the Department of Organic Chemistry of Athens University and BIOTECH 2 (Contract No ERBBIO4CT96-0464).

References

1. Dive, V.; Lucet-Levannier, K.; Georgiadis, D.; Cotton, J.; Vassiliou, S.; Cuniasse, P.; Yiotakis, A. *Biochem. Soc. T.* **2000**, *28*, 455.
2. Collinsova, M.; Jiracek, J. *Curr. Med. Chem.* **2000**, *7*, 629.
3. Caldwell, C. G.; Sahoo, S. P.; Polo, S. A.; Eversole, R. R.; Lanza, T. J.; Mills, S. G.; Niedzwiecki, L. M.; Izquierdo-Martin, M.; Chang, B. C.; Harrison, R. K.; Kuo, D. W.; Lin, T.-Y.; Stein, R. L.; Durette, P. L.; Hagmann, W. K. *Biorg. Med. Chem. Lett.* **1996**, *6*, 323.
4. Chen, H. X.; Noble, F.; Coric, P.; Fournie-Zaluski, M.-C.; Roques, B. P. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 12028.
5. Reiter, L. A.; Rizzi, J. P.; Pandit, J.; Lasut, M. J.; McGahee, S. M.; Parikh, V. D.; Blake, J. F.; Danley, D. E.; Laird, E. R.; Lopez-Anaya, A.; Lopresti-Morrow, L. L.; Mansour, M. N.; Martinelli, G. J.; Mitchell, P. G.; Owens, B. S.; Pauly, T. A.; Reeves, L. M.; Schulte, G. K.; Yocum, S. A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 127.

6. Vassiliou, S.; Mucha, A.; Cuniasse, P.; Georgiadis, D.; Lucet-Levannier, K.; Beau, F.; Kannan, R.; Murphy, G.; Knäuper, V.; Rio, M.-C.; Basset, P.; Yiotakis, A.; Dive, V. *J. Med. Chem.* **1999**, *42*, 2610.
7. Georgiadis, D.; Vazeux, G.; Llorens-Cortes, C.; Yiotakis, A.; Dive, V. *Biochemistry* **2000**, *39*, 1152.
8. Yiotakis, A.; Vassiliou, S.; Jiracek, J.; Dive, V. *J. Org. Chem.* **1996**, *61*, 6601–6605.
9. Jiracek, J.; Yiotakis, A.; Vincent, B.; Lecoq, A.; Nicolaou, A.; Checler, F.; Dive, V. *J. Biol. Chem.* **1995**, *270*, 21701.
10. Jiracek, J.; Yiotakis, A.; Vincent, B.; Checler, F.; Dive, V. *J. Biol. Chem.* **1996**, *271*, 19,606.
11. Dive, V.; Cotton, J.; Yiotakis, A.; Michaud, A.; Vassiliou, S.; Jiracek, J.; Vazeux, G.; Chauvet, M. T.; Cuniasse, P.; Corvol, P. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 4330.
12. Buchardt, J.; Ferreras, M.; Krog-Jensen, C.; Delaissé, J.-M.; Foged, N. T.; Meldal, M. *Chem. Eur. J.* **1999**, *5*, 2877.
13. Grams, F.; Dive, V.; Yiotakis, A.; Yiallouros, I.; Vassiliou, S.; Zwilling, R.; Bode, W.; Stöcker, W. *Nat. Struct. Biol.* **1996**, *3*, 671.
14. Anwer, M. K.; Spatola, A. E. *Synthesis* **1980**, 929.
15. Boyd, E. A.; Boyd, M. E. K.; Loh Jr, V. M. *Tetrahedron Lett.* **1996**, *37*, 1651.
16. Haztung, W. H.; Simonoff, R. *Org. React.* **1953**, *VII*, 263.
17. Atherton, E.; Bury, C.; Sheppard, R. C.; Williams, B. J. *Tetrahedron Lett.* **1979**, *32*, 3041.
18. Unpublished results.
19. Buchardt, J.; Meldal, M. J. *Chem. Soc., Perkin. Trans. I* **2000**, 3306.
20. Dorff, P. H.; Chiu, G.; Goldstein, S. W.; Morgan, B. P. *Tetrahedron Lett.* **1998**, *39*, 3375.
21. Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin. Trans. I* **1984**, 2845.
22. Stetter, H.; Kuhlmann, H. *Synthesis* **1979**, 29.
23. Friedrich-Bochnitschek, S.; Waldman, H.; Kunz, H. *J. Org. Chem.* **1989**, *54*, 751.